LINDHE'S

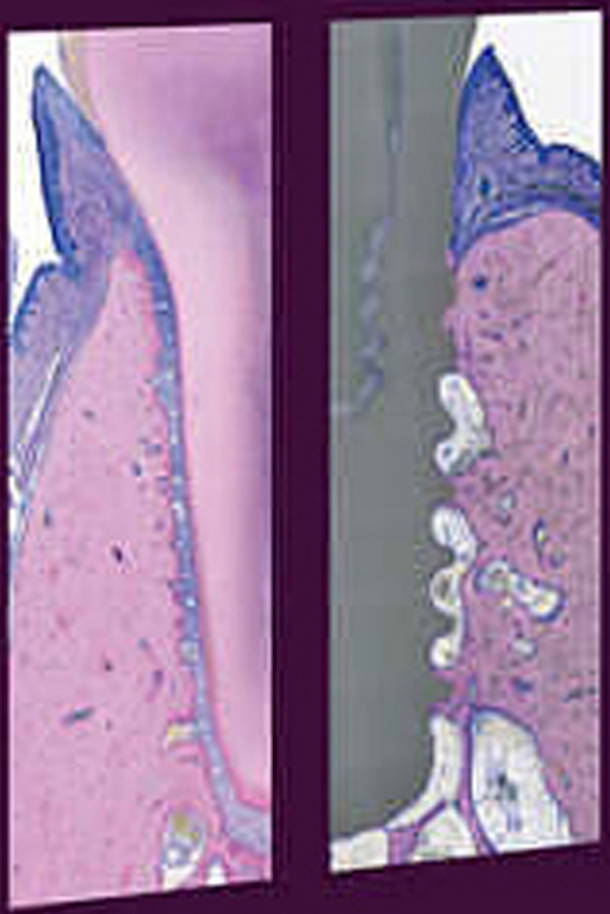
SEVENTH EDITION

Clinical Periodontology and Implant Dentistry

EDITED BY

Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz

VOLUME 1



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Lindhe's Clinical Periodontology and Implant Dentistry

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Seventh Edition

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WILEY Blackwell

Volume 1
BASIC CONCEPTS

This edition first published 2022

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Berglundh, Tord, 1954– editor. | Giannobile, William V., editor. | Lang, Niklaus Peter, editor. | Sanz, Mariano (Professor) editor.
Title: Lindhe's clinical periodontology and implant dentistry / edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, Mariano Sanz.
Other titles: Clinical periodontology and implant dentistry
Description: Seventh edition. | Hoboken : John Wiley & Sons, Inc., 2022. | Preceded by Clinical periodontology and implant dentistry / edited by Jan Lindhe and Niklaus P. Lang ; associate editors, Tord Berglundh, William V. Giannobile, Mariano Sanz. 6th edition. 2015.
Identifiers: LCCN 2021028065 (print) | LCCN 2021028066 (ebook) | ISBN 9781119438885 (cloth) | ISBN 9781119438946 (adobe pdf) | ISBN 9781119438953 (epub)
Subjects: MESH: Periodontal Diseases | Dental Implantation | Dental Implants
Classification: LCC RK667.I45 (print) | LCC RK667.I45 (ebook) | NLM WU 240 | DDC 617.6/93–dc23
LC record available at https://lccn.loc.gov/2021028065
LC ebook record available at https://lccn.loc.gov/2021028066

Cover Design: Wiley
Cover Image: Courtesy of Niklaus P. Lang

Set in 9.5/12pt Palatino by Straive, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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Preface

In 1983, Professor Jan Lindhe, University of Gothenburg, Sweden, published the first edition of *Clinical Periodontology*. This was only 2 years after the publication of a textbook on clinical periodontology in Scandinavian languages. It was a pioneer enterprise and began a new era in the study of periodontology. Up to this point, the profession was predominantly oriented towards a treatment philosophy that was based on *deductive thinking*, and very little scientific evidence had been presented.

In this light, the publication of a textbook that was based on *inductive thinking* and hypothesis testing was a true milestone and represented a novelty in teaching undergraduate and graduate students. As the field of clinical periodontology evolved, and more evidence arose from both clinical and preclinical studies, the textbook had to be revised on a regular basis. By and large, every 5 to 8 years a new edition of *Clinical Periodontology* was put together. With every edition, efforts were made to expand the circle of authors in order to obtain more information on evidence-based concepts. The textbook thus became the most internationally recognized source of information in the periodontal community.

About 20–30 years ago, implant dentistry had become an integral part of clinical periodontology. Hence, the fifth edition of *Clinical Periodontology* was substantially expanded to incorporate biological and clinical aspects of implant dentistry. As teeth and implants are to function together as separate or connected units in the same dentition, a profound knowledge of the biology of the tissues surrounding the tooth and the dental implant is of utmost importance. Owing to the large volume of new information, the fifth edition of the now titled *Clinical Periodontology and Implant Dentistry* was split into two volumes, one on *basic concepts* and another on *clinical concepts*. This division into two volumes was maintained for the sixth edition and is also maintained for this, the seventh edition.

In the last 35 years, during which the textbook evolved into the most popular source of reference, periodontology and implant dentistry have become clinical disciplines based on sound scientific evidence. As a new classification of periodontal and peri-implant diseases and conditions emerged after a world workshop staged by the American Academy of Periodontology and the European Federation of Periodontology, it was time, again, to update the textbook.

In this edition, over 90% of the content has been thoroughly revised and condensed for better understanding. Some less essential chapters have been eliminated and others merged to make the text more cohesive. A new and younger generation of authors of international reputation have been invited to contribute. Moreover, the team of Editors has been enlarged to four.

It is our hope that *Lindhe's Clinical Periodontology and Implant Dentistry* remains the key book of reference to guide treatment planning according to sound biological and evidence-based principles rather than opinions based on trial and error philosophies.

Tord Berglundh
William V. Giannobile
Niklaus P. Lang
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March 2021

Part 1: Anatomy

Chapter 1

Anatomy and Histology of Periodontal Tissues

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Introduction

This chapter provides a brief description of the characteristics of the normal periodontium. It is assumed that the reader has prior knowledge of oral embryology and histology.

The periodontium (peri = around, odontos = tooth) comprises the following tissues: (1) *gingiva*, (2) *periodontal ligament*, (3) *root cementum*, and (4) *alveolar bone proper* (Fig. 1-1). The latter lines the alveolus of the tooth and is continuous with the alveolar bone; on a radiograph it can be called *lamina dura*. The *alveolar process* that extends from the basal bone of the maxilla and mandible consists of the alveolar bone and the *alveolar bone proper*.

The main function of the periodontium is to attach the tooth to the jaw bone and to maintain the integrity of the surface of the masticatory mucosa of the oral cavity. The periodontal ligament, root cementum, and alveolar bone proper, may together be called "the attachment apparatus" or "the supporting tissues of the teeth", constituting a developmental, biologic, and functional unit which undergoes certain changes with age and is, in addition, subjected to morphologic changes related to functional alterations and alterations in the oral environment.

The development of the periodontal tissues occurs during the development and formation of teeth. This process starts early in the embryonic phase when cells from the neural crest (from the neural tube of the embryo) migrate into the first branchial arch. In this position, the neural crest cells form a band of *ectomesenchyme* beneath the epithelium of the stomatodeum (the primitive oral cavity). After the uncommitted neural crest cells have reached their location in the jaw space, the epithelium of the stomatodeum releases factors which initiate epithelial–ectomesenchymal interactions. Once these interactions have occurred, the ectomesenchyme takes the dominant role in the further development. Following the formation of the *dental lamina*, a series of processes are initiated (bud stage, cap stage, bell stage, and root development) which result in the formation of a tooth and its surrounding periodontal tissues, including the alveolar bone proper. During the cap stage, condensation of ectomesenchymal cells appears in relation to the dental epithelium (the dental organ), forming the *dental papilla* that gives rise to

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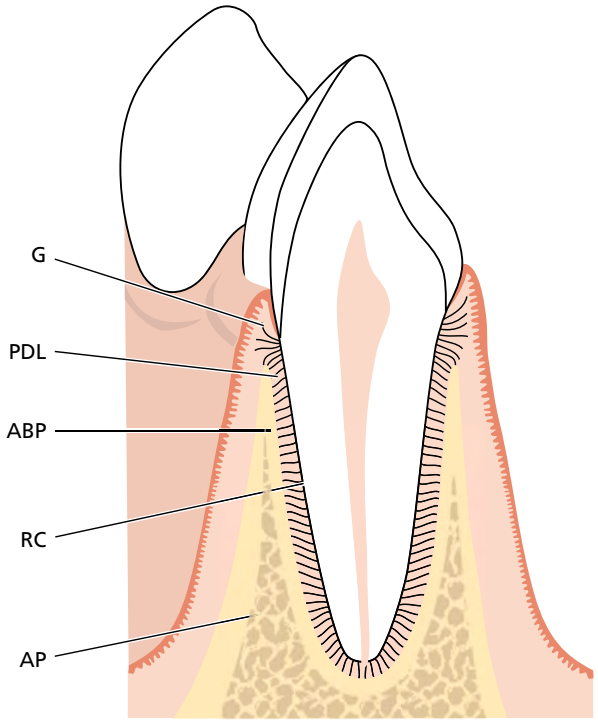

Fig. 1-1 A tooth and its periodontal tissues consisting of gingiva (G), periodontal ligament (PDL), alveolar bone proper (ABP), and root cementum (RC). AP, alveolar process.

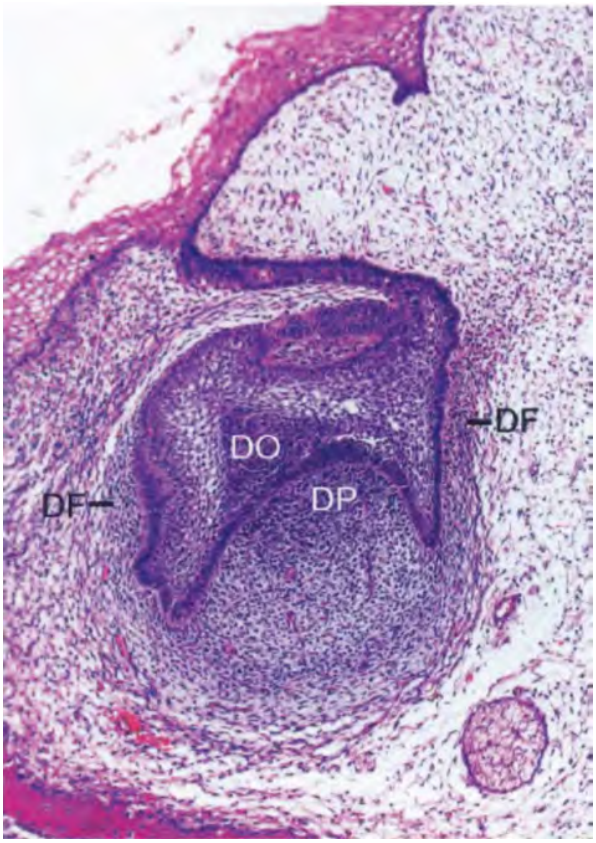

Fig. 1-2 Light micrograph of a tooth germ at the cap stage with the dental organ (DO), the dental papilla (DP), and the dental follicle (DF).

the dentin and the pulp, and the *dental follicle* that gives rise to the periodontal supporting tissues (Fig. 1-2). The decisive role played by the ectomesenchyme in this process is further established by the fact that the tissue of the dental papilla apparently also determines the shape and form of the tooth.

If a tooth germ in the bell stage of development is dissected and transplanted to an ectopic site (e.g. the connective tissue of the anterior chamber of the eye), the tooth formation process continues. The crown and the root are formed, and the supporting structures (i.e. cementum, periodontal ligament, and a thin lamina of alveolar bone proper) also develop. Such experiments document that all information necessary for the formation of a tooth and its attachment apparatus resides within the tissues of the dental organ and the surrounding ectomesenchyme. The dental organ is the formative organ of enamel, the dental papilla is the formative organ of the dentin–pulp complex, and the dental follicle is the formative organ of the attachment apparatus (cementum, periodontal ligament, and alveolar bone proper).

The development of the root and the periodontal supporting tissues follows that of the crown. Epithelial cells of the external and internal dental epithelium (the dental organ) proliferate in an apical direction, forming a double layer of cells called *Hertwig's epithelial root sheath*. The odontoblasts forming the dentin of the root differentiate from ectomesenchymal cells in the dental papilla under the inductive influence of the inner epithelial cells (Fig. 1-3). The dentin continues to form in an apical direction, producing the framework of the root. During formation of the root, the periodontal supporting tissues including the acellular extrinsic fiber cementum (AEFC) develop. Some of the events in cementogenesis are still unclear, but the following concept is now generally accepted.

At the start of root dentin formation, the inner cells of Hertwig's epithelial root sheath may synthesize and secrete enamel-related proteins, some of which belong to the amelogenin family. At the end of this process, the epithelial root sheath becomes fenestrated and ectomesenchymal cells from the dental follicle penetrate through these fenestrations and contact the root surface. The ectomesenchymal cells in contact with the root surface differentiate into cementoblasts and start to form cementoid. This cementoid represents the organic matrix of the cementum and consists of a ground substance and collagen fibers, which intermingle with collagen fibers in the not yet fully mineralized outer layer of the dentin. It is assumed that the cementum becomes firmly attached to the dentin through these fiber interactions followed by mineralization of this interface (Fig. 1-4). The formation of the CIFC, which often covers the apical third of the dental roots, differs from that of AEFC

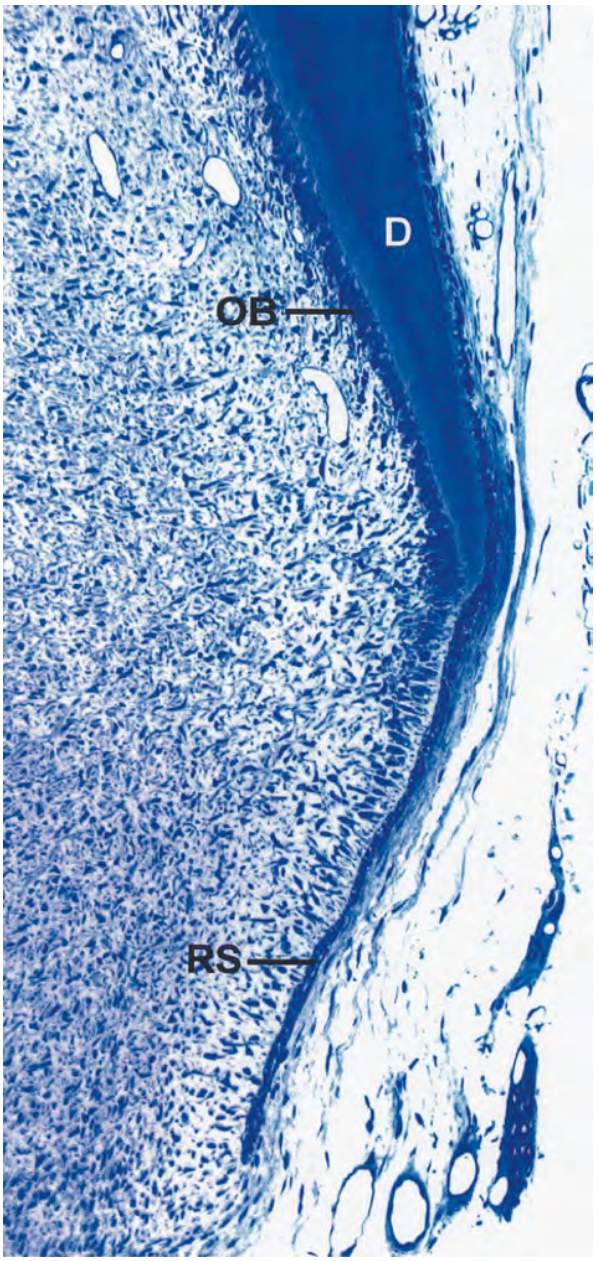

Fig. 1-3 Light micrograph illustrating the edge of a developing tooth root with the Hertwig's epithelial root sheath (RS), odontoblasts (OB), and dentin (D).

as some of the cementoblasts become embedded in the cementum.

The remaining parts of the periodontium are formed by ectomesenchymal cells from the dental follicle lateral to the cementum. Some of them differentiate into periodontal ligament fibroblasts and form the fibers of the periodontal ligament, while others become osteoblasts and form the alveolar bone proper in which the periodontal fibers are anchored. This bony structure has also been term "*bundle bone*". In other words, the bundle bone is also an ectomesenchymal product. It is likely, but still not conclusively documented, that ectomesenchymal cells remain in the mature periodontium and take part in the turnover of this tissue.

Gingiva

Anatomy

The oral mucosa is continuous with the skin of the lips and the mucosa of the soft palate and pharynx. The oral mucosa consists of: (1) the *masticatory mucosa*, which includes the gingiva and the covering of the hard palate; (2) the *specialized mucosa*, which covers the dorsum of the tongue; and (3) the remaining part, called the *lining mucosa*.

The gingiva is that part of the masticatory mucosa which covers the alveolar process and surrounds the cervical portion of the teeth (Fig. 1-5). It consists of an epithelial layer and an underlying connective tissue layer called the *lamina propria*. The gingiva obtains its final shape and texture in conjunction with eruption of the teeth.

In the coronal direction, the coral pink gingiva terminates in the *free gingival margin*, which has a scalloped outline. In the apical direction, the gingiva is continuous with the loose, darker red *alveolar mucosa* (lining mucosa) from which the gingiva is separated by a usually easily recognizable border called either the mucogingival junction, sometimes termed the mucogingival line (Fig. 1-5, arrows). As the hard palate and maxillary alveolar process are covered by a keratinizing mucosa of similar clinical appearance, no mucogingival junction is macroscopically recognizable (Fig. 1-6).

Two parts of the gingiva may be identified (Fig. 1-7): (1) the free gingiva and (2) the attached gingiva. The free gingiva is coral pink, has a dull surface and a firm consistency. It comprises the gingival tissue at the vestibular and lingual/palatal aspects of the teeth. On the vestibular and lingual sides of the teeth, the free gingiva extends from the gingival margin in an apical direction to a structure named *free gingival groove*, which is only observable in approximately one-third of the cases. The attached gingiva is demarcated by the mucogingival junction in the apical direction.

The free gingival margin is often rounded in such a way that a small invagination or sulcus is formed between the tooth and the gingiva. When a periodontal probe is inserted into this invagination and, further apically, towards the cementoenamel junction (CEJ), the gingival tissue is separated from the tooth and a "*gingival pocket*" or "*gingival crevice*" is artificially opened (Fig. 1-8). Thus, in clinically healthy gingiva, there is in fact no "gingival pocket" or "gingival crevice" present, but the gingiva is in close contact with the enamel surface. After complete tooth eruption, the free gingival margin is located on the enamel surface approximately 1.5–2 mm coronal to the CEJ.

The shape of the *interdental gingiva (the interdental papilla)* is determined by the contact relationships between the teeth, the width of the approximal tooth

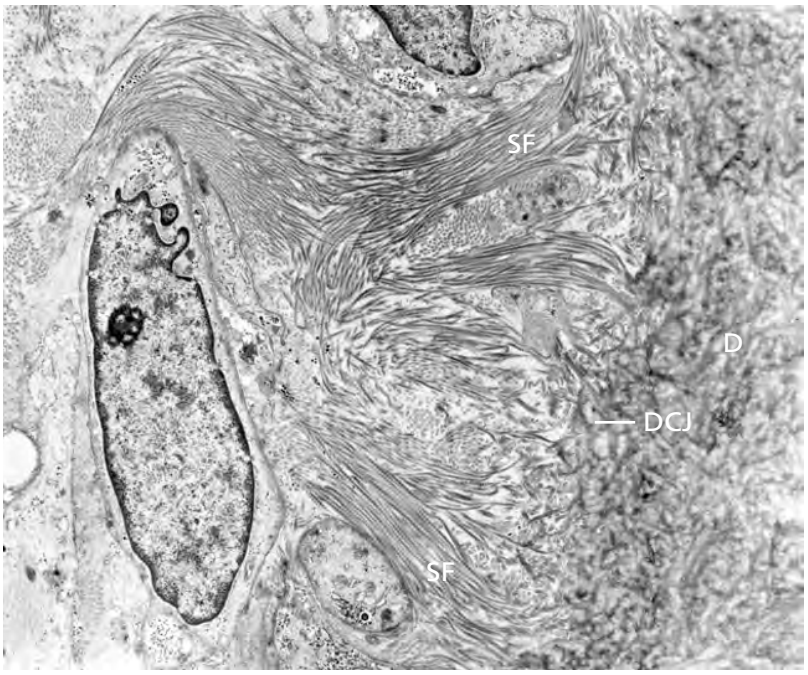

Fig. 1-4 Transmission electron micrograph illustrating the attachment of the future Sharpey's fibers (SF) to the root dentin (D) at a time where the mineralization has reached the dentinocemental junction (DCJ).

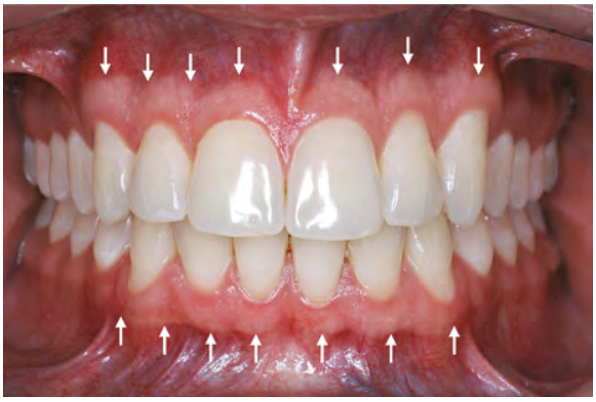

Fig. 1-5 Frontal view of the masticatory and lining mucosa. The arrows indicate the mucogingival junction, sometimes also called the mucogingival line.

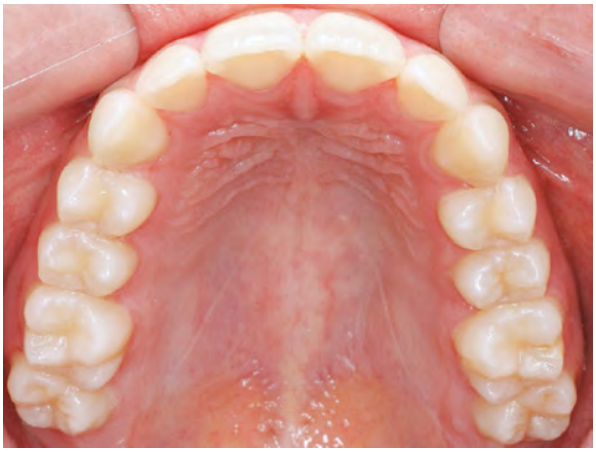

Fig. 1-6 Masticatory mucosa lining the hard palate. There is no mucogingival line present in the palate, because the hard palate and the maxillary alveolar process are covered by the same type of masticatory mucosa.

surfaces, and the course of the CEJ. In anterior regions of the dentition, the interdental papilla is of pyramidal shape (Fig. 1-9a), while in the molar regions, the papillae are flatter in the buccolingual direction (Fig. 1-9b). Due to the presence of interdental papillae, the free gingival margin follows a more or less accentuated, scalloped course through the dentition.

The interdental region in premolar and molar teeth has two papillae, a vestibular (VP) and a lingual/palatal (LP) papilla, separated by the col region. The col region is lined by a thin non-keratinized epithelium (Fig. 1-10). This epithelium has many features in common with the junctional epithelium.

The attached gingiva is demarcated in the coronal direction by the free gingival groove (Fig. 1-11) or, when such a groove is not present, by a horizontal plane placed at the level of the CEJ. In clinical examinations, it was observed that a free gingival groove is only present in about 30–40% of adults. The free gingival groove is often most pronounced on the vestibular aspect of the teeth, occurring most frequently in the incisor and premolar regions of the mandible, and least frequently in the mandibular molar and maxillary premolar regions.

The attached gingiva extends in the apical direction to the mucogingival junction, where it becomes continuous with the alveolar (lining) mucosa. It is of firm texture, coral pink in color, and often shows small depressions on the surface. The depressions, called "stippling", give the appearance of orange peel. The gingiva is firmly attached to the underlying alveolar bone and cementum by connective

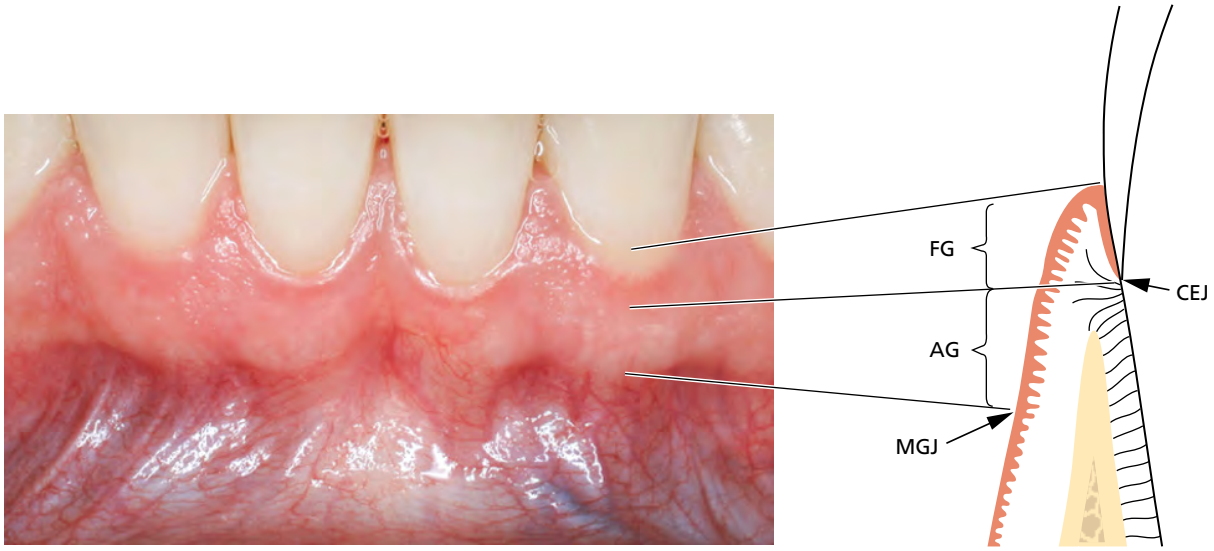

Fig. 1-7 Three parts of the gingiva can be identified: the free gingiva (FG), the interdental gingiva, and the attached gingiva (AG). The mucogingival junction (MGJ) demarcates the gingiva from the alveolar mucosa. CEJ, cementoenamel junction.

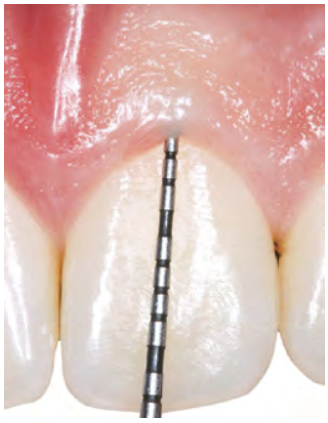

Fig. 1-8 A periodontal probe has been inserted into a clinically healthy tooth–gingiva interface and a "gingival crevice" was artificially opened approximately to the level of the cementoenamel junction.

tissue fibers, and is, therefore, comparatively immobile in relation to the underlying tissue. The darker red alveolar mucosa located apical to the mucogingival junction, on the other hand, is loosely bound to the underlying bone. Therefore, in contrast to the attached gingiva, the alveolar mucosa is mobile in relation to the underlying tissue and hence belongs to the lining mucosa.

The width of the gingiva varies in size in different parts of the dentition. In the maxilla (Fig. 1-12a), the vestibular gingiva is generally widest in the area of the incisors and narrowest adjacent to the premolars. In the mandible (Fig. 1-12b), the gingiva on the lingual aspect is particularly narrow in the area of the incisors and wide in the molar region. The range of variation is 1–9 mm. In the mandibular premolar region, the gingiva is extremely narrow (Fig. 1-13).

The result of a study in which the width of the attached gingiva was assessed and related to the

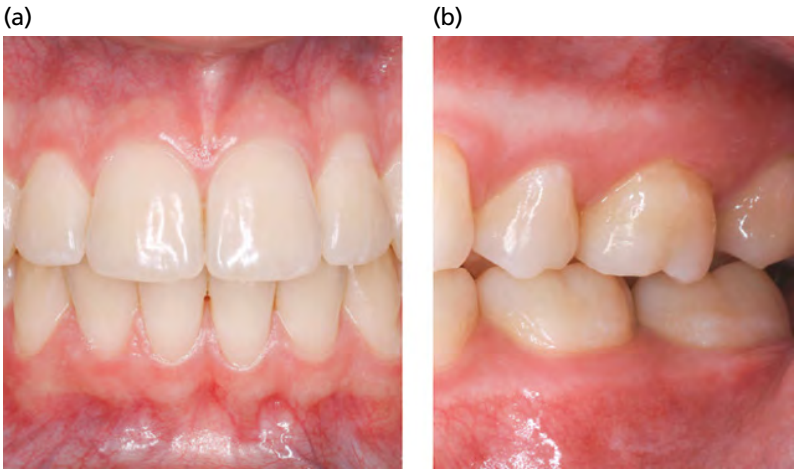

Fig. 1-9 Frontal view showing the shape of the interdental papillae in the anterior (a) and premolar/molar (b) regions.

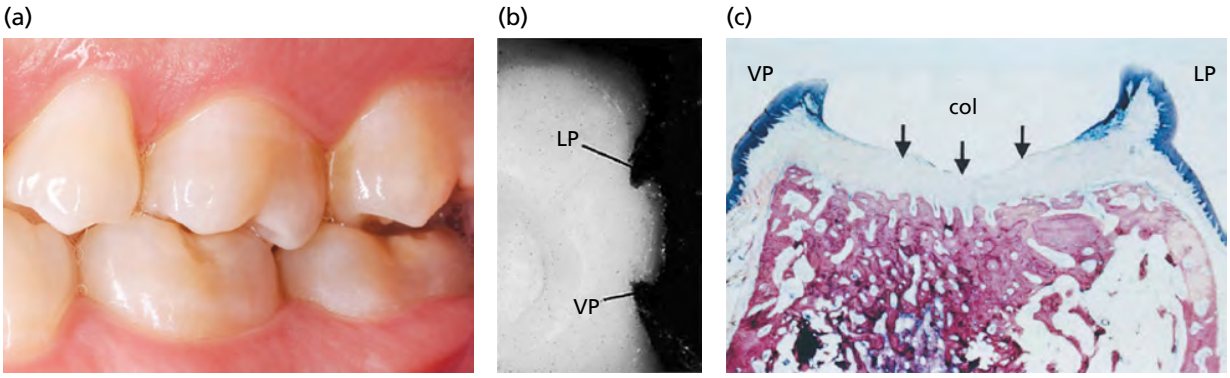

Fig. 1-10 (a) Premolar/molar regions of the dentition exhibit an approximal contact surface. (b) After removal of the distal tooth, a col can be seen between the vestibular (VP) and lingual papillae (LP). (c) Histologically, the bucco-oral section of the col region (arrows) demonstrates a thin non-keratinizing lining between the two papillae.

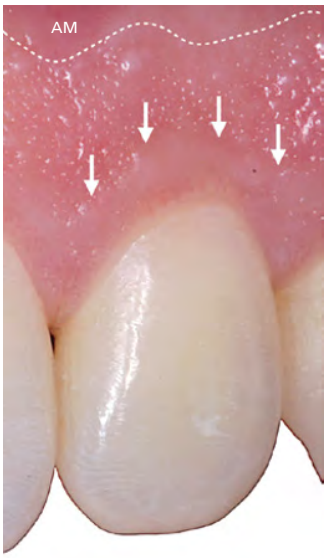

Fig. 1-11 Clinical view on the mucosal tissues. The mucogingival junction (arrows) demarcates the gingiva (masticatory mucosa) from the alveolar (lining) mucosa (AM).

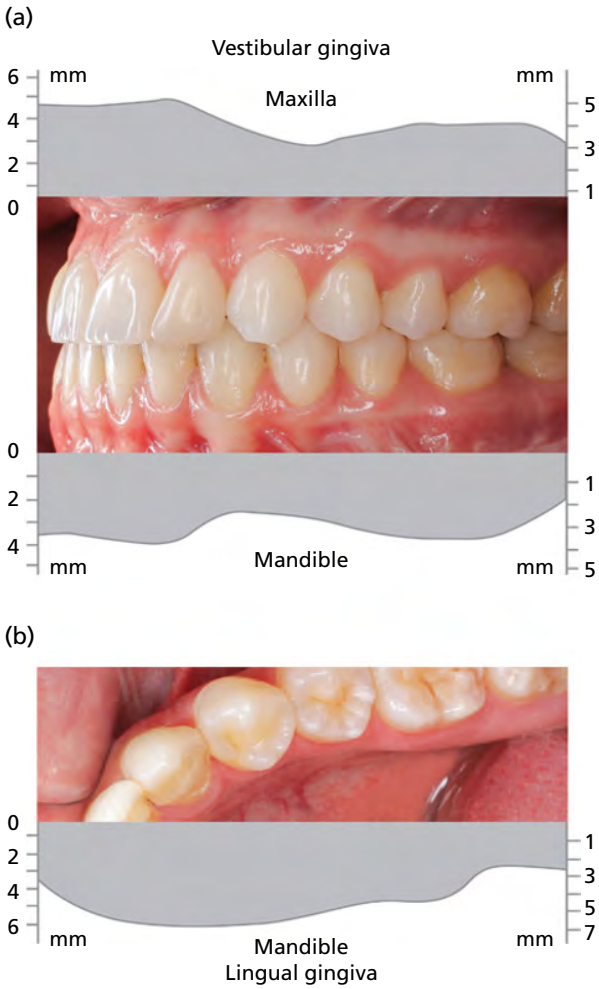

Fig. 1-12 Widths of the vestibular maxillary and mandibular gingivae (a) as well as the lingual extent of the gingiva in the mandible (b). The widths are depicted in millimeters.

age of the patients examined is depicted in Fig. 1-14 (Ainamo *et al*. 1981). The gingiva in the 63-year-olds was significantly wider than in the 40–50-year-olds. Moreover, the width of the gingiva in the 40–50-year-olds was significantly wider than that in 20–30-year-olds. This observation indicates that the width of the gingiva tends to increase with age. As the mucogingival junction remains stable throughout life in relation to the lower border of the mandible, the increasing width of the gingiva may suggest that the teeth erupt slowly throughout life as a result of occlusal wear.

Histology

Oral gingival epithelium

The dentogingival unit is schematically depicted in Fig. 1-15a. The free gingiva comprises all epithelial and connective tissue structures located coronal to a horizontal line placed at the level of the CEJ (Fig. 1-15b). The epithelium covering the free gingiva may be differentiated as follows:

- *Oral gingival epithelium*, which faces the oral cavity
- *Oral sulcular epithelium*, which faces the tooth without being in contact with the tooth surface
- *Junctional epithelium*, which provides the contact between the gingiva and the tooth.

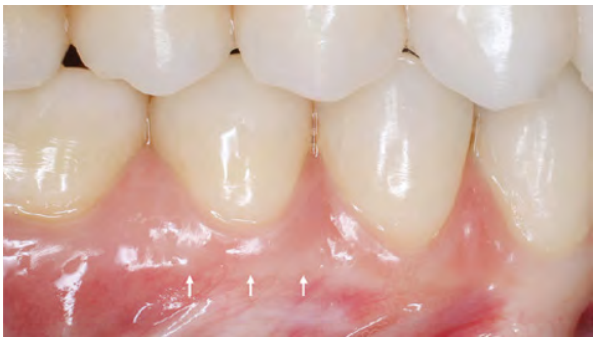

Fig. 1-13 Minimal width of the vestibular gingiva in the premolar region of the mandible. The arrows demonstrate the outline of the mucogingival junction.

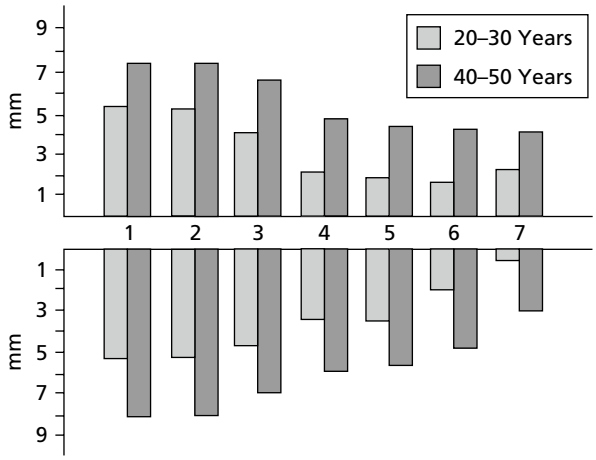

Fig. 1-14 Width of attached gingiva in two age cohorts of 20–30 years and 40–50 years. An increasing width of attached gingiva is recognizable throughout life. (Source: Ainamo & Talari 1976; Ainamo *et al*. 1981. Reproduced with permission from John Wiley & Sons.)

The boundary between the oral gingival epithelium and underlying connective tissue has a wavy course (Fig. 1-15c). The connective tissue portions, which project into the epithelium, are called *connective tissue papillae* and are separated from each other by *epithelial ridges* – so-called *rete pegs*. In non-inflamed gingiva, rete pegs and connective tissue papillae are lacking at the boundary between the junctional epithelium and its underlying connective tissue (Fig. 1-15b). Thus, a characteristic morphologic feature of the oral gingival epithelium and the oral sulcular epithelium is the presence of rete pegs: these structures are lacking in the junctional epithelium.

A wax model, constructed on the basis of magnified serial histologic sections at a magnification of 1:50, shows the subsurface of the oral epithelium of the gingiva after removing the connective tissue (Fig. 1-16). The subsurface of the oral epithelium (i.e. the surface of the epithelium facing the connective tissue) exhibits several depressions corresponding to the connective tissue papillae (see Fig. 1-17), which project into the epithelium. It can be seen that the epithelial projections, which in histologic sections separate the connective tissue papillae, constitute a continuous system of epithelial ridges.

A model of the connective tissue, corresponding to the model of the epithelium shown in Fig. 1-16 yields the connective tissue papillae which project into the space that was occupied by the oral gingival epithelium and by the oral sulcular epithelium at the back of the model (Fig. 1-17). The epithelium has been removed, thereby making the vestibular aspect of the gingival connective tissue visible.

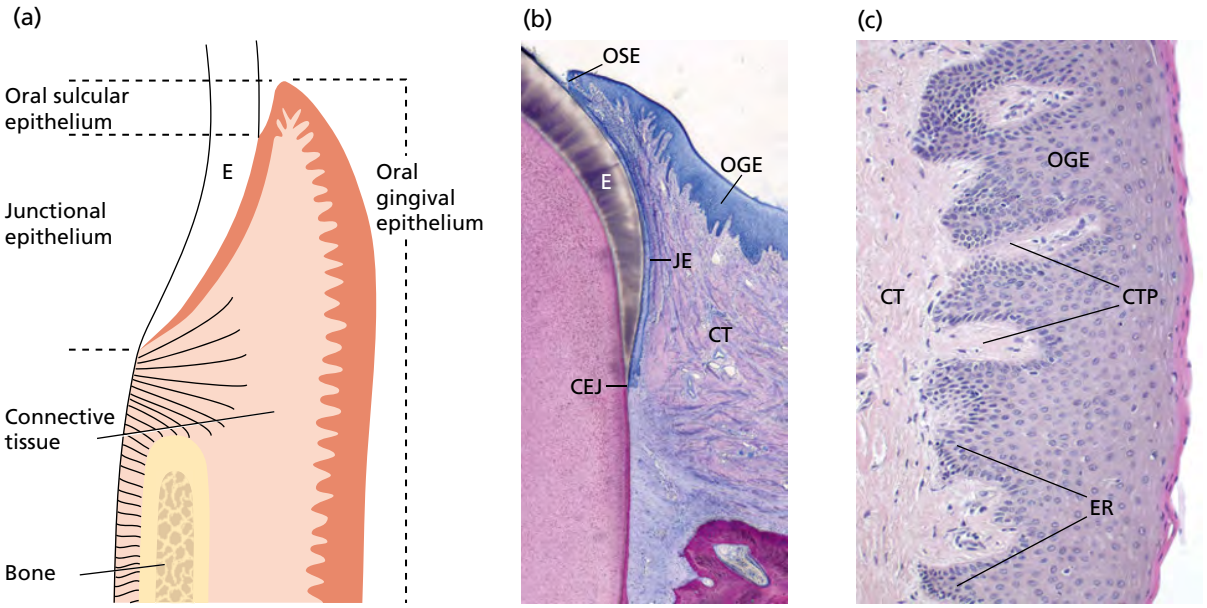

Fig. 1-15 (a) The dentogingival unit. The gingiva consists of three epithelia namely, oral gingival epithelium, oral sulcular epithelium, and junctional epithelium. (b) Histologic section with all the epithelia and soft connective tissue structures (CT). (c) Rete peg configuration (epithelial ridges, ER) interdigitating with the connective tissue papillae (CTP) in masticatory mucosa facing the oral cavity. CEJ, cementoenamel junction; E, enamel; JE, junctional epithelium; OGE, oral gingival epithelium; OSE, oral sulcular epithelium.

Fig. 1-16 Wax model illustrating the surface of the oral gingival epithelium facing the connective tissue following removal from the latter.

Fig. 1-17 Wax model of the connective tissue subjacent to the oral gingival epithelium that had been removed. OE, oral epithelium; OSE, oral sulcular epithelium.

In most adults, the attached gingiva shows a stippling on the surface (Fig. 1-18). The stippling corresponds to depressions on the surface in the areas of fusion between various epithelial ridges. Sometimes, the stippling is conspicuous (see also Fig. 1-11). However, it is not known to which degree the stippling manifests itself in different individuals.

The oral epithelium covering the free gingiva is a *keratinized, stratified, squamous epithelium* which, on the basis of the degree to which the keratin-producing cells are differentiated, can be divided into the following cell layers (Fig. 1-19a):

1. *Basal layer* (stratum basale or stratum germinativum)
2. *Prickle cell layer* (stratum spinosum)
3. *Granular cell layer* (stratum granulosum)
4. *Keratinized cell layer* (stratum corneum).

It should be observed that in the tissue section shown in Fig. 1-19a, cell nuclei are lacking in the outer cell layers. Such an epithelium is denoted *orthokeratinized*. Often, however, the cells of the stratum corneum of the epithelium of human gingiva contain remnants of the nuclei, as seen in Fig. 1-19b. In such a case, the epithelium is denoted *parakeratinized*.

In addition to the keratin-producing cells, which comprise about 90% of the total cell population, the oral gingival epithelium contains the following types of cells:

- *Melanocytes*
- *Langerhans cells*
- *Merkel's cells*
- *Inflammatory cells*.

These cell types are often stellate and have cytoplasmic extensions of various size and appearance. They are also called "clear cells", because in histologic sections, the zone around their nuclei appears lighter than that in the surrounding keratin-producing cells (Fig. 1-20). With the exception of the Merkel's cells, these "clear cells", which do not produce keratin, lack desmosomal attachment to adjacent cells. The melanocytes are pigment-synthesizing cells and are responsible for the melanin pigmentation occasionally seen on the gingiva. However, both lightly and darkly pigmented individuals have melanocytes in the epithelium.

The Langerhans cells are believed to play a role in the defense mechanism of the oral mucosa. It has been suggested that the Langerhans cells react with antigens that are in the process of penetrating the epithelium. An early immunologic response is thereby initiated, inhibiting or preventing further antigen penetration of the tissue. The Merkel's cells have been suggested to have a sensory function.

The cells in the *basal layer* are either cylindric or cuboidal, and are in contact with the *basement membrane* that separates the epithelium from the soft connective tissue (Fig. 1-21). The basal cells possess the ability to divide, that is undergo mitotic cell division. The cells marked with arrows in Fig. 1-21 are in the process of dividing. It is in the basal layer that the epithelium is renewed. Therefore, this layer is also termed *stratum germinativum*, and can be considered the *progenitor cell compartment* of the epithelium.

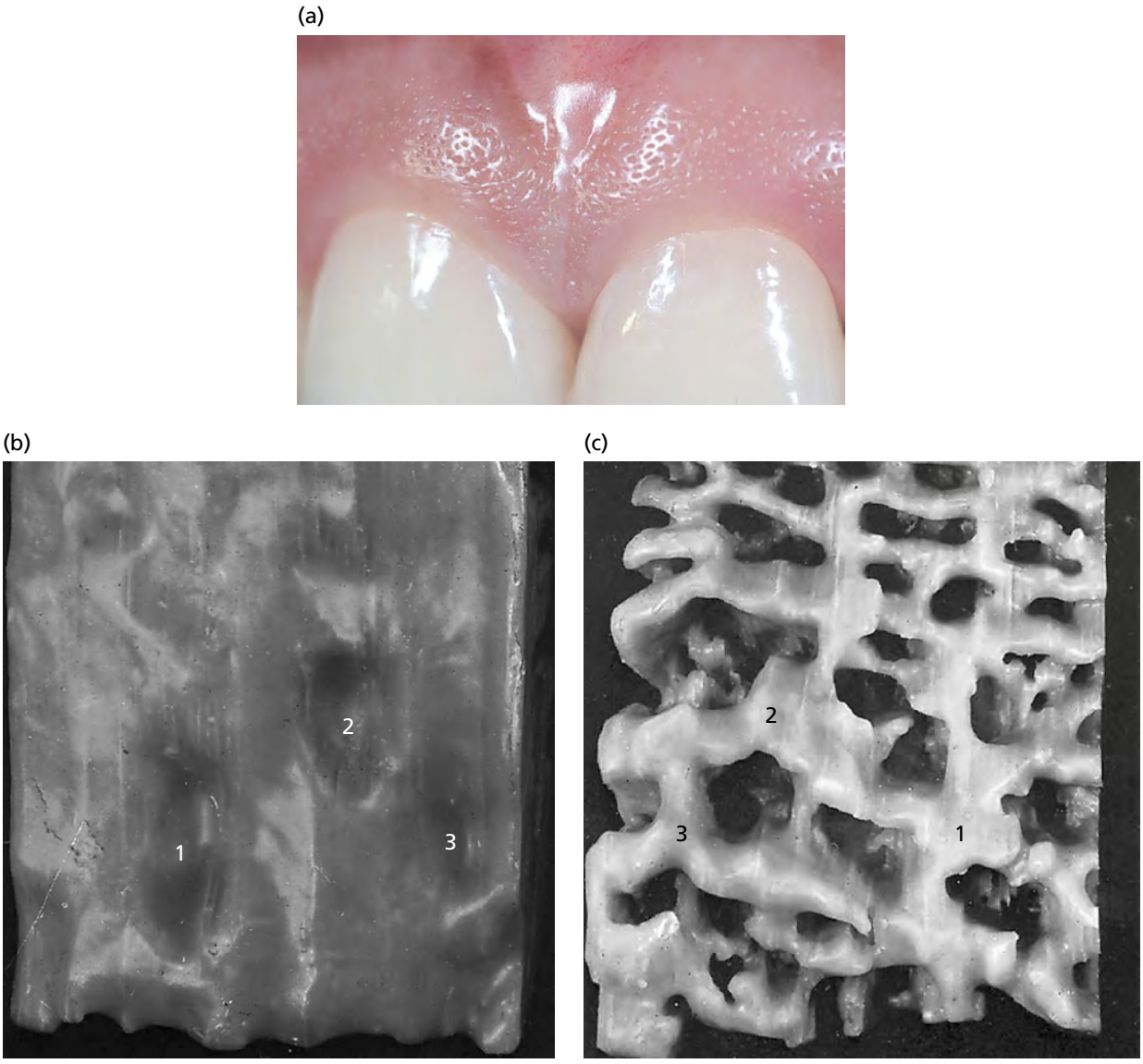

Fig. 1-18 (a) Conspicuous stippling of the masticatory mucosa of the gingiva, as seen macroscopically or clinically. (b) In a magnified model of the oral gingival epithelium of the attached gingiva, the surface exhibits the minute depressions, which give the gingiva its characteristic stippled appearance. (c) In the corresponding surface of the epithelium facing the soft connective tissue, the subsurface of the epithelium is characterized by the presence of epithelial ridges that merge at various locations. The numbers indicate the locations where the epithelial ridges merge and create the depressions seen in (b).

When two daughter cells have been formed by cell division, an adjacent "older" basal cell is pushed into the spinous cell layer and starts, as a *keratinocyte*, to traverse the epithelium (Fig. 1-22). It takes approximately 1 month for a keratinocyte to reach the outer epithelial surface, where it is shed from the stratum corneum. Within a given time, the number of cells which divide in the *basal layer* equals the number of cells which are shed from the surface. Thus, under homeostatic conditions, there is equilibrium between cell renewal and cell loss so that the epithelium maintains a constant thickness. As the basal cell migrates through the epithelium, it becomes flattened with its long axis parallel to the epithelial surface.

The basal cells are found immediately adjacent to the soft connective tissue and are separated from it by the basement membrane, probably produced by the basal cells themselves. Under the light microscope, this membrane appears as a structureless zone approximately 1–2 µm wide and reacts positively to a periodic acid-Schiff (PAS) stain (Fig. 1-23). This positive reaction demonstrates that the basement membrane contains carbohydrates (glycoproteins). The epithelial cells are surrounded by an extracellular substance which also contains protein–polysaccharide complexes.

At the ultrastructural level, the basement membrane has a complex composition (Fig. 1-24). Immediately beneath the basal cells, an approximately 400-Å wide electron-lucent zone can be seen, which is called the *lamina lucida*. Beneath the lamina lucida, an electron-dense zone of approximately the same thickness can be observed. This zone is called *lamina densa*. From the lamina densa, so-called *anchoring fibrils* project in a fan-shaped fashion into the soft connective tissue. The anchoring fibrils are approximately 1 µm

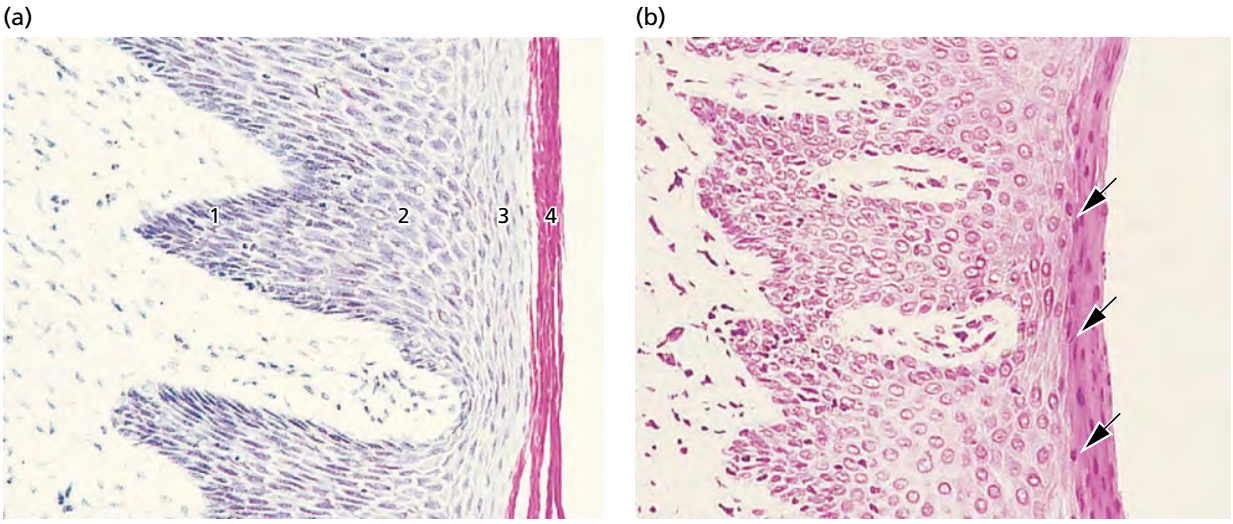

Fig. 1-19 The four layers of the oral gingival epithelium: (1) stratum basale, (2) stratum spinosum, (3) stratum granulosum, and (4) stratum corneum, as seen in the orthokeratinized (a) and parakeratinized (b) epithelium. The arrows indicate the presence of cell nuclei in the case of parakeratinization.

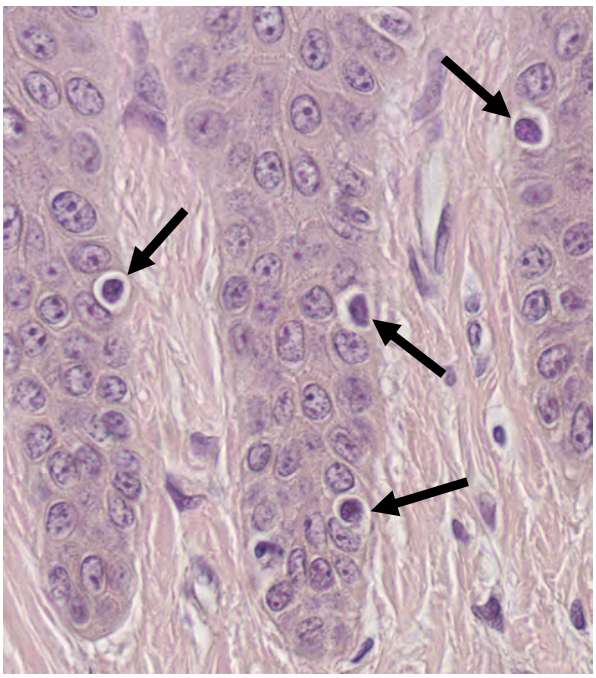

Fig. 1-20 "Clear cells" (arrows) located in or near the stratum basale of the oral gingival epithelium.

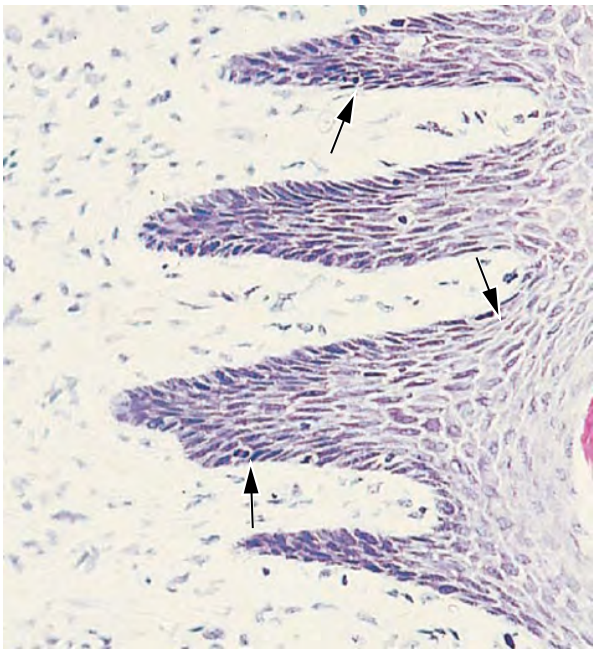

Fig. 1-21 The cells in the basal layer of the oral gingival epithelium are able to divide. The arrows indicate dividing cells.

in length and terminate freely in the soft connective tissue. The basement membrane, which under the light microscope appears as an entity, thus, in the electron micrograph, appears to comprise one lamina lucida and one lamina densa with adjacent anchoring fibrils that interdigitate with the soft connective tissue fibers. The cell membrane of the epithelial cells facing the lamina lucida harbors a number of electron-dense, thicker zones appearing at various intervals along the cell membrane. These structures are called *hemidesmosomes*. The cytoplasmic *tonofilaments* (cytokeratin filaments) in the cell converge towards the hemidesmosomes. The hemidesmosomes are involved in the attachment of the epithelium to the underlying basement membrane.

The stratum spinosum consists of 10–20 layers of relatively large, polyhedral cells, equipped with short cytoplasmic processes resembling spines (Fig. 1-25). These cytoplasmic processes occur at regular intervals and give the cells a prickly appearance. Together with intercellular protein–carbohydrate complexes, cohesion between the cells is provided by numerous "desmosomes" (pairs of hemidesmosomes), which are located between the cytoplasmic processes of adjacent cells. In the transmission electron microscope, the dark-stained structures between the individual epithelial cells represent the *desmosomes* (arrows) (Fig. 1-26). A desmosome may be considered to be two hemidesmosomes facing one another. The

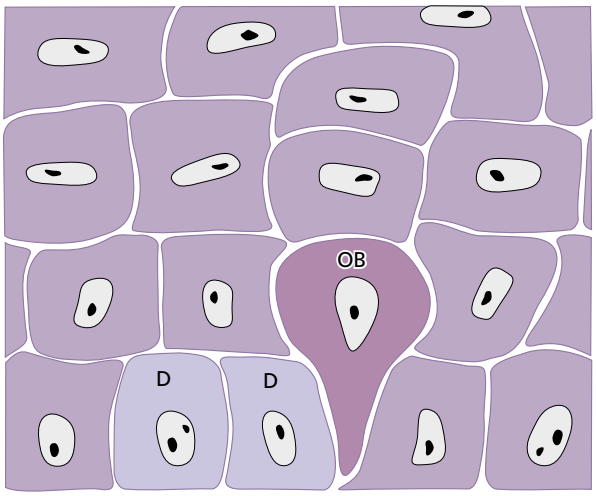

Fig. 1-22 Cell proliferation in the basal layer of the oral gingival epithelium. D, daughter cells; OB, "older" basal cell.

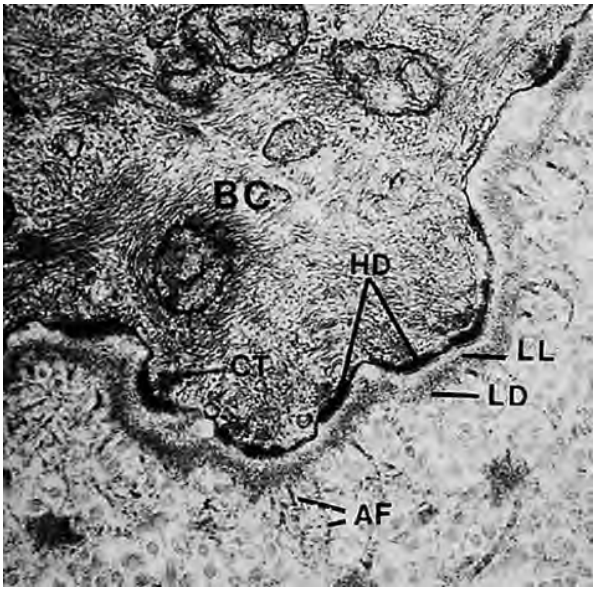

Fig. 1-24 Transmission electron micrograph (magnification ×70 000) illustrating the interfacial region of the basement membrane between a basal cell (BC) and the adjacent soft connective tissue. AF, anchoring fibrils; CT, cytoplasmic tonofilaments (cytokeratin filaments); HD, hemidesmosomes; LD, lamina densa; LL, lamina lucida.

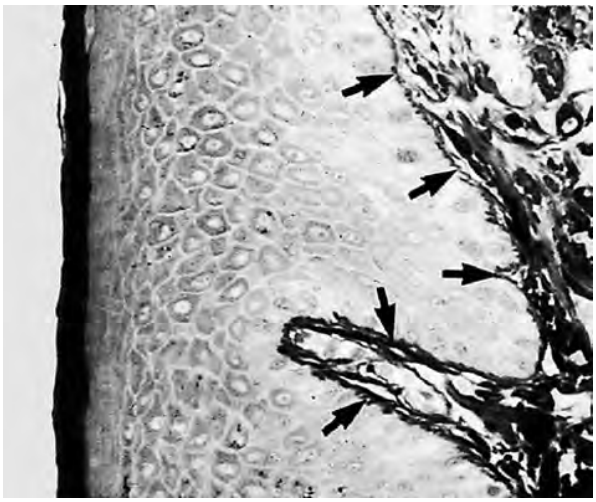

Fig. 1-23 A basement membrane (arrows), positive for periodic acid-Schiff (PAS) stain, separates the basal cells of the oral gingival epithelium from the adjacent soft connective tissue.

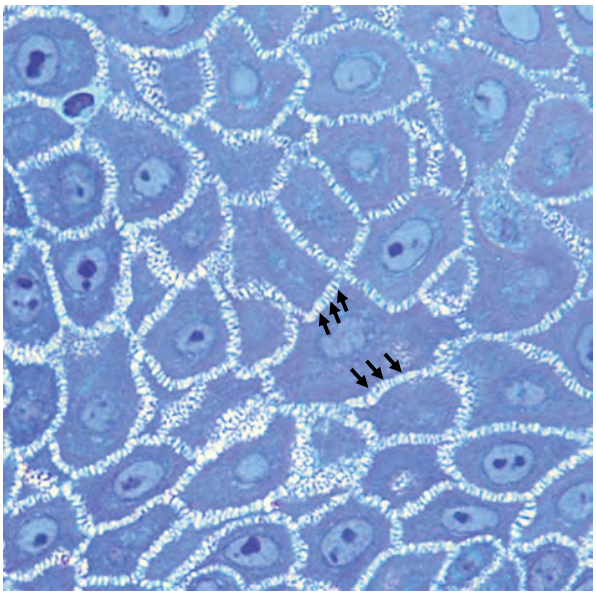

Fig. 1-25 Light micrograph depicting an area of the stratum spinosum in the oral gingival epithelium. Arrows point to short cytoplasmic processes between neighboring cells.

presence of a large number of desmosomes indicates that the cohesion between the epithelial cells is solid.

A schematic drawing of a desmosome is shown in Fig. 1-27. A desmosome can be considered to consist of two adjoining hemidesmosomes separated by a zone containing electron-dense granulated material. Thus, a desmosome comprises the following structural components: (1) the *outer leaflet* of the cell membranes of two adjoining cells; (2) the thick *inner leaflets* of the cell membranes; and (3) the *attachment plaques*, which represent granular and fibrillar material in the cytoplasm.

As mentioned previously, the oral epithelium also contains melanocytes, which are responsible for the production of the pigment melanin (Fig. 1-28). Melanocytes are present in individuals with marked pigmentation of the oral mucosa as well as in individuals in whom no clinical signs of pigmentation can be seen. In this transmission electron micrograph, a melanocyte is present in the lower portion of the stratum spinosum. In contrast to the keratinocytes, this cell contains melanin granules and has no tonofilaments or hemidesmosomes. Note the large number of tonofilaments in the cytoplasm of the adjacent keratinocytes. The inclusion of melanin granules may result in a distinct pigmentation of the oral gingival epithelium and is normally encountered in people with a dark complexion (Fig. 1-29).

As indicated previously, the keratinocytes undergo continuous differentiation and specialization when traversing the epithelium from the basal layer to the

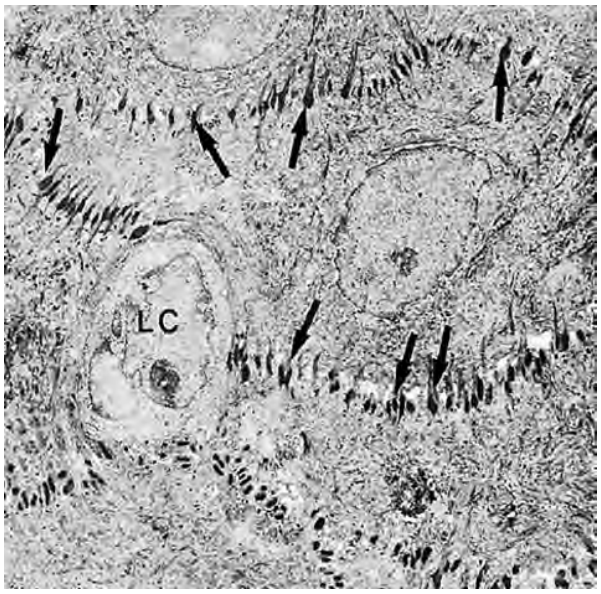

Fig. 1-26 Transmission electron micrograph of stratum spinosum highlighting (arrows) desmosomes between neighboring cells. The light cell (LC) harbors no hemidesmosomes and is, therefore, not a keratinocyte but rather a "clear cell".

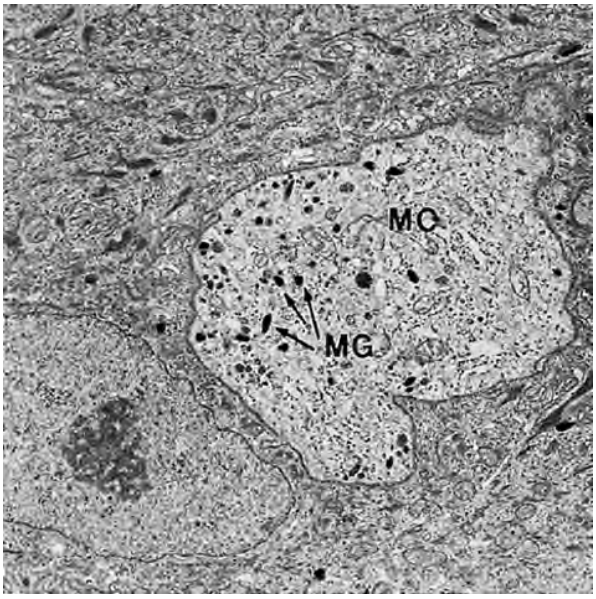

Fig. 1-28 Transmission electron micrograph illustrating a melanocyte (MC) surrounded by keratinocytes in the oral gingival epithelium. MG (arrows) points to melanin granules.

epithelial surface (Fig. 1-30). From the basal layer (stratum basale) to the granular layer (stratum granulosum) both the number of tonofilaments in the cytoplasm and the number of desmosomes increase. In contrast, the number of organelles, such as mitochondria, lamellae of rough endoplasmic reticulum, and Golgi complexes decrease in the keratinocytes on their way from the basal layer towards the surface. In the stratum granulosum, electron-dense *keratohyalin bodies* and clusters of glycogen-containing granules start to appear. Such granules are believed to be related to the synthesis of keratin.

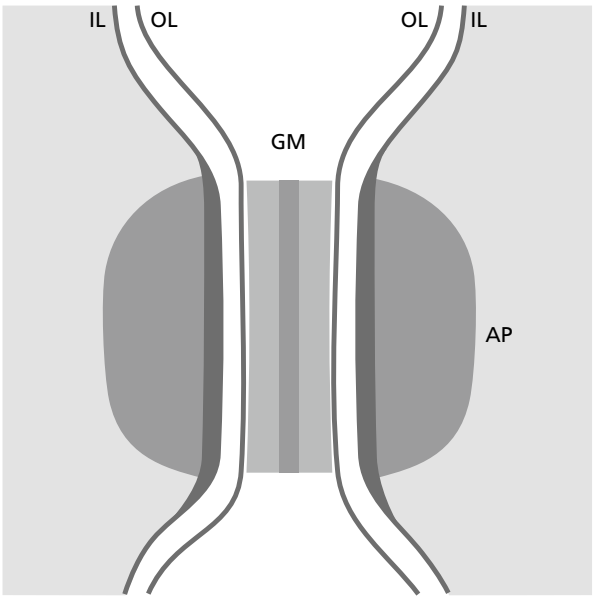

Fig. 1-27 The composition of a desmosome. AP, attachment plaque; GM, granulated material; IL, inner leaflets; OL, outer leaflets.

There is an abrupt transition of the cells from the stratum granulosum to the stratum corneum (Fig. 1-31). This is indicative of a very sudden keratinization of the cytoplasm of the keratinocyte and its conversion into a horny squame. The cytoplasm of the cells in the stratum corneum is filled with keratin and the entire apparatus for protein synthesis and energy production, that is the nucleus, the mitochondria, the endoplasmic reticulum, and the Golgi complex, is lost. In a parakeratinized epithelium, however, the cells of the stratum corneum contain remnants of nuclei. Keratinization is considered a process of differentiation rather than degeneration. It is a process of protein synthesis which requires energy and is dependent on functional cells (i.e. cells containing a nucleus and a normal set of organelles).

In contrast to the oral gingival epithelium, the epithelium of the alveolar (lining) mucosa has no stratum corneum. Cells containing nuclei can be identified in all layers, from the basal layer to the surface of the epithelium (Fig. 1-32).

Dentogingival epithelium

The tissue components of the dentogingival region achieve their final structural characteristics in conjunction with the eruption of the teeth. This is illustrated in Fig. 1-33a–d.

When the enamel of the tooth is fully developed, the enamel-producing cells (ameloblasts) become reduced in height, produce a basal lamina, and form, together with cells from the outer enamel epithelium, the so-called reduced enamel epithelium. The basal lamina lies in direct contact with the enamel. The contact between this lamina and the epithelial cells is maintained by hemidesmosomes. The reduced enamel epithelium surrounds the crown of the tooth

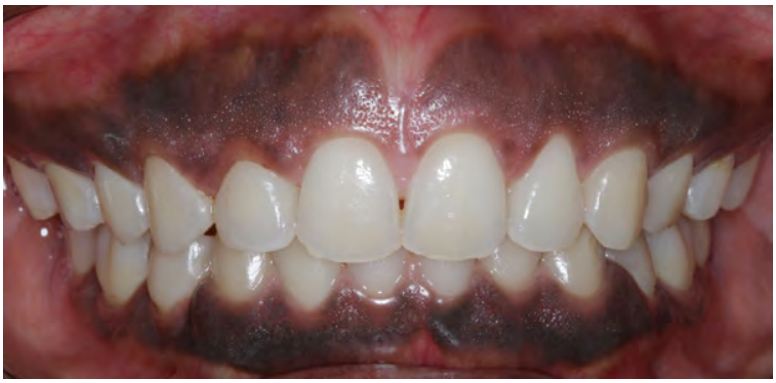

Fig. 1-29 The frontal view of the gingiva and alveolar mucosa. Distinct pigmentation of the oral gingival epithelium can be seen because of inclusion of melanin granules.

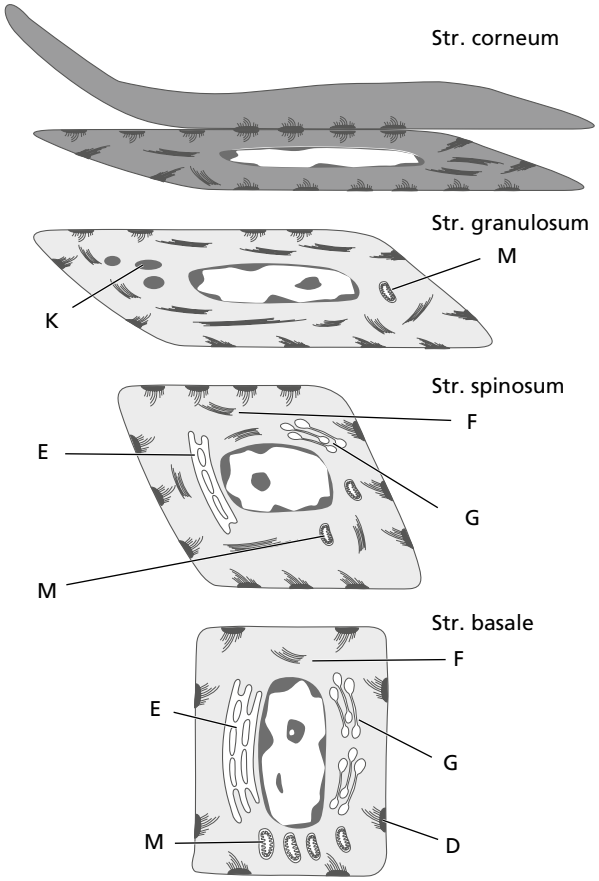

Fig. 1-30 A keratinized stratified squamous epithelium. From the basal layer to the epithelial surface, the keratinocytes undergo continuous differentiation and specialization. The many changes the cells undergo are indicated in this diagram. D, desmosomes; E, rough endoplasmic reticulum; F, tonofilaments; G, Golgi complexes; K, keratohyalin bodies; M, mitochondria.

from the moment the enamel is properly mineralized until the tooth starts to erupt (Fig. 1-33a).

As the erupting tooth approaches the oral epithelium, the cells of the outer layer of the reduced enamel epithelium, as well as the cells of the basal layer of the oral epithelium, show increased mitotic activity and start to migrate into the underlying connective tissue. The migrating epithelium produces an epithelial mass between the oral epithelium and

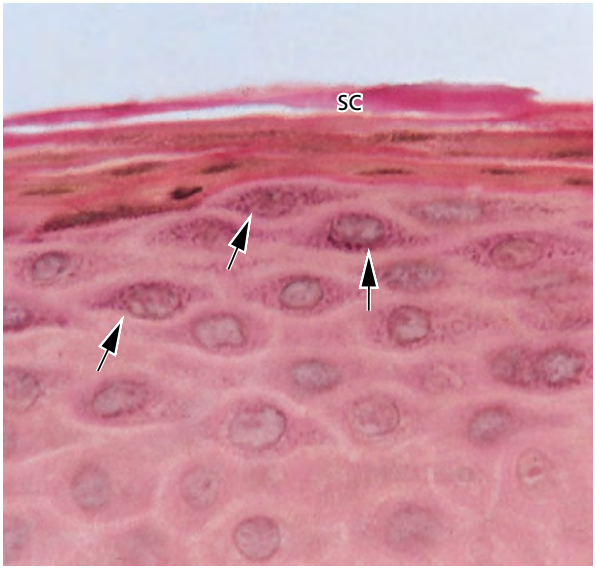

Fig. 1-31 Photomicrograph of the stratum granulosum and stratum corneum (SC). Keratohyalin granules (arrows) are seen in the stratum granulosum.

the reduced enamel epithelium so that the tooth can erupt without bleeding. The former ameloblasts do not divide (Fig. 1-33b).

When the tooth has penetrated into the oral cavity, large portions immediately apical to the incisal area of the enamel are covered by a transformed reduced enamel epithelium, which is now termed *junctional epithelium* and that contains only a few layers of cells. The cervical region of the enamel, however, is still covered by reduced ameloblasts and outer cells of the reduced enamel epithelium (Fig. 1-33c).

During the later phases of tooth eruption, all cells of the reduced enamel epithelium are replaced by *junctional epithelium*. This epithelium is continuous with the oral epithelium and provides the attachment between the tooth and the gingiva (Fig. 1-33d). If the free gingiva is excised after the tooth has fully erupted, a new junctional epithelium, indistinguishable from that found following tooth eruption, will develop during healing. The fact that this new junctional epithelium has developed from the oral epithelium indicates that the cells of the oral epithelium

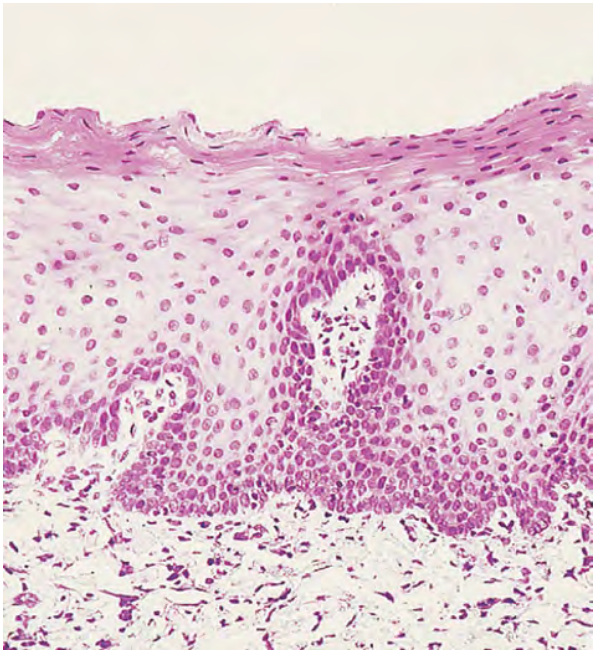

Fig. 1-32 Photomicrograph illustrating a portion of the epithelium of the alveolar (lining) mucosa and the adjacent soft connective tissue. The epithelium of the alveolar mucosa has no stratum corneum.

possess the ability to differentiate into cells of the junctional epithelium.

Figure 1-34 is a histologic section through the border area between the tooth and the gingiva, that is the *dentogingival region*. The oral sulcular epithelium covers the shallow groove, the gingival sulcus, located between the enamel and the top of the free gingiva. The junctional epithelium differs morphologically from the oral sulcular epithelium and oral epithelium, while the latter two are structurally very similar. Although individual variation may occur, the junctional epithelium is usually widest in its coronal portion (about 15–20 cells) but becomes thinner (3–4 cells) towards the CEJ. The borderline between the junctional epithelium and the underlying connective tissue does not have epithelial rete pegs, except when inflamed.

The junctional epithelium has a free surface at the bottom of the *gingival sulcus* (Fig. 1-35). Like the oral sulcular epithelium and the oral gingival epithelium, the junctional epithelium is continuously renewed through cell division in the basal layer. The cells migrate to the base of the gingival sulcus from where they are shed. The cells of the oral sulcular

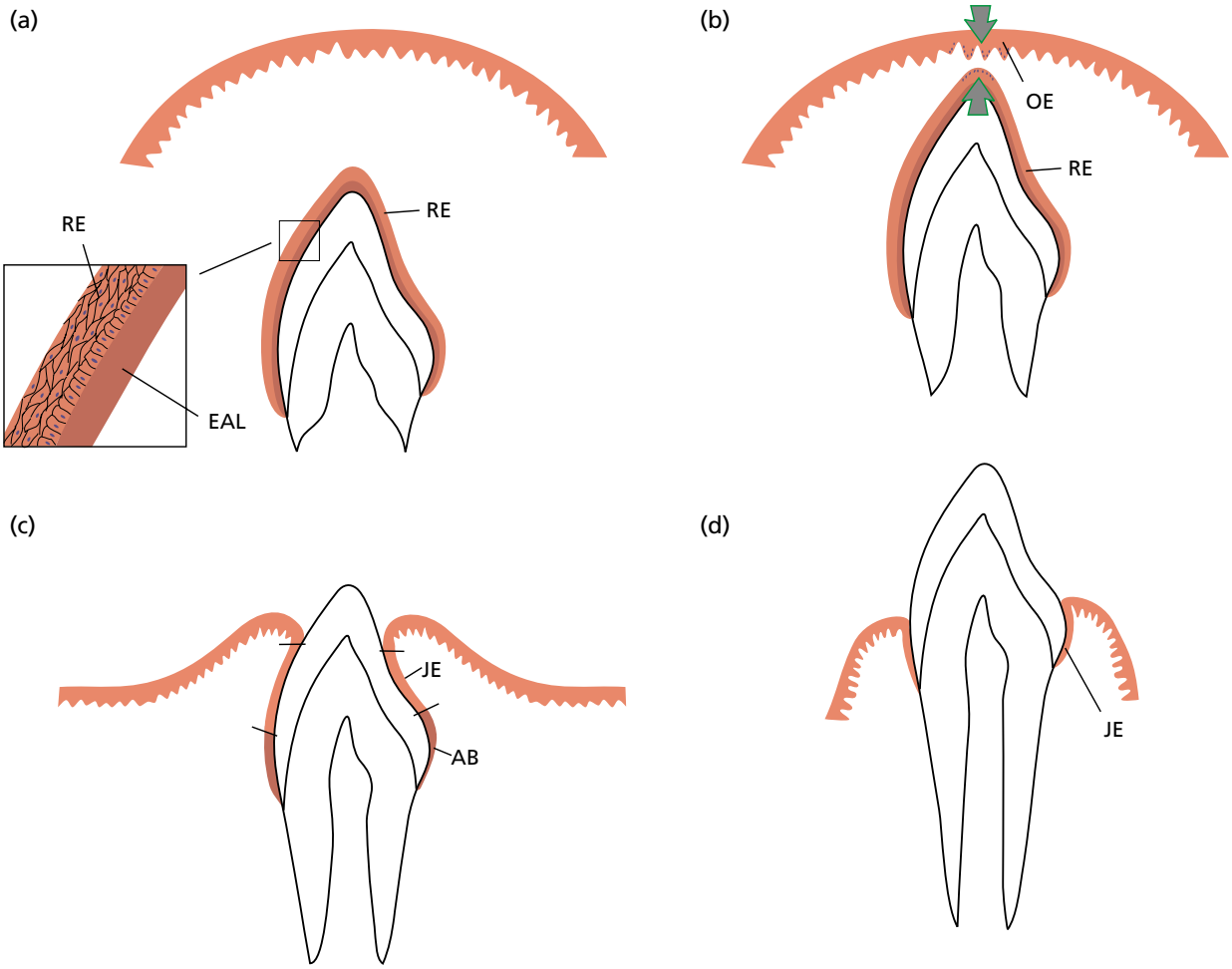

Fig. 1-33 The development of the dentogingival junction during tooth eruption. (a) Before tooth eruption when the enamel is fully developed. (b) Shortly before tooth eruption and before the cells of the reduced enamel epithelium contact the epithelial cells of the oral mucosa. The arrows point to increased mitotic activity. (c) Shortly after emergence of the tooth in the oral cavity. (d) When the tooth is in function and has reached the occlusal plane. AB, ameloblasts; EAL, epithelial attachment lamina; JE, junctional epithelium; OE, oral epithelium; RE, reduced dental epithelium.

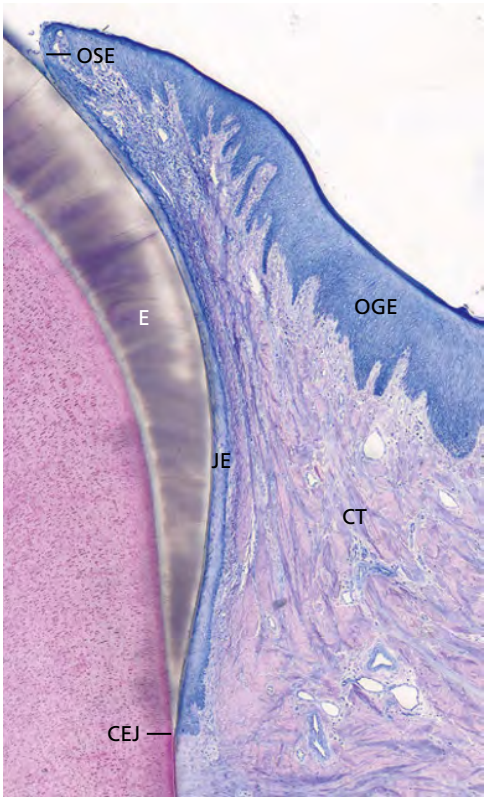

Fig. 1-34 Histologic section through the border area between the tooth and the gingiva (i.e. the dentogingival region). The enamel (E) is to the left. To the right are the junctional epithelium (JE), the oral sulcular epithelium (OSE), and the oral gingival epithelium (OGE). CEJ, cementoenamel junction, CT, soft connective tissue.

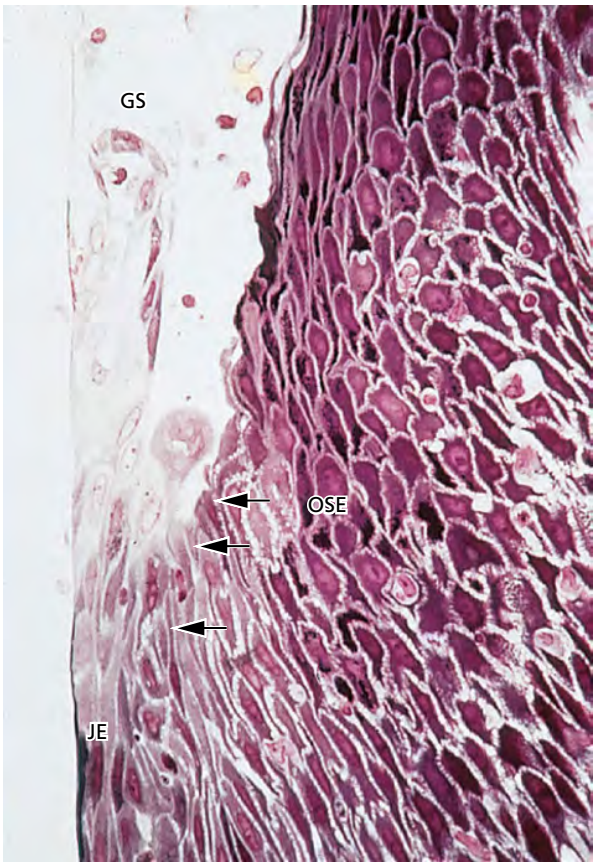

Fig. 1-35 Histologic section showing the junctional epithelium (JE) at the bottom of the gingival sulcus (GS). The arrows indicate the interface between the junctional epithelium and the oral sulcular epithelium (OSE).

epithelium are cuboidal and the surface of this epithelium is non-keratinized.

The cells of the junctional epithelium are arranged into one basal layer and several suprabasal layers (Fig. 1-36a). The basal cells as well as the suprabasal cells are flattened with their long axis parallel to the tooth surface (Fig. 1-36b).

There are distinct differences between the oral sulcular epithelium, the oral gingival epithelium, and the junctional epithelium:

- The size of the cells in the junctional epithelium is, relative to the tissue volume, larger than in the oral gingival epithelium.
- The intercellular space in the junctional epithelium is, relative to the tissue volume, comparatively wider than in the oral gingival epithelium.
- The number of desmosomes is smaller in the junctional epithelium than in the oral gingival epithelium.

Between the enamel and the junctional epithelium, one electron-dense zone and one electron-lucent zone can be seen (Fig. 1-36c). The electron-lucent zone is in contact with the cells of the junctional epithelium. These two zones have a structure very similar to that of the lamina densa and lamina lucida in the basement membrane area (i.e. the epithelium–connective tissue interface) described in Fig. 1-24. Furthermore, as seen in Fig. 1-36d, the cell membrane of the junctional epithelial cells harbors hemidesmosomes towards the enamel and towards the soft connective tissue. Thus, the interface between the enamel and the junctional epithelium is somehow similar to the interface between the epithelium and the connective tissue.

In a schematic drawing (Fig. 1-37), it can be seen that the electron-dense zone between the junctional epithelium and the enamel can be considered a continuation of the lamina densa in the basement membrane of the connective tissue side. Similarly, the electron-lucent zone can be considered a continuation of the lamina lucida. It should be noted, however, that at variance with the epithelium–connective tissue interface, there are no anchoring fibrils attached to the lamina densa-like structure adjacent to the enamel. On the other hand, like the basal cells adjacent to the basement membrane (at the connective tissue interface), the cells of the junctional epithelium facing the lamina lucida-like structure harbor hemidesmosomes. Thus, the interface between the junctional epithelium and the enamel is structurally very similar to the epithelium–connective tissue interface, which means that the junctional epithelium is not only in contact with the enamel but is actually physically attached to the tooth via hemidesmosomes.

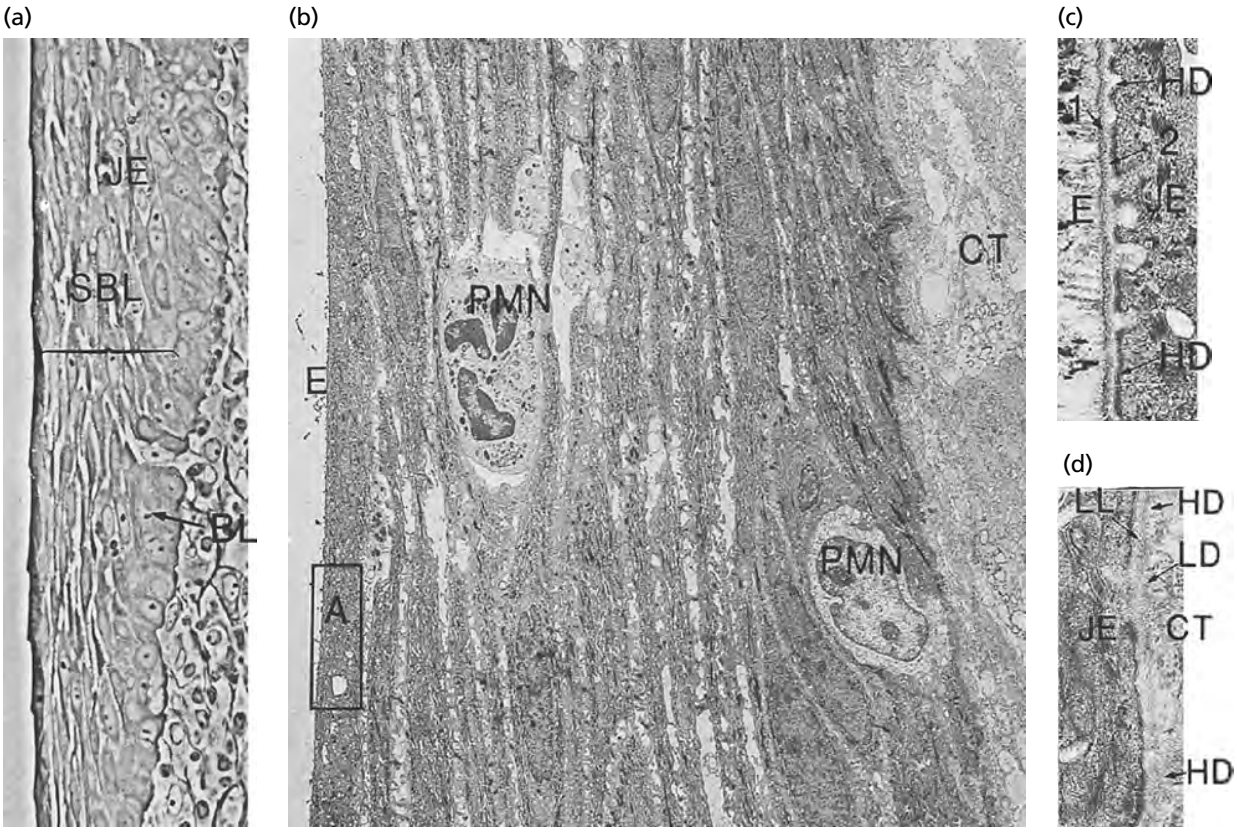

Fig. 1-36 Light (a) and transmission electron (b-d) micrographs illustrating different characteristics of the junctional epithelium (JE). Note the comparatively wide intercellular spaces between the oblong cells of the junctional epithelium, and the presence of two neutrophilic granulocytes (PMN) which are traversing the epithelium (b). The framed area (A) in (b) is shown in a higher magnification in (c), from which it can be seen that the basal cells of the junctional epithelium are not in direct contact with the enamel (E). Between the enamel and the junctional epithelium, one electron-dense zone (1) and one electron-lucent zone (2) can be seen. Likewise, an electron-dense (LD, lamina densa) and an electron-lucent (LL, lamina lucida) zone is present in the basement membrane constituting the epithelium-connective tissue interface (d). Hemidesmosomes (HD) are part of both the basal lamina and the basement membrane. BL, basal layer; CT, soft connective tissue; E, enamel space; PMN, polymorphonuclear leukocytes; SBL, suprabasal layer.

Lamina propria

The predominant tissue component of the gingiva is the connective tissue (lamina propria). The major components of the connective tissue are *collagen fibers* (around 60% of connective tissue volume), *fibroblasts* (around 5%), and *vessels and nerves* (around 35%), which are embedded in an amorphous extracellular matrix containing non-collagenous proteins (Fig. 1-38).

Cells

The different types of cells present in the connective tissue are: (1) *fibroblasts*, (2) *mast cells*, (3) *macrophages*, and (4) *inflammatory cells*.

The *fibroblast* is the predominant connective tissue cell (65% of the total cell population). The fibroblast is engaged in the production of various types of fibers found in the connective tissue but is also instrumental in the synthesis of the connective tissue matrix. The fibroblast is a spindle-shaped or stellate cell with an oval-shaped nucleus containing one or more nucleoli (Fig. 1-39). The cytoplasm contains a well-developed rough endoplasmic reticulum with ribosomes. The Golgi complex is usually of considerable size and the mitochondria are large and numerous. Furthermore, the cytoplasm contains many fine filaments, which resemble tonofilaments.

The *mast cell* is responsible for the production of components of the matrix (Fig. 1-40). This cell also produces vasoactive substances, which can affect the function of the microvascular system and control the flow of blood through the tissue. The cytoplasm is characterized by the presence of a large number of vesicles of varying size. These vesicles contain biologically active substances such as proteolytic enzymes, histamine, and heparin. The Golgi complex is well-developed, while rough endoplasmic reticulum structures are scarce. A large number of small cytoplasmic projections (i.e. microvilli) are present along the periphery of the cell.

The *macrophage* has a number of different phagocytic and synthetic functions in the tissue (Fig. 1-41). They are derived from circulating blood monocytes, which migrate into the tissue, play an important role in our immune system, and respond to necrotic tissue and foreign bodies in the form of microorganisms or biomaterials. The nucleus is characterized by numerous invaginations of varying size. A zone

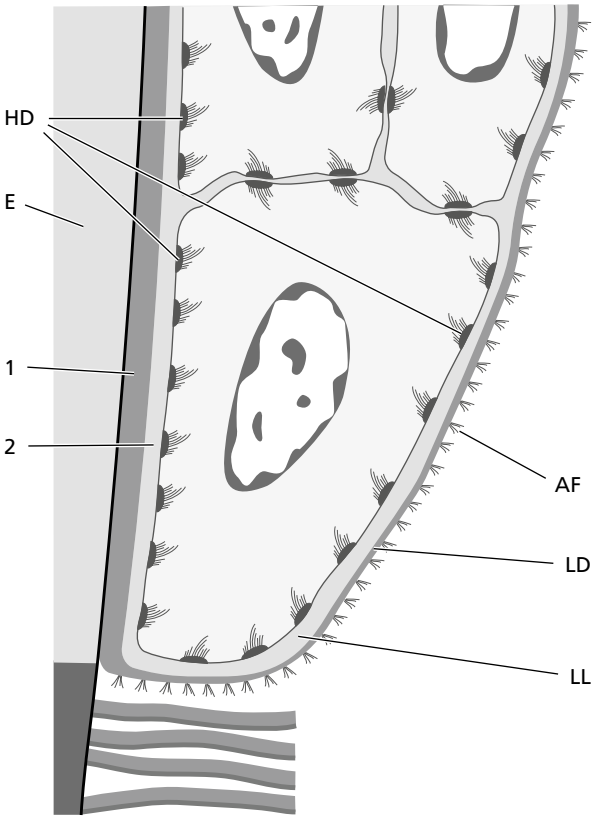

Fig. 1-37 The most apically positioned cell in the junctional epithelium. The enamel (E) is depicted to the left. The electron-dense zone (1) represents the lamina densa (LD), whereas the electron-lucent zone (2) represents the lamina lucida (LL) of the basal lamina at the epithelium–enamel interface. Anchoring fibrils (AF) are present only in the basement membrane where the epithelial cells face the soft connective tissue. Hemidesmosomes (HD), however, are part of both the basal lamina and the basement membrane.

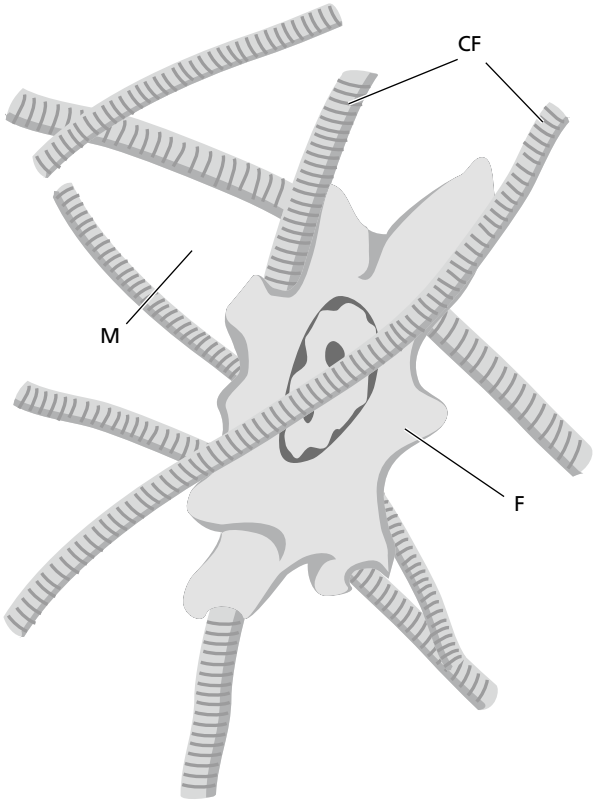

Fig. 1-38 A fibroblast (F) residing in a network of connective tissue fibrils (CF). The intervening space is filled with non-collagenous extracellular matrix (M), which constitutes the "environment" for the cell.

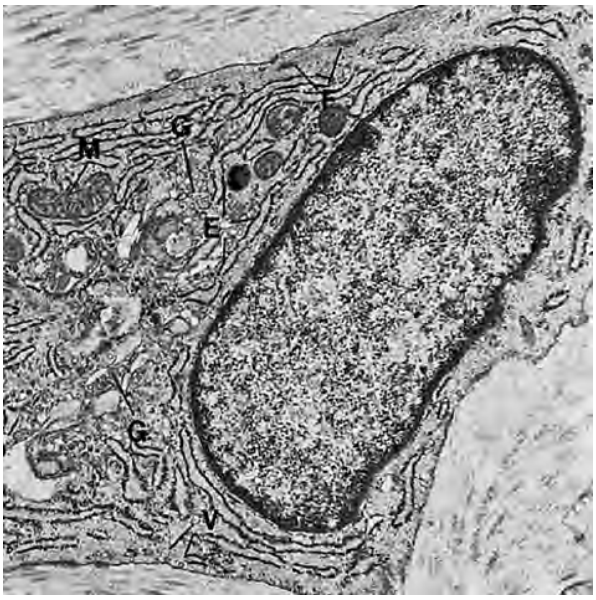

Fig. 1-39 Transmission electron micrograph illustrating a part of a fibroblast. A well-developed rough endoplasmic reticulum (E), a Golgi complex (G), and numerous large mitochondria (M) and vesicles (V) constitute the cytoplasm. At the cell periphery, many fine filaments (F) resembling tonofilaments can be seen.

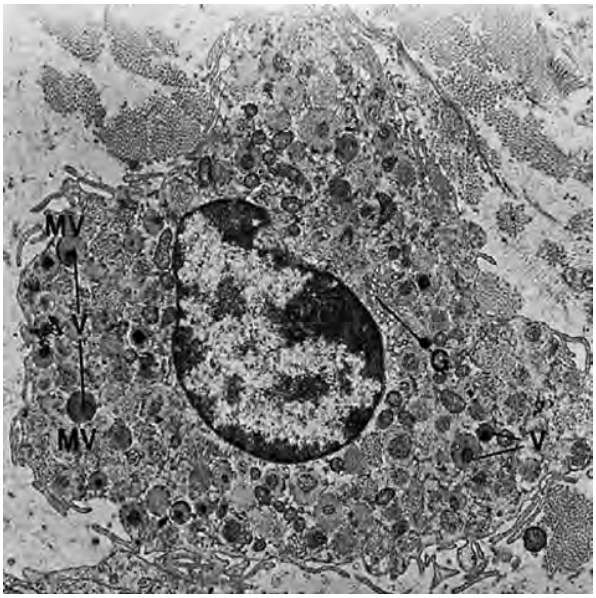

Fig. 1-40 Transmission electron micrograph showing a mast cell. The cytoplasm contains a well-developed Golgi complex (G) and a large number of vesicles (V). Many microvilli (MV), small cytoplasmic projections, can be seen extending from the cell periphery.

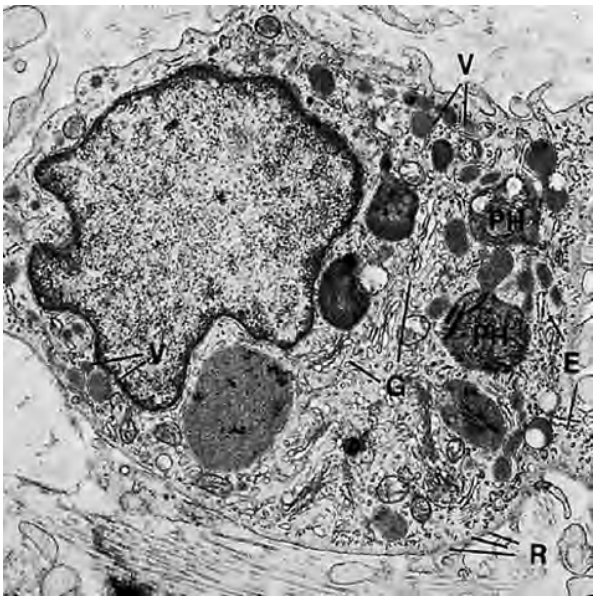

Fig. 1-41 Transmission electron micrograph demonstrating a macrophage. E, rough endoplasmic reticulum; G, Golgi complex; PH, phagosomes; R, ribosomes; V, vesicles.

of electron-dense chromatin condensations can be seen along the periphery of the nucleus. The Golgi complex is well developed and numerous vesicles of varying size are present in the cytoplasm. Rough endoplasmic reticulum is scarce, but a certain number of free ribosomes are evenly distributed in the cytoplasm. Remnants of phagocytosed material, called phagosomes, are often found in lysosomal vesicles. In the periphery of the cell, a large number of microvilli of varying size can be seen. Macrophages are particularly numerous in inflamed tissue.

Besides fibroblasts, mast cells, and macrophages, the connective tissue also harbors *inflammatory cells* of various types, for example neutrophilic granulocytes, lymphocytes, and plasma cells (Fig. 1-42).

The *neutrophilic granulocytes*, also called *polymorphonuclear leukocytes*, have a characteristic appearance (Fig. 1-42a). The nucleus is lobulated and numerous lysosomes, containing lysosomal enzymes, are found in the cytoplasm.

The *lymphocytes* (Fig. 1-42b) are characterized by an oval to spherical nucleus containing localized areas of electron-dense chromatin. The narrow border of cytoplasm surrounding the nucleus contains numerous free ribosomes, a few mitochondria, and, in localized areas, rough endoplasmic reticulum. Lysosomes are also present in the cytoplasm.

The *plasma cells* (Fig. 1-42c) contain an eccentrically located spherical nucleus with radially deployed electron-dense chromatin. Rough endoplasmic reticulum is abundantly found randomly distributed in the cytoplasm. In addition, the cytoplasm contains numerous mitochondria and a well-developed Golgi complex.

Fibers

The connective tissue fibers are produced by the fibroblasts and can be divided into: (1) *collagen fibers*, (2) *reticulin fibers*, (3) *oxytalan fibers*, and (4) *elastic fibers*.

The *collagen fibers* predominate in the gingival connective tissue and constitute the most essential components of the periodontium. The collagen fibrils have a characteristic cross-banding with a periodicity of 700 Å between the individual dark bands (Fig. 1-43).

Figure 1-44 illustrates some important features of the synthesis and the composition of collagen fibers produced by fibroblasts. The smallest unit, the collagen molecule, is often referred to as *tropocollagen*. A

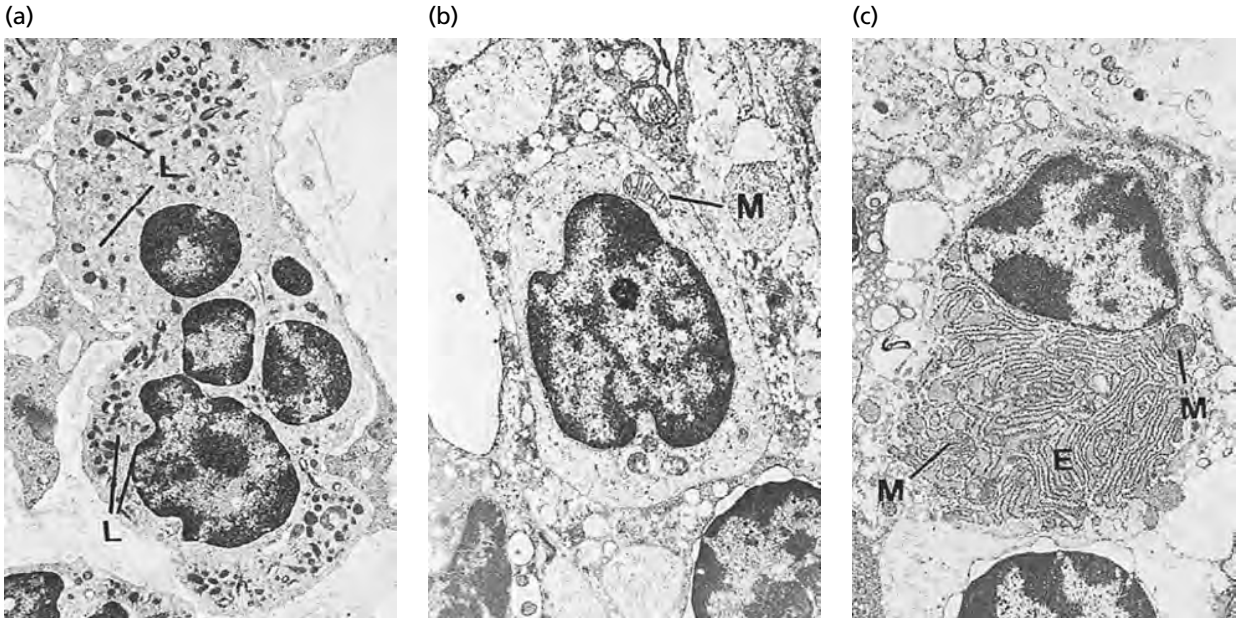

Fig. 1-42 Transmission electron micrographs showing a polymorphonuclear leukocyte (a), a lymphocyte (b), and a plasma cell (c). E, rough endoplasmic reticulum; L, lysosomes; M, mitochondria.

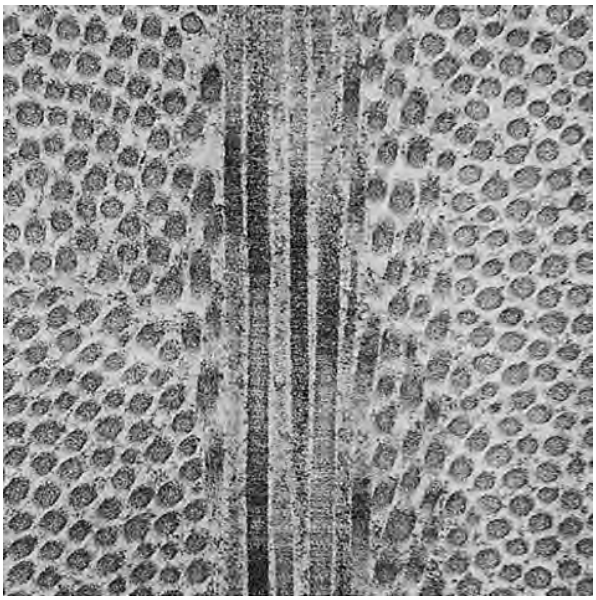

Fig. 1-43 Transmission electron micrograph demonstrating cross-sections and longitudinal sections of collagen fibrils.

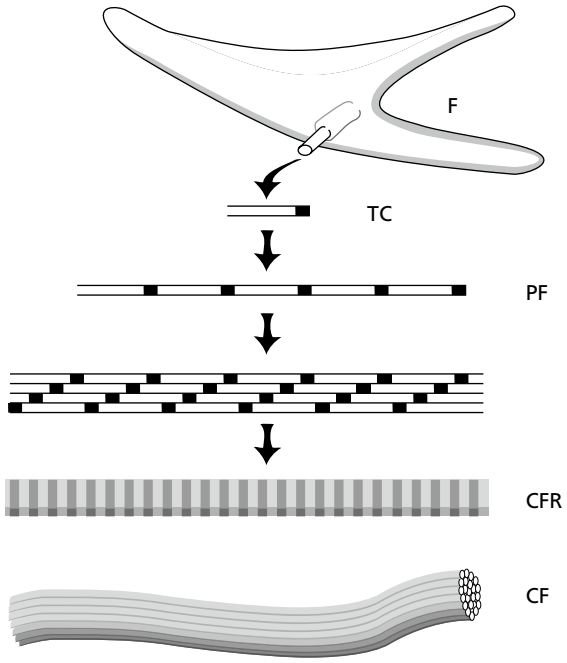

Fig. 1-44 Some important features of the synthesis and composition of collagen fibers (CF) produced by fibroblasts (F). CFR, collagen fibril; PF, protofibril; TC, tropocollagen molecule.

tropocollagen molecule, is approximately 3000 Å long and has a diameter of 15 Å. It consists of three polypeptide chains intertwined to form a helix. Each chain contains about 1000 amino acids. One-third of these are glycine and about 20% proline and hydroxyproline, the latter being found almost exclusively in collagen. Tropocollagen synthesis takes place inside the fibroblast from which the tropocollagen molecule is secreted into the extracellular space. Thus, the polymerization of tropocollagen molecules to collagen fibrils takes place in the extracellular compartment. First, tropocollagen molecules are aggregated longitudinally to form *protofibrils*, which are subsequently laterally aggregated parallel to *collagen fibrils*, with the tropocollagen molecules overlapping by about 25% of their length. Due to the fact that special refraction conditions develop after staining at the sites where the tropocollagen molecules adjoin, a cross-banding with a periodicity of approximately 640 Å is seen in the transmission electron microscope. The *collagen fibers* are bundles of collagen fibrils, aligned in such a way that the fibers also exhibit a cross-banding with a periodicity of 640 Å. In the tissue, the fibers are usually arranged in bundles. As the collagen fibers mature, covalent cross-links are formed between the tropocollagen molecules, resulting in an age-related reduction in collagen solubility.

Reticulin fibers exhibit argyrophilic staining properties and are numerous in the tissue adjacent to the basement membrane (Fig. 1-45). However, reticulin fibers also occur in large numbers in the loose connective tissue surrounding the blood vessels. Thus, reticulin fibers are present at the epithelium–connective tissue and the endothelium–connective tissue interfaces.

Oxytalan fibers are scarce in the gingiva but numerous in the periodontal ligament (Fig. 1-46). They are composed of long thin fibrils with a diameter of approximately 150 Å. These connective tissue fibers can be demonstrated under light microscopy only after previous oxidation with peracetic acid.

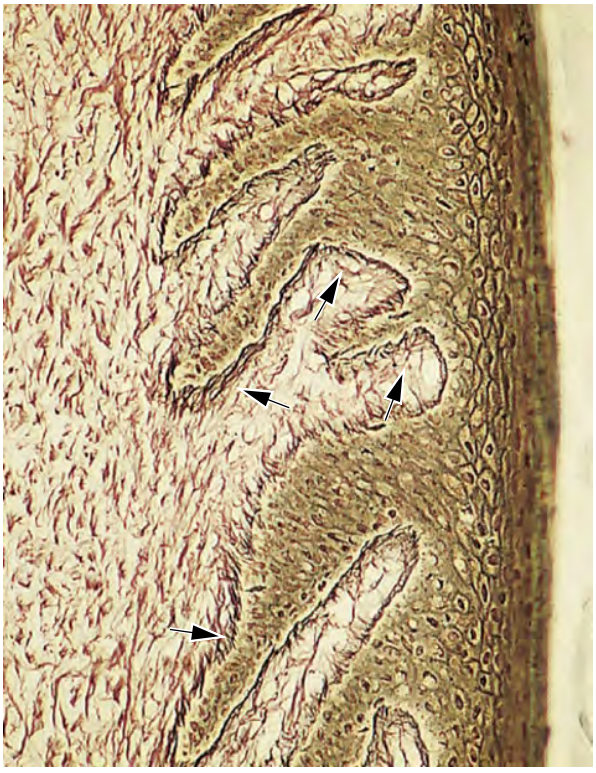

Fig. 1-45 Light micrograph showing reticulin fibers adjacent to the basement membrane between epithelium and soft connective tissue. Argyrophilic staining produces a black staining of the reticulin fibers (arrows).

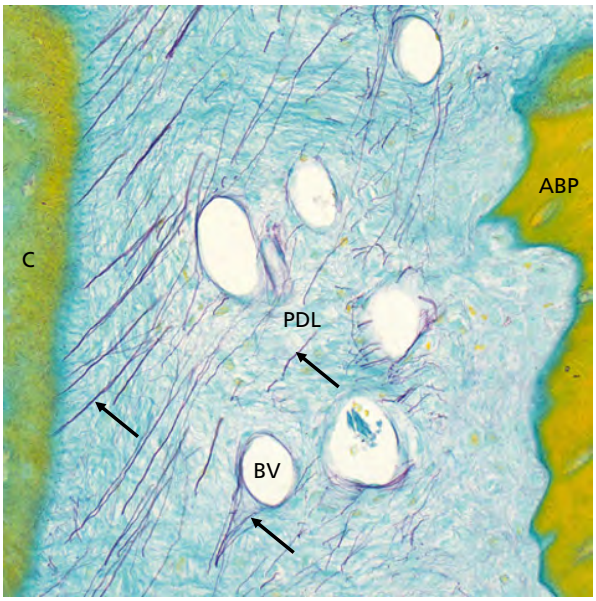

Fig. 1-46 Light micrograph demonstrating oxytalan fibers (arrows) in the periodontal ligament (PDL). Note that the oxytalan fibers insert into the cementum (C) and are associated with blood vessels (BV). ABP, alveolar bone proper.

The photomicrograph illustrates oxytalan fibers in the periodontal ligament, where they have a course mainly parallel to the long axis of the tooth and insert into cementum. Oxytalan fibers are elastic in nature and are largely associated with blood vessels. They may have a function in mechanotransduction.

Elastic fibers in the connective tissue of the gingiva and periodontal ligament are only present in association with blood vessels. However, the lamina propria and submucosa of the alveolar (lining) mucosa contain numerous elastic fibers (Fig. 1-47).

Although many of the collagen fibers in the gingiva and the periodontal ligament are irregularly or randomly distributed, most tend to be arranged in groups of bundles with a distinct orientation. According to their insertion and course in the tissue, the oriented bundles in the gingiva can be divided into the following groups (Fig. 1-48):

1. *Circular fibers* are fiber bundles which run their course in the free gingiva and encircle the tooth in a cuff-like fashion.
2. *Dentogingival fibers* are embedded in the cementum of the supra-alveolar portion of the root and project out from the AEFC in a fan-like configuration into the free gingival tissue of the facial, lingual, and interproximal surfaces.
3. *Dentoperiosteal fibers* are embedded in the same portion of the cementum as the dentogingival fibers but run their course apically over the vestibular and lingual bone crest and terminate in the tissue of the attached gingiva. In the border area between the free and attached gingiva, the epithelium often lacks support from underlying oriented collagen fiber bundles. In this area, the free gingival groove may sometimes be observed.

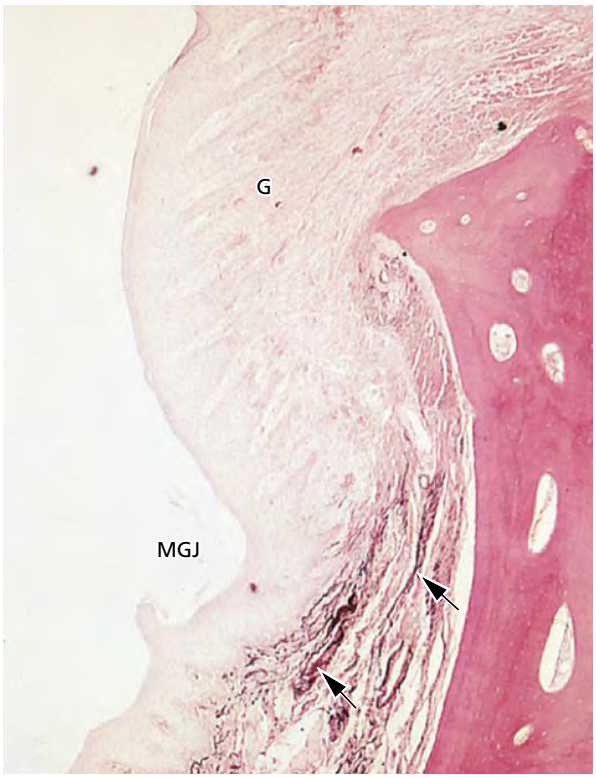

Fig. 1-47 Light micrograph illustrating elastic fibers (arrows) in the lamina propria and submucosa of the alveolar mucosa. The gingiva (G) seen coronal to the mucogingival junction (MGJ) contains no elastic fibers except in association with the blood vessels.

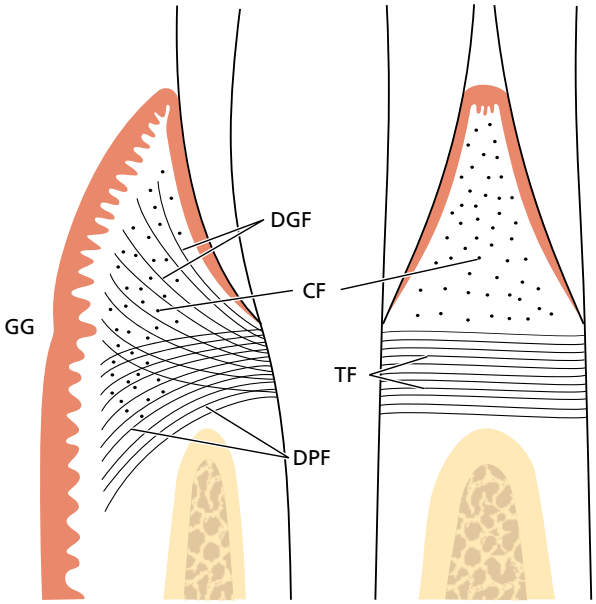

Fig. 1-48 The arrangement of collagen fiber bundles in the gingiva in a buccolingual (left) and mesiodistal (right) section. CF, circular fibers; DGF, dentogingival fibers; DPF, dentoperiosteal fibers; GG, gingival groove; TF, trans-septal fibers.

4. *Trans-septal fibers* extend between the supra-alveolar cementum of approximating teeth. The transseptal fibers run straight across the interdental septum and are embedded in the AEFC of adjacent teeth.

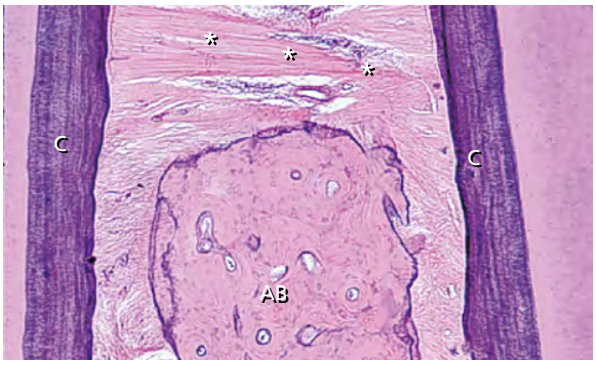

Fig. 1-49 Histologic section illustrating the orientation of the trans-septal fiber bundles (asterisks) in the supra-alveolar portion of the interdental area. The trans-septal fibers are embedded in acellular extrinsic fiber cementum (C) and also in the crest of the alveolar bone (AB).

It should be observed that, besides connecting the cementum of adjacent teeth, the trans-septal fibers also connect the supra-alveolar cementum with the crest of the alveolar bone (Fig. 1-49). The four groups of collagen fiber bundles shown in Fig. 1-48 reinforce the gingiva and provide the resilience and tone which is necessary for maintaining its architectural form and the integrity of the dentogingival attachment.

Extracellular matrix

The extracellular *matrix* of the connective tissue is produced mainly by the fibroblasts, although some constituents are produced by mast cells and others are derived from the blood. The matrix is the medium in which the connective tissue cells are embedded and it is essential for the maintenance of the normal function of the connective tissue. Thus, the transportation of water, electrolytes, nutrients, metabolites, etc., to and from the individual connective tissue cells occurs within the matrix. The main constituents of the connective tissue matrix are protein–carbohydrate macromolecules. These complexes are normally divided into *proteoglycans* and *glycoproteins*. The proteoglycans contain *glycosaminoglycans* as the carbohydrate units (hyaluronan sulfate, heparan sulfate, etc.), which are attached to one or more protein chains via covalent bonds. The carbohydrate component is always predominant in the proteoglycans. The glycosaminoglycan, called hyaluronan or "hyaluronic acid", is probably not bound to protein. The glycoproteins (fibronectin, osteonectin, etc.) also contain polysaccharides, but these macromolecules are different from glycosaminoglycans. The protein component predominates in glycoproteins. In the macromolecules, mono- or oligo-saccharides are connected to one or more protein chains via covalent bonds.

Normal function of the connective tissue depends on the presence of proteoglycans and glycosaminoglycans. The carbohydrate moieties of the proteoglycans, the glycosaminoglycans, are large, flexible, chains of negatively charged molecules, each of which occupies a rather large space. In such a space, smaller molecules, for example water and electrolytes, can be incorporated, while larger molecules are prevented from entering. The proteoglycans thereby regulate diffusion and fluid flow through the matrix and are important determinants for the fluid content of the tissue and the maintenance of the osmotic pressure. In other words, the proteoglycans act as a molecule filter and, in addition, play an important role in the regulation of cell migration (movement) in the tissue. Due to their structure and hydration, the macromolecules resist deformation, thereby serving as regulators of the consistency of the connective tissue. If the gingiva is suppressed, the macromolecules become deformed. When the pressure is eliminated, the macromolecules regain their original form. Thus, the macromolecules are important for the resilience of the gingiva.

Epithelial–mesenchymal interactions

During the embryonic development of various organs, a mutual inductive influence occurs between the epithelium and the connective tissue. The development of the teeth is a characteristic example of this phenomenon. The connective tissue is, on the one hand, a determining factor for normal development of the tooth bud, while, on the other hand, the enamel epithelia exert a definite influence on the development of the mesenchymal components of the teeth.

It has been suggested that tissue differentiation in the adult organism can be influenced by environmental factors. The skin and mucous membranes, for instance, often display increased keratinization and hyperplasia of the epithelium in areas which are exposed to mechanical stimulation. Thus, the tissues seem to adapt to environmental stimuli. The presence of keratinized epithelium on the masticatory mucosa has been considered to represent an adaptation to mechanical irritation released by mastication. However, research has demonstrated that the characteristic features of the epithelium in such areas are genetically determined. Some pertinent observations are discussed below.

In an experimental study, separate tissue flaps of the buccal gingiva and alveolar mucosa adjacent to premolar teeth were transposed by a surgical procedure (Karring *et al*. 1971). An area in a monkey where the gingiva and the alveolar mucosa have been transposed is shown in Fig. 1-50. The alveolar mucosa is placed in close contact with the teeth, while the gingiva is positioned in the area of the alveolar mucosa.

Four months later, the same area as seen in Fig. 1-50 shows that the transplanted gingiva has retained its characteristic morphologic features of a masticatory mucosa, despite the fact that the transplanted gingiva is mobile in relation to the underlying bone (Fig. 1-51). A narrow zone of new keratinized gingiva has formed between the alveolar mucosa and the teeth.

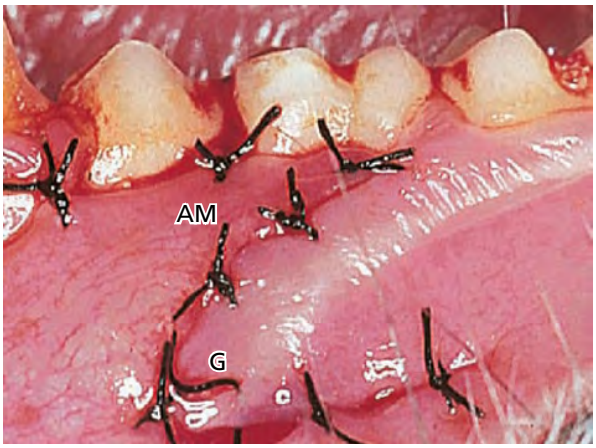

Fig. 1-50 A buccal site in a monkey where the gingiva (G) and the alveolar mucosa (AM) have been surgically transposed.

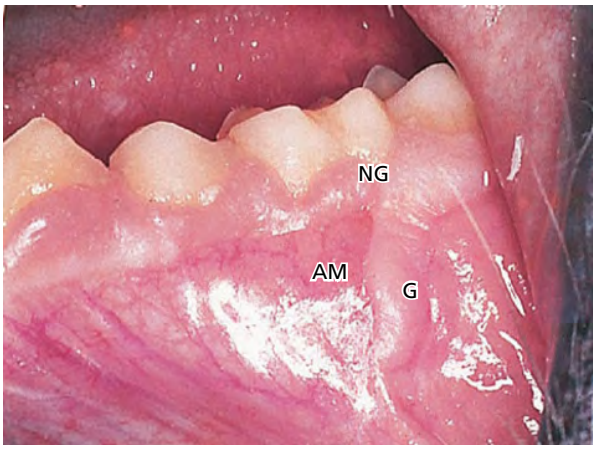

Fig. 1-51 The same area as seen in Fig. 1-50, but 4 months later. The transplanted gingiva (G) has retained its characteristic morphologic features and a narrow zone of new keratinized gingiva (NG) has formed between the alveolar mucosa (AM) and the teeth.

A histologic section through the transplanted gingiva seen in Fig. 1-51 is shown in Fig. 1-52. Since elastic fibers are lacking in the gingival connective tissue but are numerous in the connective tissue of the alveolar mucosa, the transplanted gingival tissue can readily be identified. The epithelium covering the transplanted gingival tissue exhibits a distinct keratin layer on the surface, and the configuration of the epithelium–connective tissue interface (i.e. rete pegs and connective tissue papillae) is similar to that of normal non-transplanted gingiva. Thus, the heterotopically located gingival tissue has maintained its original specificity. This observation demonstrates that the characteristics of the gingiva are genetically determined rather than being the result of functional adaptation to environmental stimuli.

After surgery, the alveolar mucosa transplant was positioned in close contact with the teeth, as seen in Fig. 1-50. After healing, a narrow zone of keratinized gingiva developed coronal to the alveolar mucosa transplant (see Fig. 1-51). This zone of new gingiva is covered by keratinized epithelium and the connective tissue contains no purple-stained elastic fibers (Fig. 1-53). In addition, it is important to note that the junction between keratinized and non-keratinized epithelium corresponds exactly to the junction between "elastic" and "non-elastic" connective tissue. The connective tissue of the new gingiva has regenerated from the connective tissue of the supraalveolar and periodontal ligament compartments and has separated the alveolar mucosal transplant from the tooth (see Fig. 1-54). It is likely that the epithelium which covers the new gingiva has migrated from the adjacent epithelium of the alveolar mucosa. This indicates that it is the connective tissue that determines the quality of the epithelium.

The development of the new gingival tissue in contact with the teeth is illustrated in a schematic drawing (Fig. 1-54). Granulation tissue has proliferated coronally along the root surface and has separated the alveolar mucosa transplant from its original contact with the tooth surface (Fig. 1-54a). Epithelial

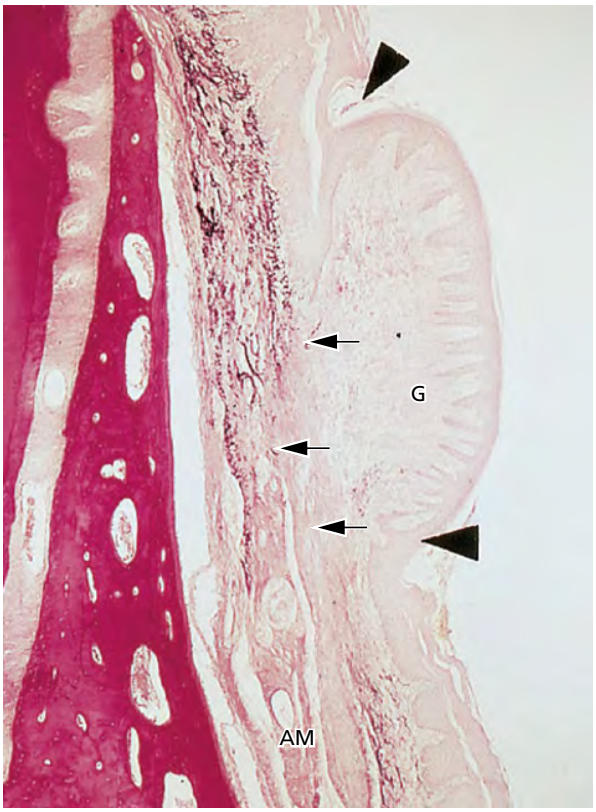

Fig. 1-52 Histologic section through the transplanted gingiva (G) seen in Fig. 1-51. The transposed gingiva exhibits a keratinized epithelium (between arrowheads) and lacks elastic fibers in the lamina propria. In contrast, elastic fibers are numerous (arrows) in the connective tissue of the alveolar mucosa (AM) adjacent to the lamina propria of the gingiva. The elastic fibers are purple-stained.

vcells have migrated from the alveolar mucosal transplant to the newly formed gingival connective tissue (Fig. 1-54b). Thus, the newly formed gingiva has become covered with a keratinized epithelium that originated from the non-keratinized epithelium of the alveolar mucosa. This implies that the newly

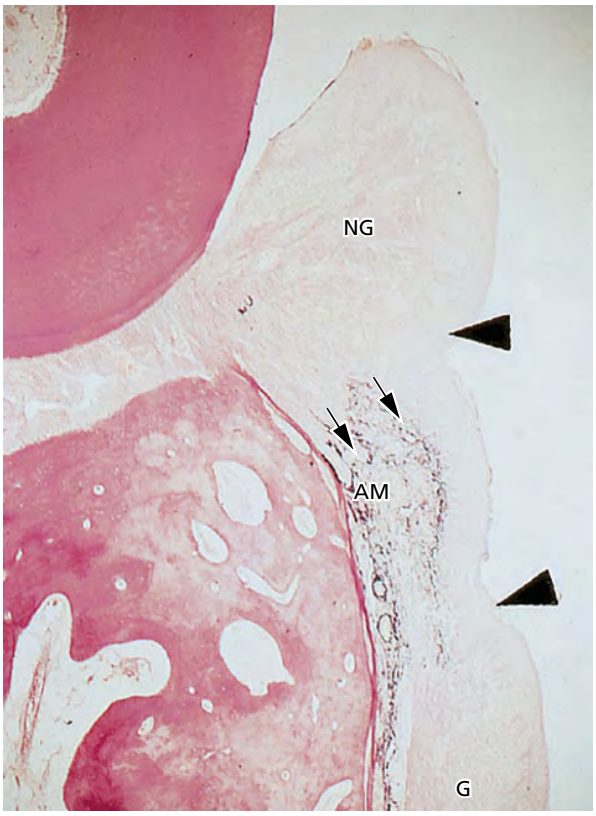

Fig. 1-53 Histologic section through the coronal portion of the area of transplantation seen in Fig. 1-51 showing the transplanted gingival tissue (G) in the lower portion of the photomicrograph and a newly formed narrow zone of gingiva (NG) between the teeth and the transplanted alveolar mucosa (AM, between arrowheads). Note that the junctions between keratinized and non-keratinized epithelium (arrowheads) correspond exactly to the junction between "elastic" (arrows) and "non-elastic" connective tissue. The elastic fibers are purple-stained.

formed gingival connective tissue possesses the ability to induce changes in the differentiation of the epithelium originating from the alveolar mucosa. This epithelium, which is normally non-keratinized, apparently differentiates to keratinized epithelium because of stimuli arising from the newly formed gingival connective tissue.

In another experimental study, the role of the soft connective tissue in determining the type of epithelium was further studied (Karring *et al*. 1975). In this experiment, free connective tissue grafts, without epithelium, were transplanted from either the keratinized gingiva or the non-keratinized alveolar mucosa into pouches created in the soft connective tissue of the alveolar mucosa (Fig. 1-55). The transplants were placed as close as possible to the overlying epithelium, which was removed after 3–4 weeks to allow epithelialization from the surrounding non-keratinized alveolar mucosa. The gingival connective tissue grafts became covered with keratinized epithelium, which displayed the same characteristics as those of normal gingival epithelium (Fig. 1-56). In contrast, the alveolar mucosa transplants were covered with non-keratinized epithelium.

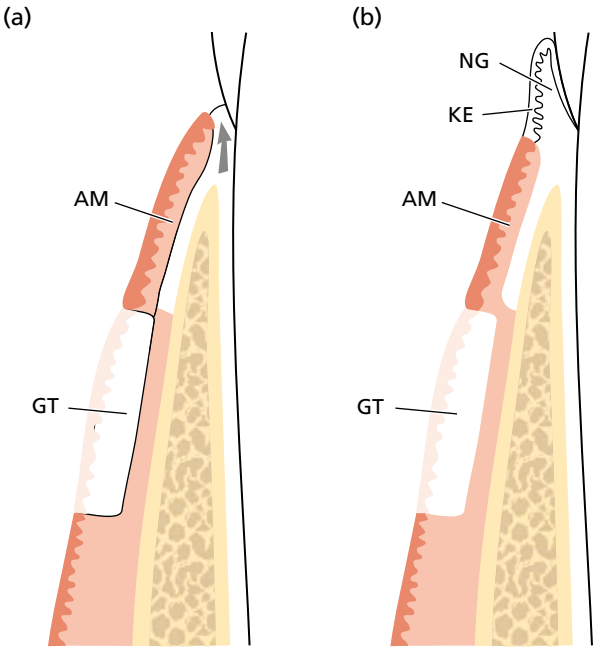

Fig. 1-54 The development of the new, narrow zone of keratinized gingiva seen in Figs. 1-51 and 1-53. (a) Granulation tissue has proliferated coronally along the root surface (arrow) and has separated the alveolar mucosa transplant (AM) from its original contact with the tooth surface. (b) Epithelial cells have migrated from the alveolar mucosal transplant (AM) to the newly formed gingival connective tissue (NG) where they transformed into keratinized epithelial cells (KE). GT, gingival transplant.

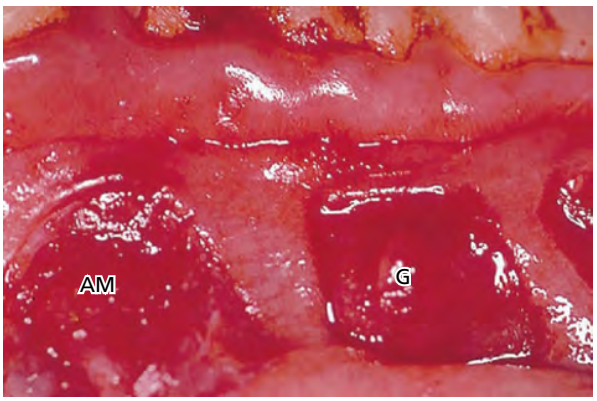

Fig. 1-55 A portion of gingival connective tissue (G) and alveolar mucosal connective tissue (AM) which, after transplantation, has healed into wound areas in the alveolar mucosa. Epithelialization of these transplants can only occur through migration of epithelial cells from the surrounding alveolar mucosa.

Histological sections through the area of the transplanted gingival connective tissue (Fig. 1-57) show that:

- Transplanted gingival connective tissue is covered by keratinized epithelium.
- Epithelium–connective tissue interface has the same wavy course (i.e. rete pegs and connective tissue papillae) as seen in the pristine gingiva.

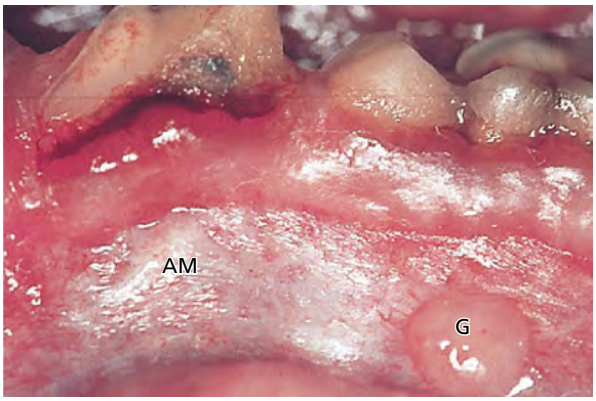

Fig. 1-56 The transplanted gingival connective tissue (G) after re-epithelialization. This tissue portion has attained an appearance similar to that of the normal gingiva, indicating that this connective tissue is now covered by keratinized epithelium. The transplanted connective tissue from the alveolar mucosa (AM) is covered by non-keratinized epithelium and has the same appearance as the surrounding alveolar mucosa.

At a higher magnification, the distinct relationship between keratinized epithelium and "inelastic" connective tissue, and between non-keratinized epithelium and "elastic" connective tissue is evident (Fig. 1-57c, d). The establishment of such a close relationship during healing implies that the transplanted gingival connective tissue possesses the ability to alter the differentiation of epithelial cells, as previously suggested (Fig. 1-54). While starting as non-keratinizing cells, the cells of the epithelium of the alveolar mucosa have evidently become keratinizing cells. This means that the specificity of the gingival epithelium is determined by genetic factors inherent in the connective tissue.

Periodontal ligament

The periodontal ligament is the soft, richly vascular and cellular connective tissue that surrounds the roots of the teeth and joins the root cementum with the socket wall. In the coronal direction, the periodontal ligament is continuous with the lamina propria of the gingiva and is demarcated from the gingiva by the collagen fiber bundles which connect the alveolar bone crest to the root (the alveolar crest fibers).

On radiographs, two types of alveolar bone can be distinguished (Fig. 1-58):

1. The part of the alveolar process which covers the alveolus, denoted "lamina dura".
2. The portion of the alveolar process which, on the radiograph, has the appearance of a meshwork, denoted "trabecular bone".

The periodontal ligament is situated in the space between the roots of the teeth and the bone of the socket wall. The alveolar bone surrounds the tooth from the apex to a level approximately 1 mm apical to the CEJ. The coronal border of the bone is called the *bone crest*.

The periodontal ligament space has the shape of an hourglass and is narrowest at the mid-root level. The width of the periodontal ligament is approximately 0.2 mm and depends on type of species, age, distance from the CEJ, and function. The presence of a periodontal ligament permits forces, elicited during masticatory function and other tooth contacts, to be distributed to and absorbed by the alveolar process via the alveolar bone proper. The periodontal ligament is also essential for the mobility of the teeth. Tooth mobility is to a large extent determined by the width and height of the periodontal ligament (see Chapters 13 and 43).

The tooth is joined to the bone by bundles of collagen fibers that can be divided into the following main groups according to their location and arrangement (Fig. 1-59):

1. *Alveolar crest fibers*
2. *Horizontal fibers*
3. *Oblique fibers*
4. *Apical fibers*.

The periodontal ligament and the root cementum develop from the loose connective tissue (the dental follicle), which surrounds the tooth bud. The principal fiber bundles of the periodontal ligament develop from coronal to apical, while the root develops and the tooth erupts. The various stages in the organization of the periodontal ligament, which forms concomitantly with the development of the root and the eruption of the tooth, is illustrated in Fig. 1-60.

The tooth bud is formed in a crypt of the bone (Fig. 1-60a). The collagen fibers produced by the fibroblasts in the loose connective tissue around the tooth bud are embedded, during the process of their maturation, into the newly formed cementum immediately apical to the CEJ. These fiber bundles oriented towards the coronal portion of the bone crypt will later form the dentogingival, the dentoperiosteal, and the trans-septal fiber groups, which belong to the oriented fibers of the gingiva (see Fig. 1-48).

The true periodontal ligament fibers, the *principal fibers*, develop in conjunction with the eruption of the tooth (Fig. 1-60b). First, fibers can be identified entering the most marginal portion of the alveolar bone. Later, more apically positioned bundles of oriented collagen fibers are seen (Fig. 1-60c).

The orientation of the collagen fiber bundles alters continuously during the phase of tooth eruption. First, when the tooth has reached contact in occlusion and is fully in function, the fibers of the periodontal ligament associate into groups of well-oriented dentoalveolar collagen fibers (Fig. 1-60d). These collagen structures undergo constant remodeling (i.e. resorption of old and formation of new fibers).

The development of the principal fibers of the periodontal ligament is illustrated in Fig. 1-61. First, small,

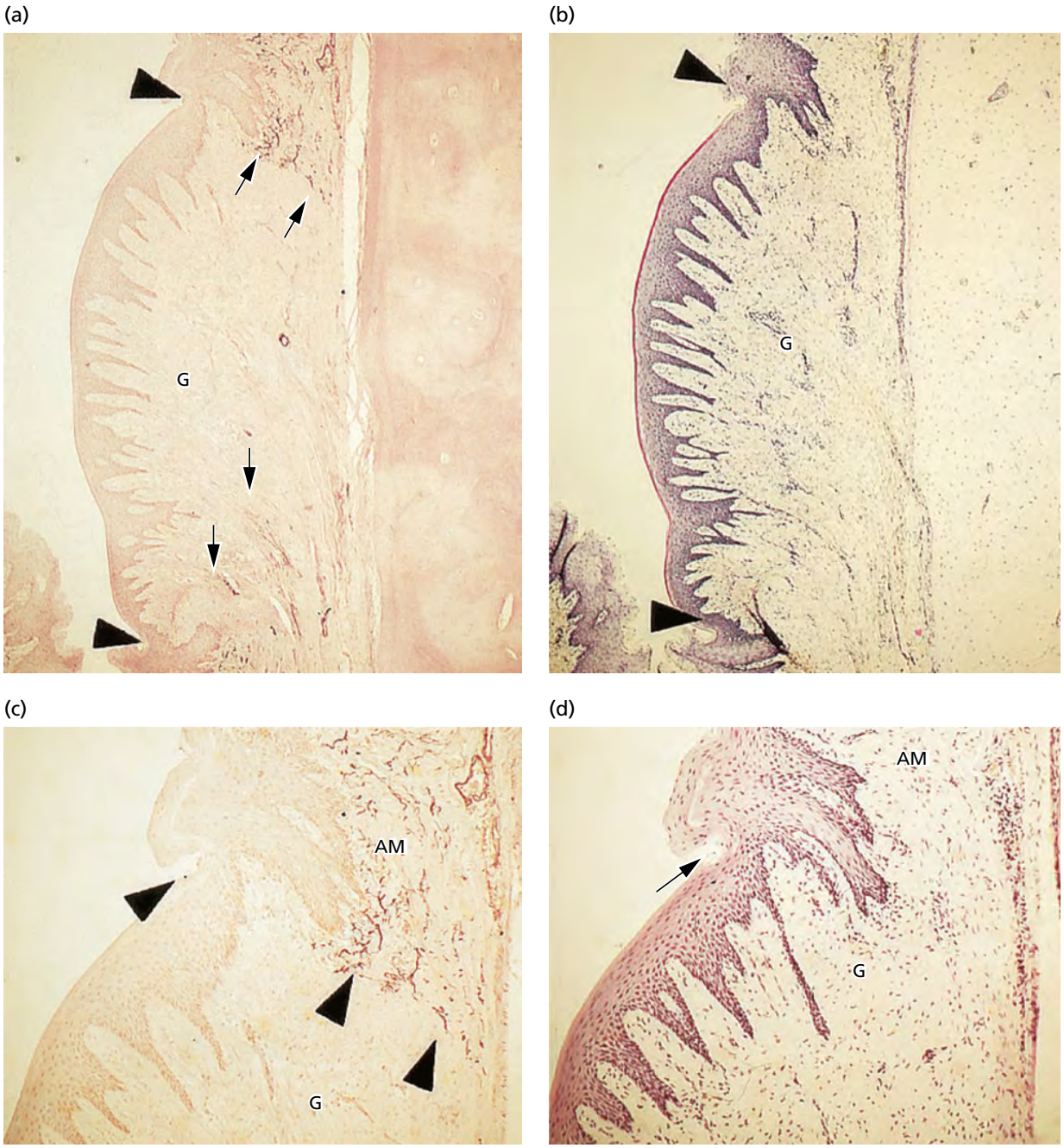

Fig. 1-57 Two histologic sections through the area of the transplanted gingival connective tissue. Sections were stained for elastic fibers (arrows) (a, c) and with hematoxylin and eosin (b, d) and are illustrated at medium (a, b) and high (c, d) magnifications. (a, b) The tissue in the middle (between arrowheads) without elastic fibers is the transplanted gingival connective tissue covered with a keratinized epithelium. (c) Note that the purple-stained elastic fibers in the connective tissue of the alveolar mucosa (AM) (2 arrowheads) end where the connective tissue of the gingiva (G) begins. (d) The arrow indicates the site where the keratinized epithelium adjacent to the gingival connective tissue meets the non-keratinized epithelium over the alveolar mucosa.

fine, brush-like collagenous fiber stubs arise from the root cementum and project into the periodontal ligament space (Fig. 1-61a). At this stage, the surface of the bone is covered by osteoblasts and only a small number of radiating, thin fiber stubs can be seen.

Later on, the number and thickness of fibers embedded in the bone increase (Fig. 1-61b). These fibers radiate towards the loose connective tissue in the mid-portion of the periodontal ligament space, which contains more or less randomly oriented collagen fibers. The fibers originating from the cementum are still short, while those entering the bone gradually lengthen. The terminal portions of these fibers carry finger-like projections.

The fibers originating from the cementum subsequently increase in length and thickness and fuse in the periodontal ligament space with the fibers originating from the alveolar bone (Fig. 1-61c). When the tooth, following eruption, reaches contact in occlusion and starts to function, the principal fibers become organized into bundles and run continuously from the bone to the cementum.

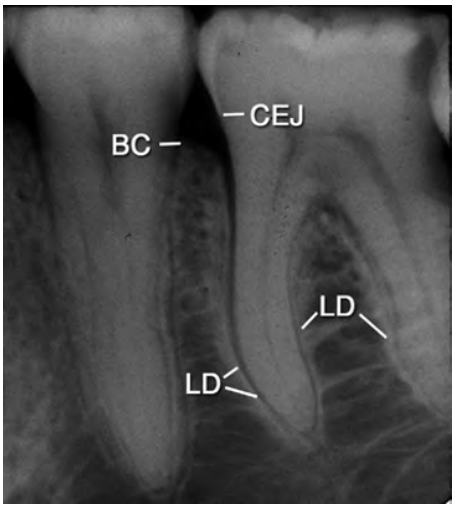

Fig. 1-58 Radiograph of a mandibular premolar region. Two types of alveolar bone can be distinguished: the lamina dura (LD) is that part of the alveolar process that covers the alveolus, whereas the trabecular bone, which has the appearance of a meshwork, constitutes the rest of the alveolar process. The coronal border of the bone is called bone crest (BC). The distance between the bone crest and the cementoenamel junction (CEJ) measures approximately 1 mm.

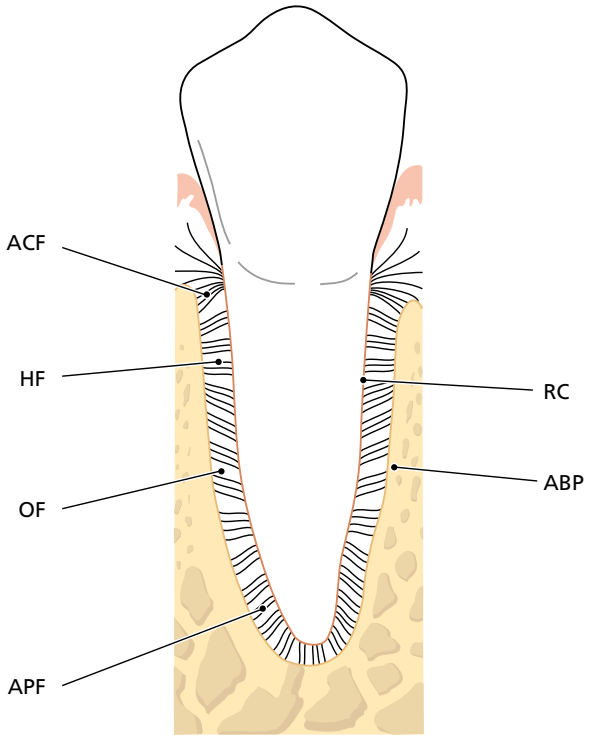

Fig. 1-59 This schematic drawing illustrates how the periodontal ligament is situated between the alveolar bone proper (ABP) and the root cementum (RC) and indicates the groups of collagen fibers that join the tooth to the surrounding bone. From coronal to apical, these groups of fibers constitute the alveolar crest fibers (ACF), the horizontal fibers (HF), the oblique fibers (OF), and the apical fibers (APF).

A histologic section shows how the principal fibers of the periodontal ligament run continuously from the root cementum to the alveolar bone proper (Fig. 1-62a). The principal fibers embedded in the cementum (*Sharpey's fibers*) have a smaller diameter, but are more numerous than those embedded in the alveolar bone proper (also called Sharpey's fibers).

Under polarized light, the Sharpey's fibers can be seen penetrating not only the cementum but also the entire width of the alveolar bone proper (Fig. 1-62b). The periodontal ligament also contains a few elastic fibers associated with the blood vessels. Oxytalan fibers (see Fig. 1-46) are also present in the periodontal ligament. They have a mainly apico-occlusal orientation and are located in the ligament closer to the root than to the alveolar bone. Very often, they insert into the cementum. Their function may be related to mechanotransduction.

The cells of the periodontal ligament are: *fibroblasts*, *osteoblasts*, *cementoblasts*, *osteoclasts*, odontoclasts,

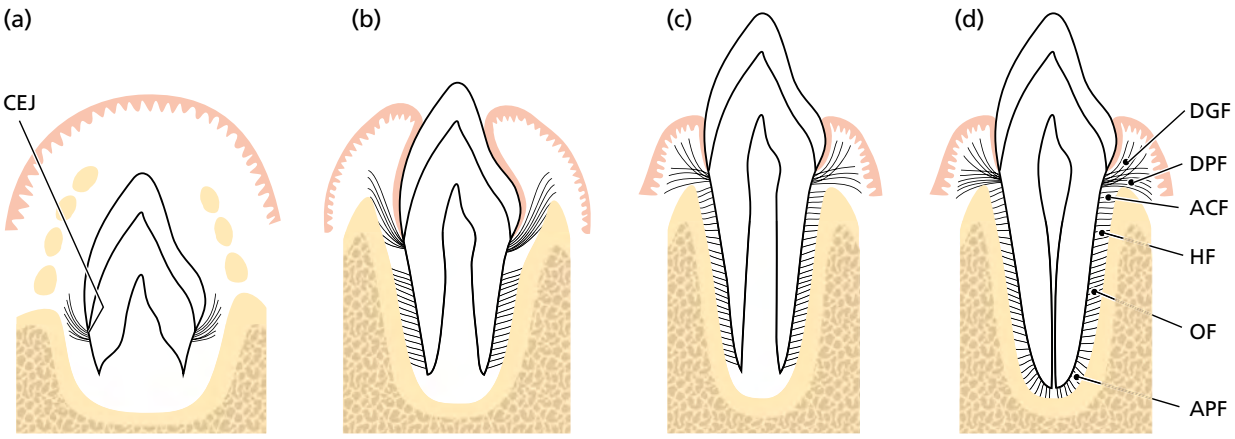

Fig. 1-60 The various stages in the organization of the periodontal ligament, while the tooth root(s) develop and the tooth erupts. (a) Tooth bud with a short root portion developed and before eruption into the oral cavity. (b) The tooth during eruption into the oral cavity. (c) The tooth has reached the occlusal plane but root formation is not complete yet. (d) The tooth in occlusion with closed root apex. The development of the collagen fibers inserting into the cementum starts in closest proximity to the cementoenamel junction (CEJ). The principal fiber bundles of the periodontal ligament develop from coronal to apical, while the root develops and the tooth erupts. First, the dentogingival fibers (DGF) and the dentoperiosteal fibers (DPF) develop, followed by the alveolar crest fibers (ACF), the horizontal fibers (HF), the oblique fibers (OF), and finally the apical fibers (APF).

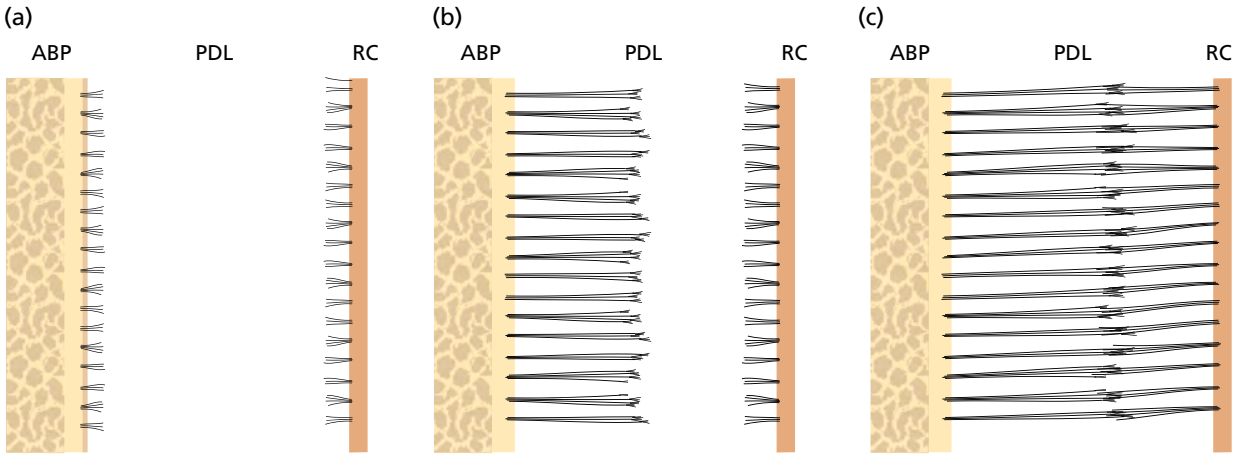

Fig. 1-61 The development of the principal periodontal ligament fibers. (a) First, short, brush-like collagenous fiber stubs embedded in the root cementum (RC) and alveolar bone proper (ABP) project into the periodontal ligament (PDL) space. (b) Later, the short fiber stubs gradually extend into the periodontal ligament space. (c) The collagen fibers originating from the root cementum and bone increase in length and thickness and fuse to form the principal periodontal ligament fibers.

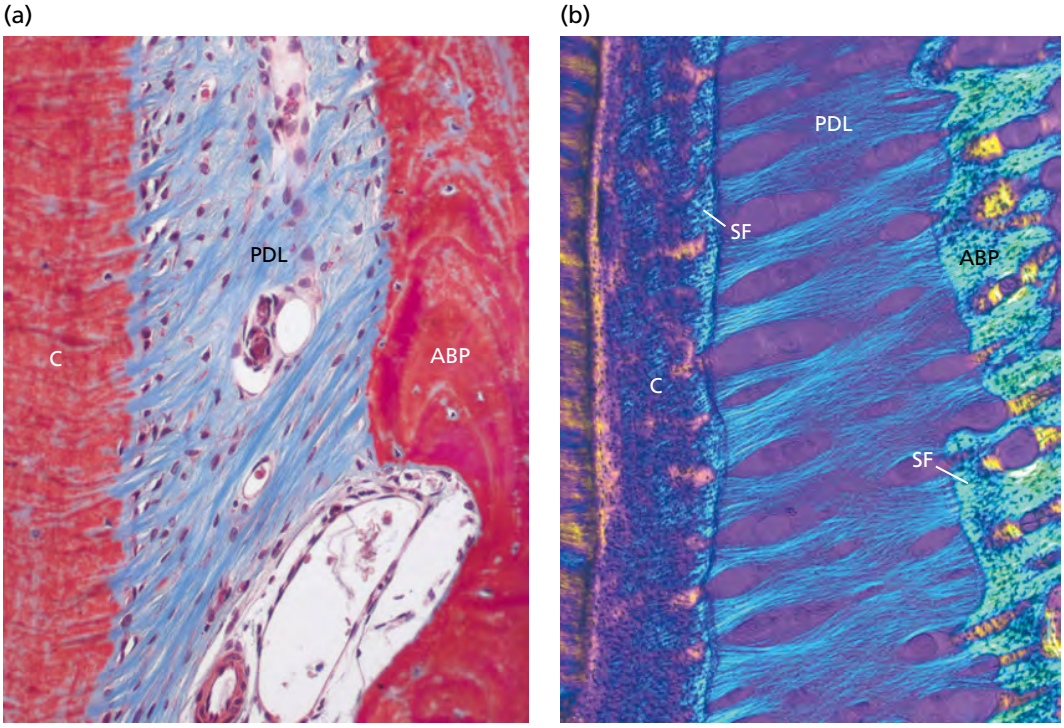

Fig. 1-62 Histologic sections viewed under transmitted (a) and polarized (b) light illustrating how the principal periodontal ligament (PDL) fibers run between the root cementum (C) and the alveolar bone proper (ABP). The collagen fibers inserting into both root cementum and bone are called Sharpey's fibers (SF).

histiocytes as well as *epithelial cells*, *nerve fibers*, *and blood vessels*. The fibroblasts are aligned along the principal fibers, while cementoblasts line the surface of the cementum and the osteoblasts line the bone surface.

Clusters of epithelial cells in the periodontal ligament, called the *epithelial cell rests of Malassez* (ERM), represent remnants of the Hertwig's epithelial root sheath (Fig. 1-63a). The epithelial cell rests are situated in the periodontal ligament at a distance of 15–75 µm from the cementum on the root surface. One large group of such epithelial cell rests is seen in a higher magnification in Fig. 1-63b.

In the transmission electron microscope, it can be seen that the epithelial cell rests are surrounded by a basement membrane and that the cell membranes of the epithelial cells exhibit the presence of desmosomes as well as hemidesmosomes (Fig. 1-64). The epithelial cells contain only a few mitochondria and have a poorly developed endoplasmic reticulum. This means that they are vital, but resting, cells with minute metabolism.

When the periodontal ligament is cut tangential to the root surface, it becomes evident that the epithelial cell rests of Malassez, which in ordinary histologic sections appear as isolated groups of epithelial

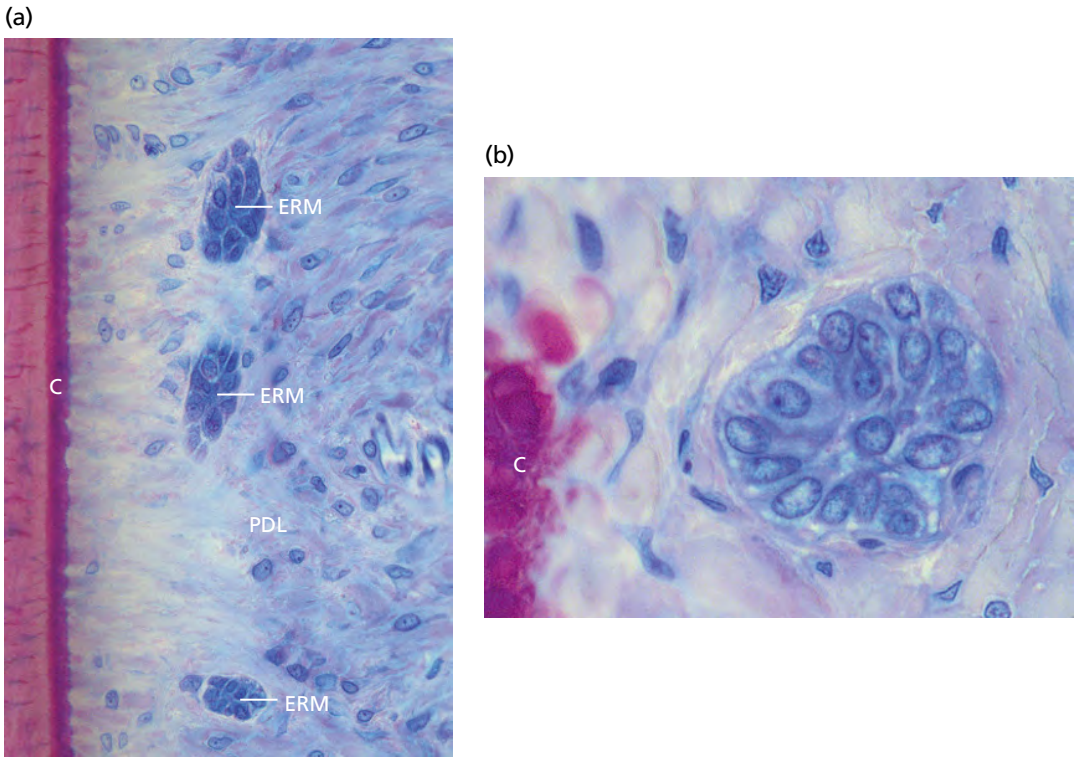

Fig. 1-63 (a) Light micrograph showing three clusters of epithelial cells, called the epithelial cell rests of Malassez (ERM), in the periodontal ligament (PDL) close to the cementum (C) surface. (b) Higher magnification of a large cluster of epithelial cell rests of Malassez near the cementum surface.

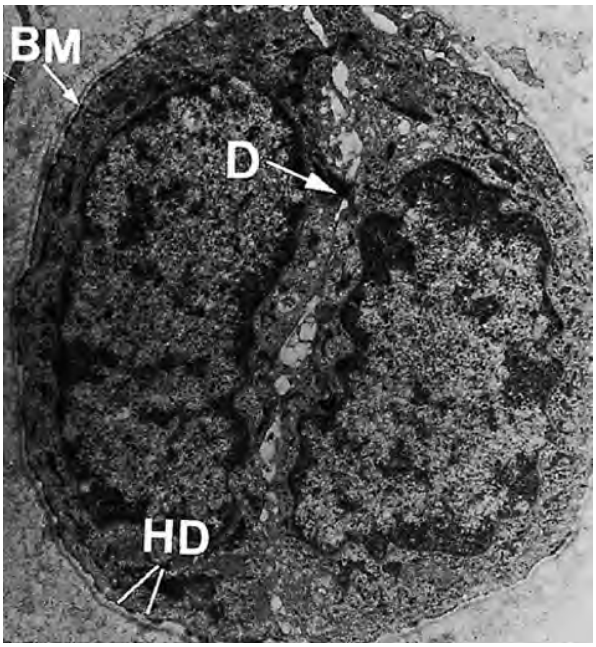

Fig. 1-64 Transmission electron micrograph illustrating epithelial cell rests of Malassez surrounded by a basement membrane (BM) and hemidesmosomes (HD). Desmosomes (D) connect neighboring epithelial cells.

cells, in fact form a continuous network of epithelial cells surrounding the root (Fig. 1-65). Their function is unknown at present. Yet, it has been shown that the epithelial network is in contact with the junctional epithelium. Moreover, nerve endings are in contact

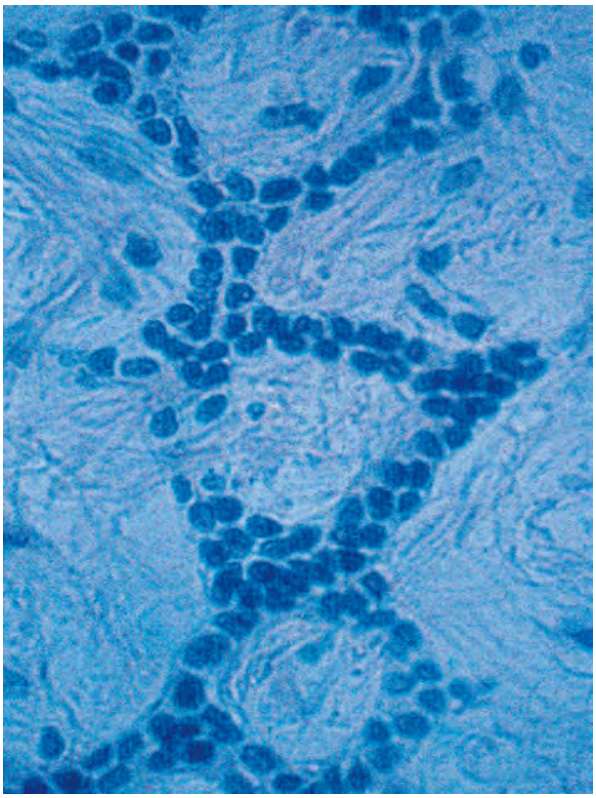

Fig. 1-65 Photomicrograph of a periodontal ligament removed from an extracted tooth and sectioned tangential to the root surface showing that the epithelial cell rests of Malassez form a continuous network of epithelial cells surrounding the root.

with both the epithelial cell rests of Malassez and the junctional epithelium.

Root cementum

The cementum is a specialized mineralized tissue covering the root surfaces and, occasionally, small portions of the crown of the teeth. It may also extend into the root canal. In humans and unlike bone, the cementum contains no blood or lymph vessels, has no innervation, does not undergo physiologic resorption or remodeling, but is characterized by continuing deposition throughout life. Like other mineralized tissues, it contains collagen fibrils embedded in an organic matrix. Its mineral content, which is mainly hydroxyapatite, is about 65% by weight, a little more than that of bone (60%). The various cementum types serve different functions. One cementum type attaches the principal periodontal ligament fibers to the root. Another cementum type contributes to the process of repair after damage to the root surface and may also serve to adjust the tooth position to new requirements.

Different forms of cementum have been described:

1. *Acellular afibrillar cementum* (AAC) is found mainly at the cervical portion of the enamel.
2. *Acellular extrinsic fiber cementum* (AEFC) is found in the coronal and middle portions of the root and contains mainly bundles of Sharpey's fibers. This type of cementum is an important part of the attachment apparatus and connects the tooth with the bundle bone (alveolar bone proper). It may be termed "attachment cementum".
3. *Cellular mixed stratified cementum* (CMSC) occurs in the apical third of the roots and in the furcations. It contains both extrinsic and intrinsic fibers as well as cementocytes. It may be termed "reactive cementum", as it reacts more readily to mechanical strain.
4. *Cellular intrinsic fiber cementum* (CIFC) is found mainly in resorption lacunae and it contains intrinsic fibers and cementocytes. It may be called "reparative cementum".

Histological examples of the tooth attachment apparatus are shown in Fig. 1-66. Viewed under polarized light (Fig. 1-66a), it can be seen that the principal collagen fibers of the periodontal ligament span between the root covered with cementum and the alveolar process covered with bundle bone. The portions of the principal fibers of the periodontal ligament that are embedded in the root cementum and in the bundle bone are called Sharpey's fibers. Oxytalan fibers are particularly found in the periodontal

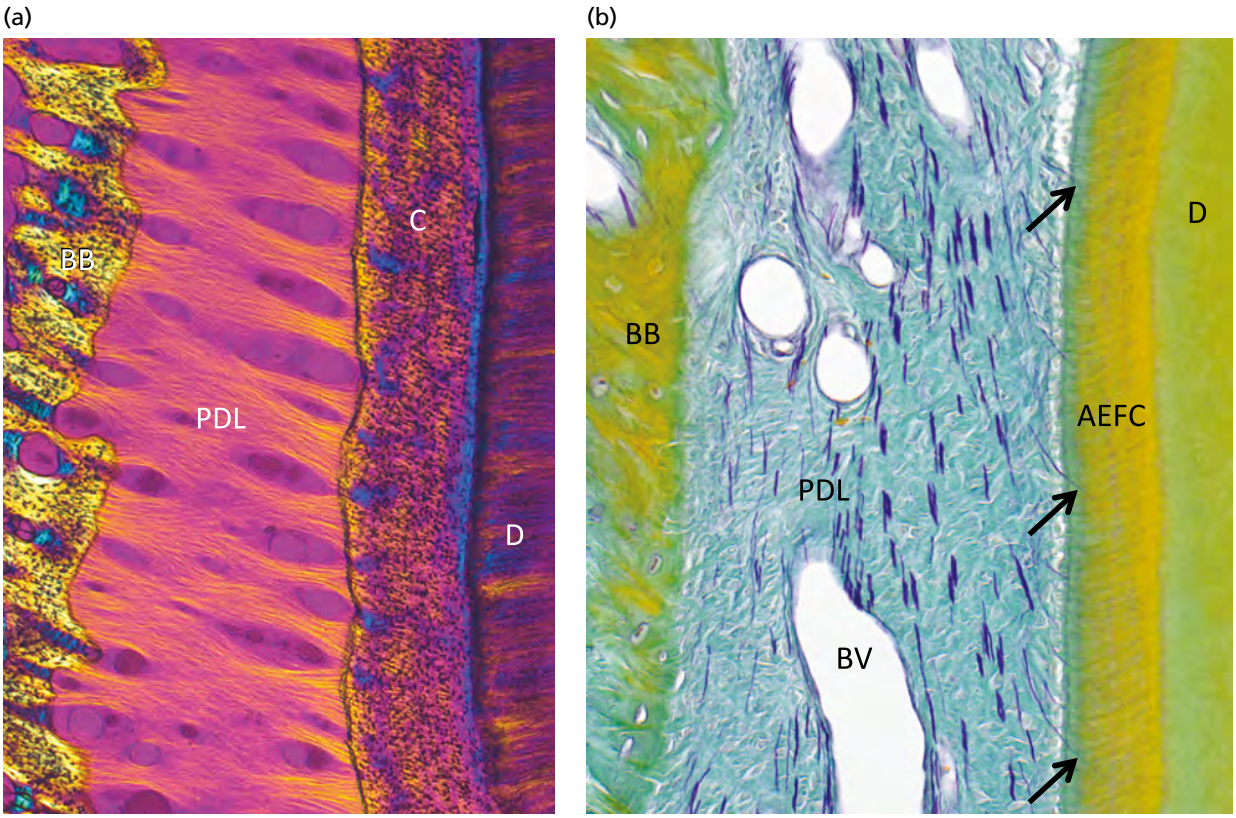

Fig. 1-66 Photomicrographs illustrating the tooth attachment apparatus. (a) Viewed under polarized light, it can be seen that the principal collagen fibers of the periodontal ligament (PDL) span between the root covered with cementum (C) and the socket wall covered with alveolar bone proper or bundle bone (BB). (b) When a paraffin section is stained with the oxone-aldehyde-fuchsin-Halmi technique, oxytalan fibers show an apicocoronal arrangement with some fibers inserting (arrows) into the acellular extrinsic fiber cementum (AEFC). Many oxytalan fibers are associated with blood vessels (BV). D, dentin.

ligament (Fig. 1-66b). They run parallel to the root with some fibers bending to cementum where they attach. Many oxytalan fibers are seen around the blood vessels in the periodontal ligament. Oxytalan fibers may have a function in mechanotransduction between the root and the periodontal ligament.

Acellular afibrillar cementum

The AAC prevails in the region of the CEJ where it covers minor areas of the cervical enamel (Fig.1-67a). It neither contains cells nor collagen fibrils. It may form isolated patches on the enamel or be contiguous with the AEFC. The AAC may form when the reduced enamel epithelium recedes or focally disintegrates so that the exposed enamel surface comes into contact with the surrounding soft connective tissue. In the transmission electron microscope, the AAC extends from the AEFC in the coronal direction (Fig. 1-67b). The layered appearance of the AAC is indicative of periods of deposition and rest. The function of the AAC is unclear.

Acellular extrinsic fiber cementum

The AEFC is formed concomitantly with the formation of the root dentin. At the beginning of root development, the Hertwig's epithelial root sheath, which lines the newly formed predentin, becomes fragmented. Cementoblasts then begin to synthesize collagen fibers that are implanted roughly at a right angle to the root surface. During the continuous formation of AEFC, portions of these short collagen fibers adjacent to the root become embedded in the mineralized cementum. Figure 1-68 shows the advancement of mineralization of the AEFC. Short collagenous fibers, resembling fringes and constituting the future Sharpey's fibers, cover the root surface and protrude from the dentin into the periodontal ligament space (Fig. 1-68a). A cementum layer is not visible yet. Later, however, a layer of mineralized cementum, into which the bases of the short collagen fibers are embedded as Sharpey's fibers, is discernible (Fig. 1-68b). When the tooth approaches the occlusal level, the short collagen fibers become elongated and eventually merge with the collagen fibers protruding from bone into the periodontal ligament (Fig. 1-68c) (see also Fig. 1-61).

These micrographs demonstrate that the Sharpey's fibers in the cementum are a direct continuation of the principal fibers in the periodontal ligament and the supra-alveolar connective tissue. The AEFC increases throughout life with a very slow growth rate of 1.5–4.0 µm/year. On mesial root surfaces, the growth is slower than on distal root surfaces, a phenomenon related to the mesial drift of the teeth.

A scanning electron micrograph of a non-decalcified fracture surface of acellular extrinsic fiber cement demonstrates how the extrinsic fibers attach to the dentin, traverse the mineralized cementum layer as Sharpey's fibers, and leave the cementum layer as the principal collagen fibers of the periodontal ligament (Fig. 1-69a). In an ultrathin tissue section, it can be seen that the Sharpey's fibers (i.e. the extrinsic collagen fibers of AEFC) pass from the dentin surface through the mineralized cementum layer and continue

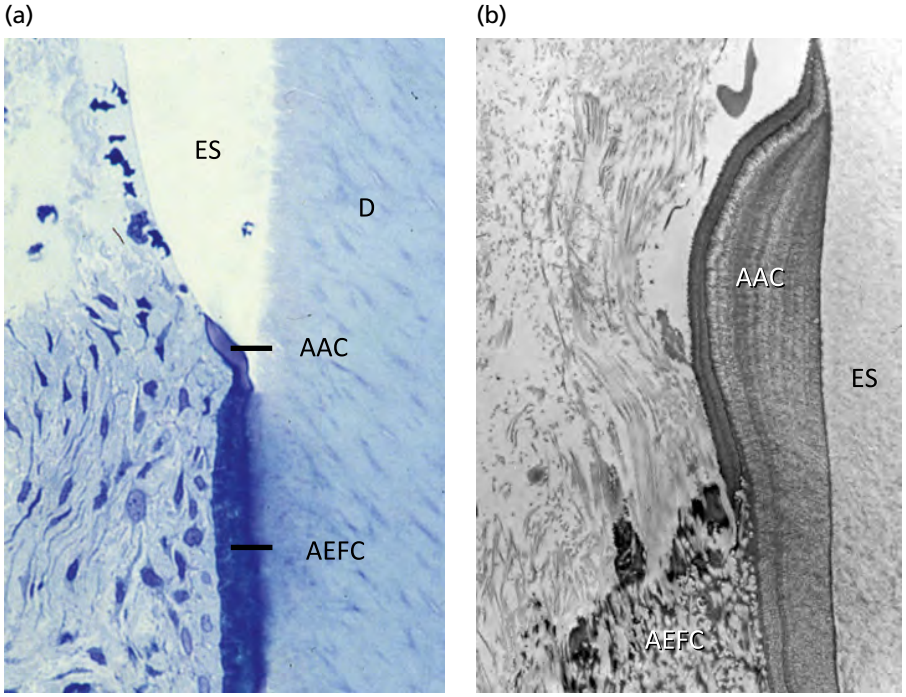

Fig. 1-67 Light (a) and transmission electron (b) micrographs illustrating the morphology of acellular afibrillar cementum (AAC), which prevails in the region of the cementoenamel junction. The moderately electron-dense material in the enamel space (ES) adjacent to the AAC represents residual enamel matrix. AEFC, acellular extrinsic fiber cementum; D, dentin.

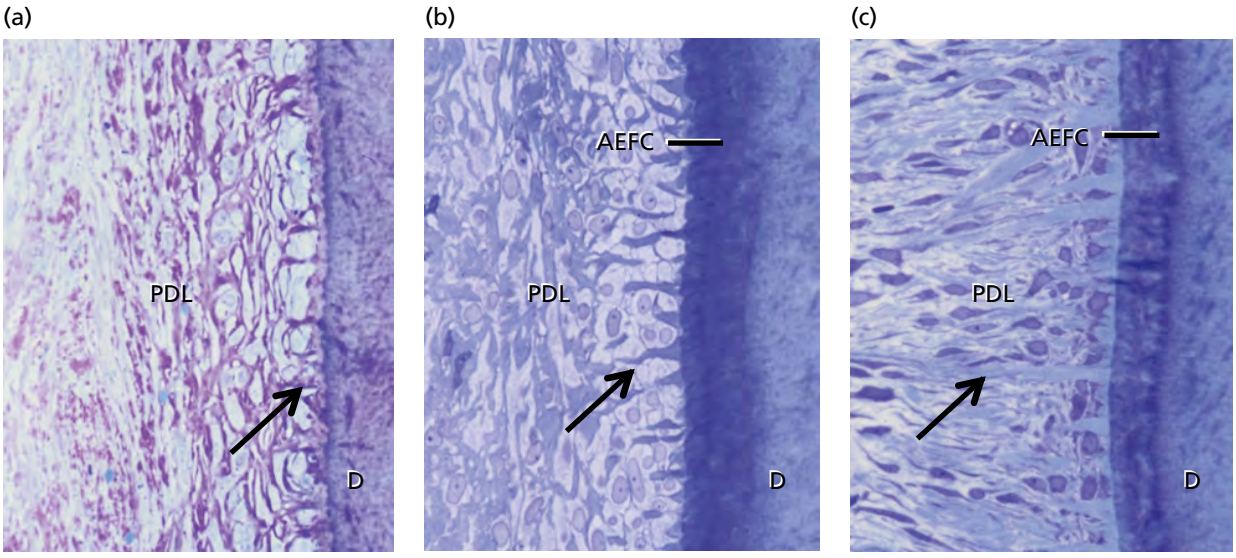

Fig. 1-68 These photomicrographs illustrate the developmental stages of the acellular extrinsic fiber cementum (AEFC). (a) Short collagenous fiber stubs (arrow), the future Sharpey's fibers, protrude from the dentin (D) surface into the periodontal ligament (PDL) before a cementum layer is discernible. (b) Later, the bases of the short collagen fibers (arrow) are embedded in the mineralized cementum. (c) Even later, most collagen fibers are now elongated (arrows) and continue into the periodontal ligament space.

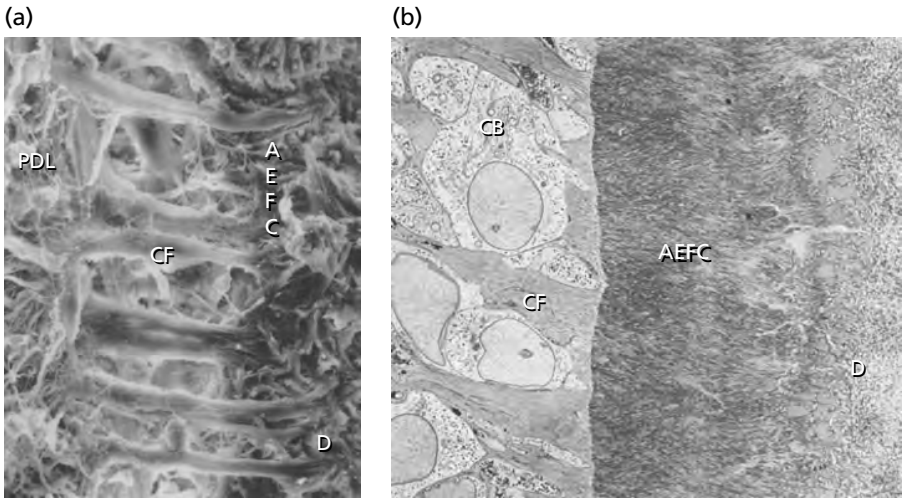

Fig. 1-69 Scanning (a) and transmission (b) electron micrographs illustrating acellular extrinsic fiber cementum (AEFC). Collagen fibers (CF), leaving the cementum layer at the mineralization front, continue into the periodontal ligament (PDL) space. Cementoblasts (CB) occupy the spaces between the protruding collagen fibers. (a) Fracture of a non-decalcified sample. (b) Ultrathin section of a decalcified sample. D, dentin.

outside the cementum as principal collagen fibers into the periodontal ligament (Fig. 1-69b). A higher magnification demonstrates how the Sharpey's fibers leave the cementum at the mineralization front and continue as principal periodontal ligament fibers (Fig. 1-70a). Cementoblasts occupy the space between the densely packed collagen fibrils. The characteristic cross-banding of the collagen fibrils is masked in the cementum because of the presence of non-collagenous proteins. Mineralization occurs by the deposition of hydroxyapatite crystals, first within the collagen fibers, later upon the fiber surface, and finally in the interfibrillar matrix. High-resolution immunolabeling of AEFC at the mineralization front shows the distribution of bone sialoprotein, a non-collagenous protein involved in the regulation of mineralization of collagen-based hard tissues (Fig. 1-70b). Gold particles label the interfibrillar matrix of the mineralized cementum, whereas the unmasked collagen fibrils that leave the cementum and extend into the periodontal ligament space are not labeled.

Cellular mixed stratified cementum

In contrast to AEFC, CIFC contains cells and intrinsic fibers. It is built up of alternating layers of AEFC and CIFC (Fig. 1-71a). While the extrinsic Sharpey's fibers traverse the cementum layer and leave it at the mineralization front, the intrinsic fibers reside completely within the cementum. The cells that are incorporated into the cementum are called *cementocytes*. The CMSC is laid down throughout the functional period of the tooth. The stratification of CMSC is usually irregular. CMSC is found at the mid-root and apical

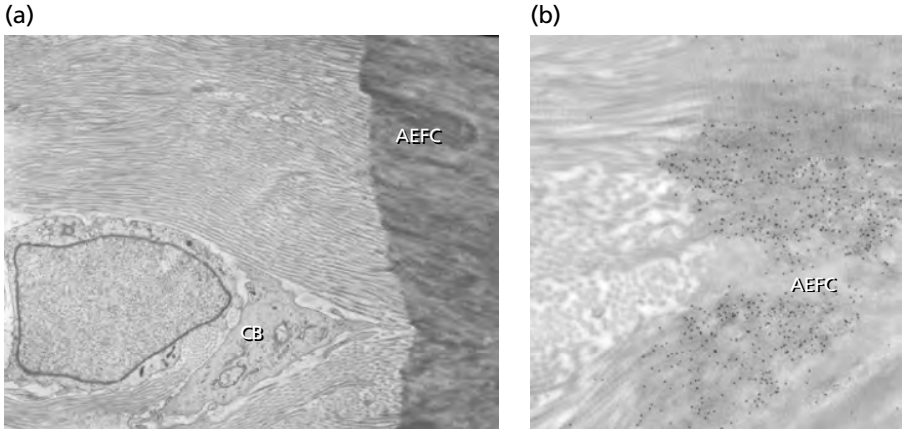

Fig. 1-70 Transmission electron micrographs of acellular extrinsic fiber cementum (AEFC) at the mineralization front. (a) The Sharpey's fibers leave the cementum at the mineralization front and continue as principal periodontal ligament fibers. Cementoblasts (CB) occupy the space between the densely packed collagen fibrils. (b) High-resolution immunohistochemistry with immunogold labeling for bone sialoprotein shows (small black dots) that this non-collagenous protein is mainly present in the interfibrillar matrix of cementum.

root surfaces and in the furcations. The cementum becomes considerably wider in the apical portion of the root than in the cervical portion. In the apical root portion, the cementum is often 150–250 µm wide or even more. The cementum often contains incremental lines, indicating alternating periods of formation and rest.

Cellular intrinsic fiber cementum

This cementum type is either part of the CMSC or is found alone at sites on the root surface undergoing repair after root resorption. Cementocytes are numerous and reside in lacunae in the mineralized matrix (Fig. 1-71b). Cementocytes communicate with each other through a network of cytoplasmic processes running through canaliculi in the cementum. Most cell processes point to the cementum surface. The cementocytes also communicate with the cementoblasts on the surface through cytoplasmic processes. The presence of cementocytes allows transportation of nutrients and waste products through the cementum and contributes to the maintenance of the vitality of this mineralized tissue.

The cementoid, the not yet mineralized cementum matrix, is lined by the cementoblast. They are large, cuboidal cells with a round, euchromatin-rich nucleus. The abundance of rough endoplasmic reticulum indicates that these cells are highly active and produce proteins that are secreted into the extracellular space. They elaborate a cementoid seam consisting of a collagenous matrix that later mineralizes.

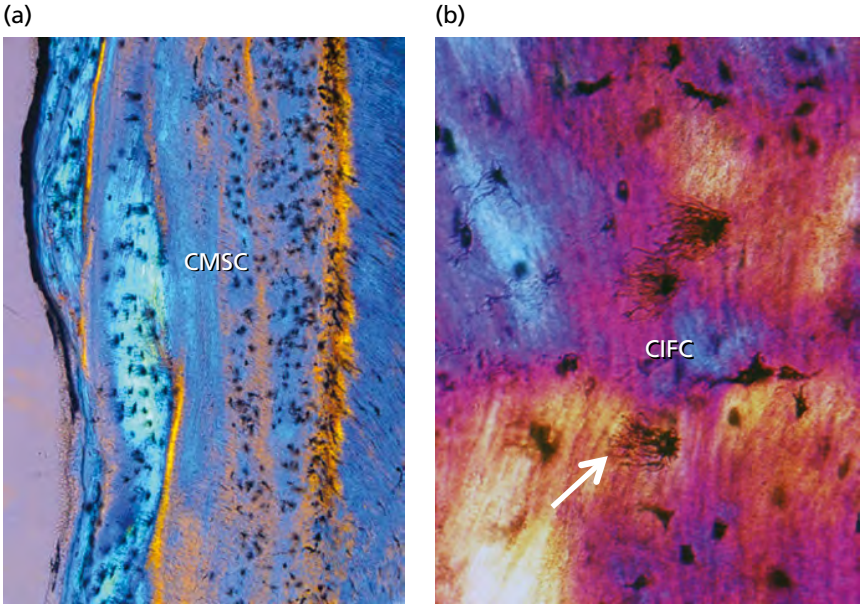

Fig. 1-71 Ground sections viewed under polarized light illustrating (a) cellular mixed stratified cementum (CMSC) and (b) cellular intrinsic fiber cementum (CIFC). The black cells are cementocytes that reside in lacunae in the CIFC. The arrow points to cytoplasmic processes.

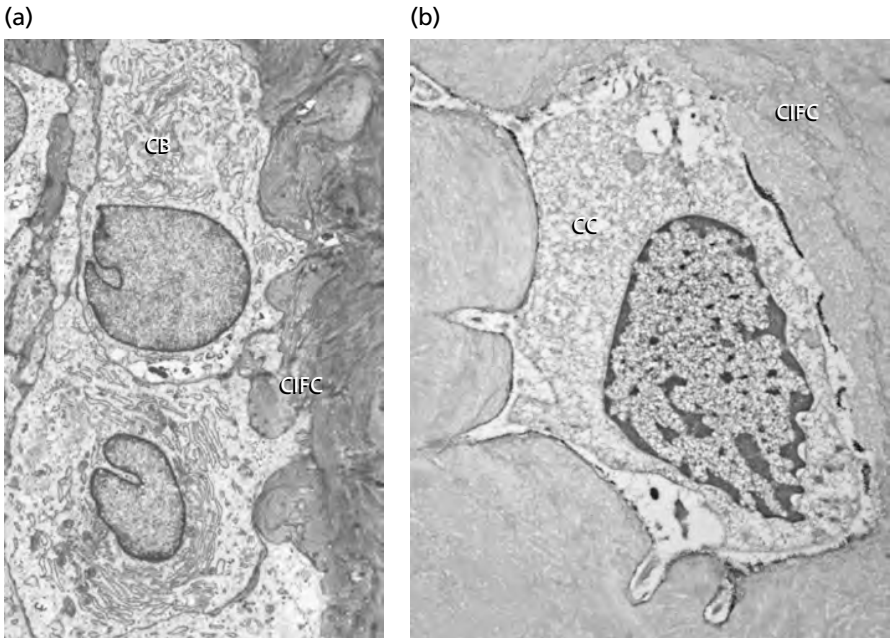

Fig. 1-72 Transmission electron micrographs illustrating (a) the surface of the cellular intrinsic fiber cementum (CIFC) covered with cementoblasts (CB) and (b) a cementocyte (CC) in its lacuna and surrounded by mineralized matrix.

Generally, the AEFC is more mineralized than CMSC and CIFC. Sometimes only the periphery of the Sharpey's fibers of the CMSC is mineralized, leaving an unmineralized core within the fiber. The cementocytes are cementoblasts that become entrapped in the cementum matrix. They are present in lacunae from which several canaliculi traverse the cementum matrix and communicate with neighboring cementocytes (Fig. 1-72b). Cementocyte lacunae in deeper portions of the cementum often appear empty, which may be attributed to the fact that the critical distance for exchange of metabolites is surpassed.

Bone of the alveolar process

Macroscopic anatomy

The alveolar process is defined as the parts of the maxilla and the mandible that form and support the sockets of the teeth. The alveolar process extends from the basal bone of the jaws and develops in conjunction with the development and eruption of the teeth (see Fig. 1-60). The alveolar process consists of bone that is formed both by cells from the dental follicle (to produce the alveolar bone proper) and cells which are independent of this follicle (to produce the alveolar bone). Together with the root cementum and the periodontal ligament, the alveolar bone proper constitutes the attachment apparatus of the teeth, the main function of which is to distribute forces generated by, for example, mastication and other tooth contacts.

In a cross-section through the alveolar process (pars alveolaris) of the maxilla at the mid-root level of the teeth, it can be seen that the bone which covers the root surfaces is considerably thicker at the palatal than at the buccal aspect of the jaw (Fig. 1-73). Anatomically, the walls of the sockets (alveolar bone proper; arrows), as well as the outer walls of the alveolar process are made up of *cortical bone*. The area enclosed by the cortical bone walls is occupied by *cancellous (spongy) bone*. Thus, the cancellous bone occupies most of the interdental septa but only a relatively small portion of the buccal and palatal bone walls. The cancellous bone contains *bone trabeculae*, the architecture and size of which are partly genetically determined and partly the result of the forces to which the teeth are exposed during function. Note how the bone on the buccal and palatal aspects of the alveolar process varies in thickness from one region to another.

In the mandible, the bone lining the wall of the sockets (alveolar bone proper) is often continuous with the compact or cortical bone at the lingual and buccal aspects of the alveolar process (Fig. 1-74). Note how the bone on the vestibular and lingual aspects of the alveolar process varies in thickness from one region to another. In the incisor and premolar regions, the bone plate at the buccal aspects of the teeth is considerably thinner than at the lingual aspect. In the molar region, the bone is thicker at the buccal aspect than at the lingual aspect.

At the buccal aspect, particularly in the front region, of the jaws, the bone coverage of the roots is occasionally very thin or entirely missing (Fig. 1-75). An area without bone coverage in the marginal portion of the root is called *dehiscence*. If some bone is present in the most coronal portion of the buccal bone but the defect is located more apically, it is denoted *fenestration*. These defects often occur where a tooth during eruption is displaced out of the arch and are more frequent over anterior than posterior teeth. The root in such defects is covered only by a soft connective tissue attachment and overlying mucosa.

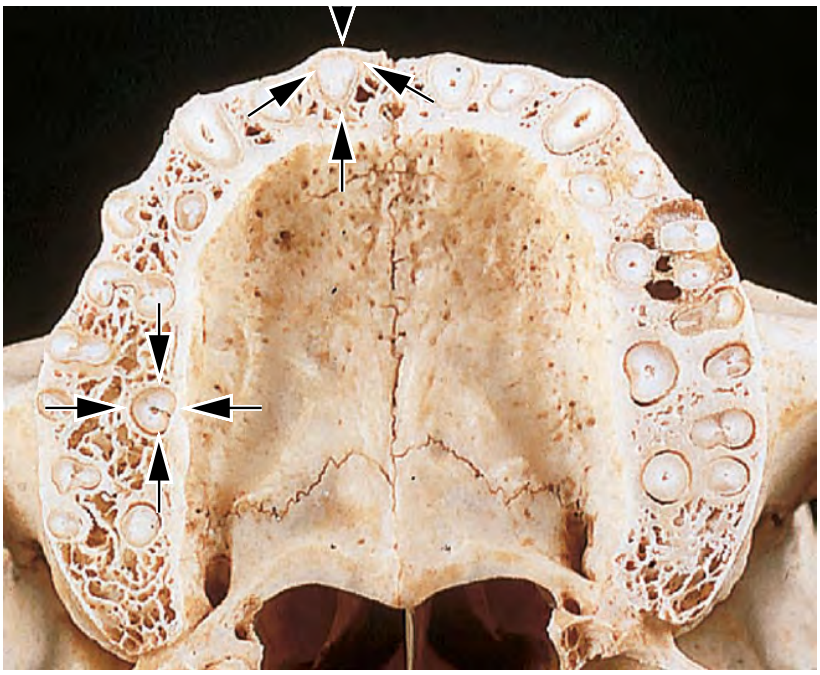

Fig. 1-73 Cross-section through the alveolar process (pars alveolaris) of the maxilla at the mid-root level of the teeth. The arrows indicate the walls of the sockets, the alveolar bone proper.

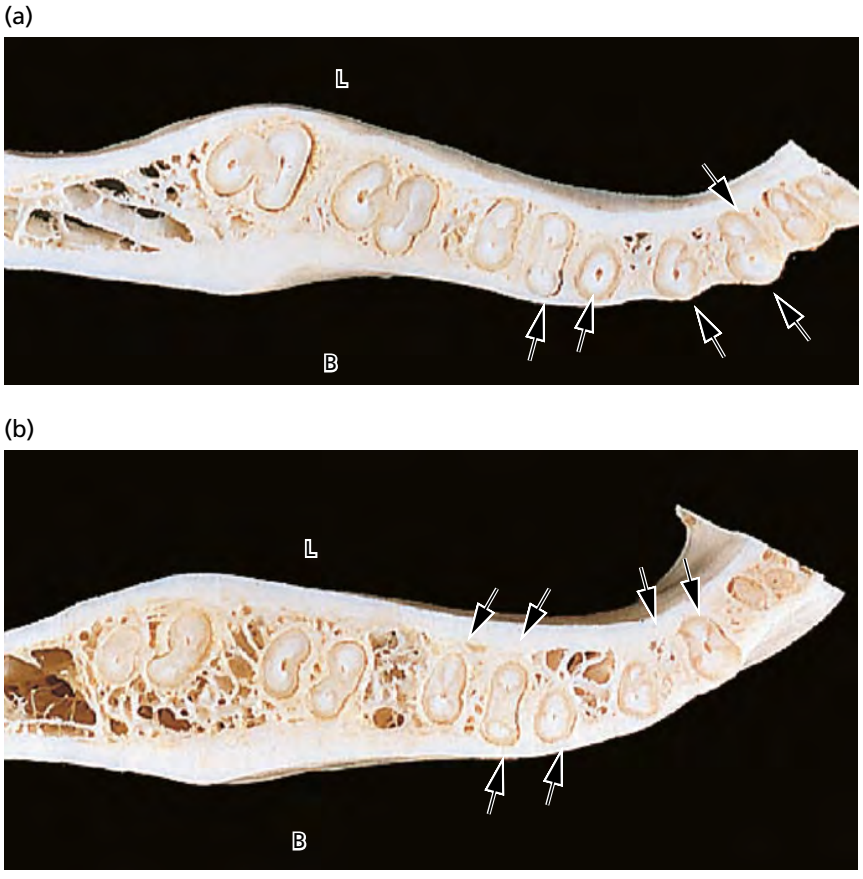

Fig. 1-74 Cross-sections through the mandibular alveolar process at levels corresponding to the coronal (a) and apical (b) thirds of the roots. Arrows indicate the bone of the alveolar process. B, buccal; L, lingual.

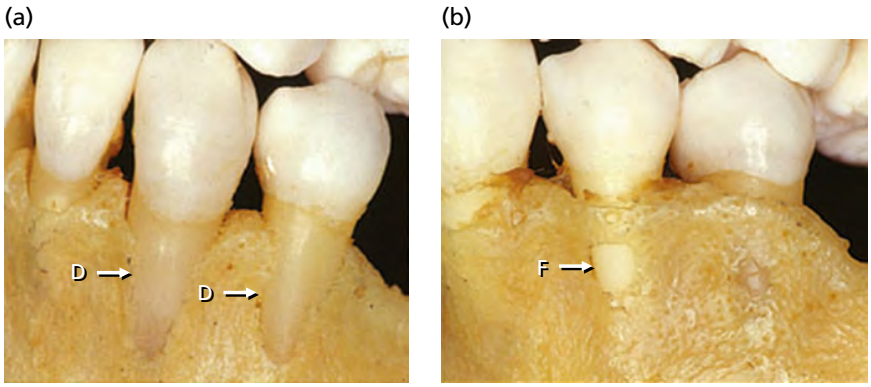

Fig. 1-75 Buccal aspect of the jaws. The bone coverage of the roots is occasionally very thin or entirely missing. (a) A dehiscence (D) is an area without bone coverage in the marginal portion of the root. (b) A fenestration (F) is a bone defect where some bone is present coronal to the defect region.

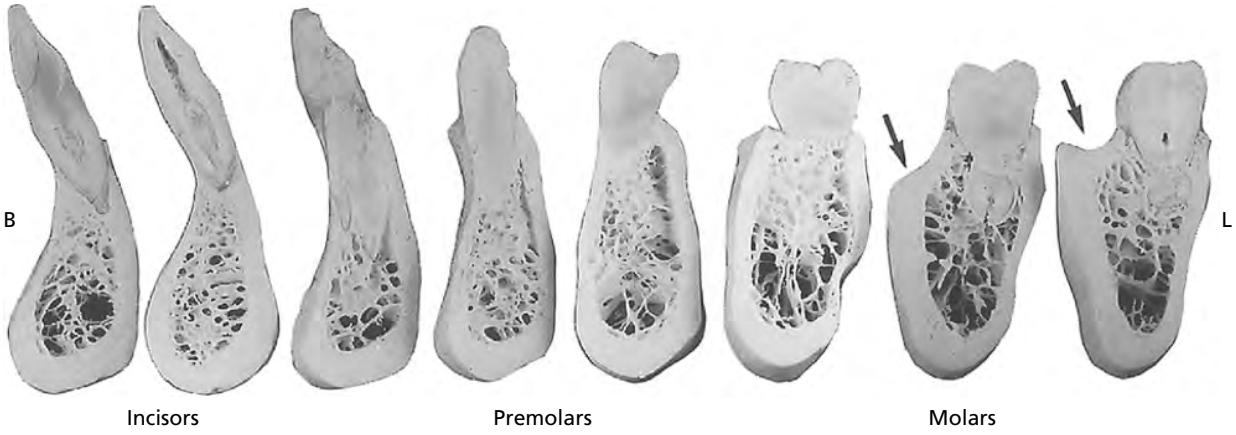

Fig. 1-76 Vertical sections through various regions of the mandibular dentition. The bone wall at the buccal (B) and lingual (L) aspects of the teeth varies considerably in thickness. The arrows indicate a shelf-like bone process at the buccal aspect of the second and third molars.

Vertical sections through various regions of the mandibular dentition show how the bone wall thickness varies considerably at the vestibular and lingual aspects of the teeth, for example from the premolar to the molar region (Fig. 1-76). Note, for instance, how the presence of the oblique line (*linea obliqua*) results in a shelf-like bone process at the buccal aspect of the second and third molars.

Microscopic anatomy

In a histologic section through the interproximal septum between two premolars, the dense alveolar bone proper is seen facing the periodontal ligament of the two teeth, while cancellous bone occupies the area between the alveolar bone proper (Fig. 1-77).

The mineralized bone in the furcation area, as well as in the interproximal septum (Fig. 1-77), is made up of lamellar bone (including circumferential lamellae, concentric lamellae osteons, and interstitial lamellae), while the bone marrow contains adipocytes and vascular structures (Fig. 1-78).

The mineralized bone facing the periodontal ligament, the alveolar bone proper or the bundle bone, is about 250–500 µm wide (Fig. 1-79). The alveolar bone proper is made up of lamellar bone including circumferential lamellae. As stated above, the alveolar bone proper, together with the periodontal ligament and the cementum, is responsible for the attachment between the tooth and the skeleton. Unlike the alveolar bone proper, the alveolar bone is a tissue of mesenchymal origin and it is not considered as part of the genuine attachment apparatus. Both alveolar bone and alveolar bone proper may, as a result of altered functional demands, undergo adaptive changes.

The composition of the hard tissue in the furcation area is illustrated in a schematic drawing in Fig. 1-80. The lamellar bone includes three brown osteons with a blood vessel in the centrally located Haversian canal. An interstitial lamella is located between the osteons and represents an old and partly remodeled osteon. The alveolar bone proper lines the lamellae and is represented by the dark lines. Sharpey's fibers insert into the alveolar bone proper.

Osteons constitute the building blocks of lamellar bone (Fig. 1-81). In the center of an osteon is the Haversian canal, which harbors a blood vessel. The space between the osteons is filled with so-called interstitial lamellae, remnants of older osteons. The osteons are not only structural, but also metabolic units. Thus, the nutrition of the bone cells (osteoblasts, osteocytes, osteoclasts) is secured by the blood

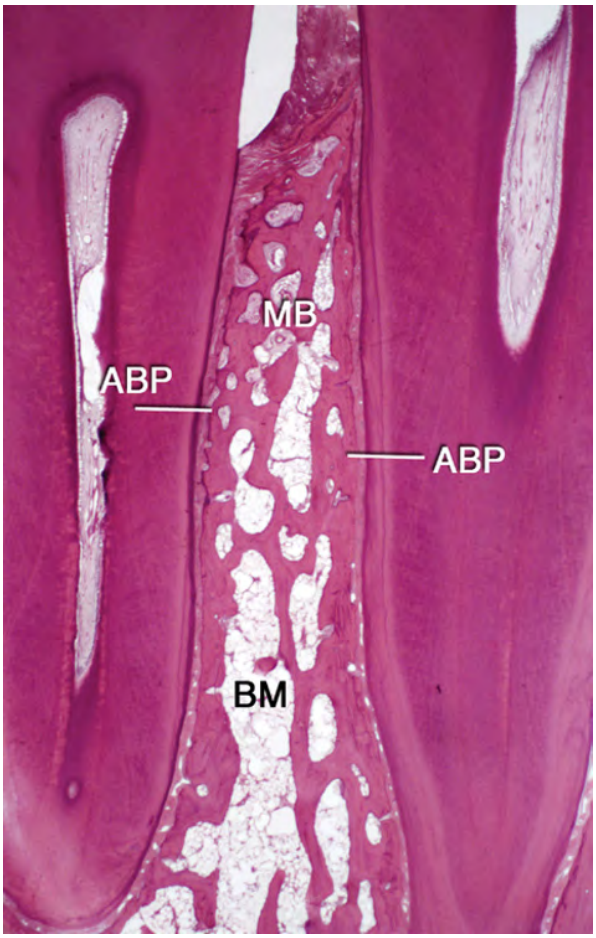

Fig. 1-77 Histologic section illustrating the bone of the interproximal septum between two premolars. The alveolar bone proper (ABP) is facing the periodontal ligament of the two teeth. BM, bone marrow; MB, mineralized matrix of cancellous bone.

vessels in the Haversian canals and the vessels in the so-called Volkmann canals.

The borderline region between the alveolar bone proper, the bundle bone, and the alveolar bone, highlights the characteristic features of the two types

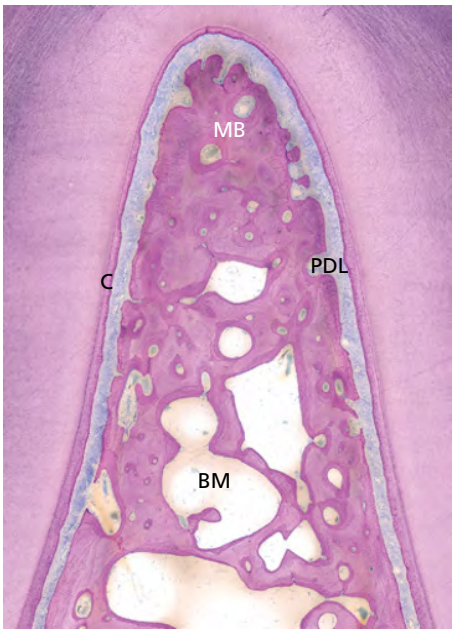

Fig. 1-78 Histologic section showing the bone tissue within the furcation area of a mandibular molar. BM, bone marrow; C, root cementum; MB, mineralized bone; PDL, periodontal ligament.

of bone (Fig. 1-82). The alveolar bone is lamellar in nature and thus composed of osteons, which include a Haversian canal with blood vessels in the center of each osteon. In contrast, the alveolar bone proper is not made up of osteons. It contains Sharpey's fibers, resting lines, and many osteocytes but no blood vessels. Also, the osteon contains a large number of osteocytes. They reside in lacunae within the lamellar bone and connect to each other via canaliculi that contain cytoplasmic protrusions of the osteocytes (Fig. 1-83). Canaliculi also connect the peripheral osteocytes with the osteoblasts on the bone surface (Fig. 1-84).

Osteocytes possess many cytoplasmic processes that radiate in different directions (Fig. 1-85) and

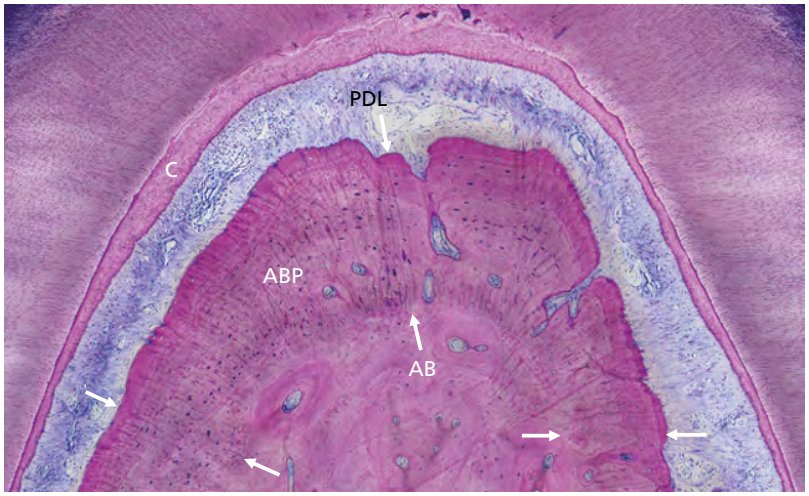

Fig. 1-79 Histologic section through the furcation area showing the alveolar bone proper (ABP) or the bundle bone (between arrows). AB, alveolar bone proper; C, root cementum; PDL, periodontal ligament.

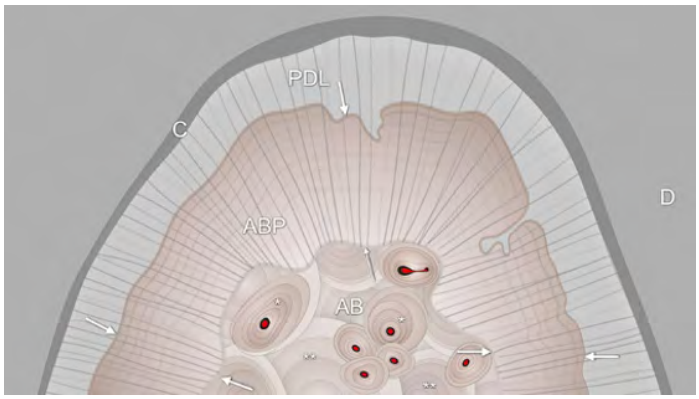

Fig. 1-80 The composition of the hard tissue of the furcation area in Fig. 1-79. Note the inserting Sharpey's fibers into the alveolar bone proper (ABP, arrows) and the package of osteons in the alveolar bone (AB). C, cementum; D, Dentin; PDL, periodontal ligament; *, concentric lamellae; **, interstitial lamellae.

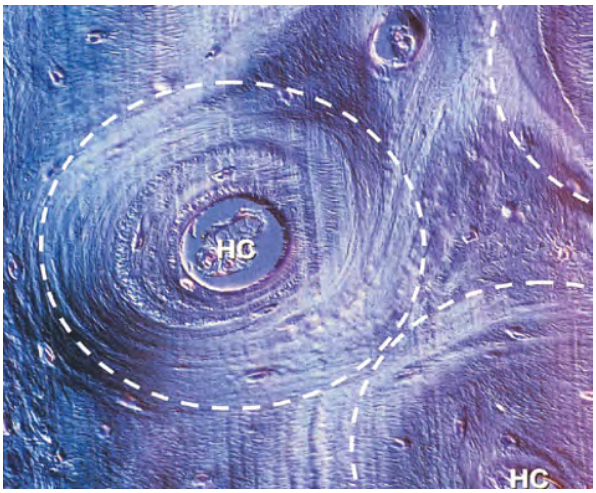

Fig. 1-81 Histologic section showing a portion of lamellar bone that contains osteons (white circles). Each osteon harbors a Haversian canal (HC) in the center.

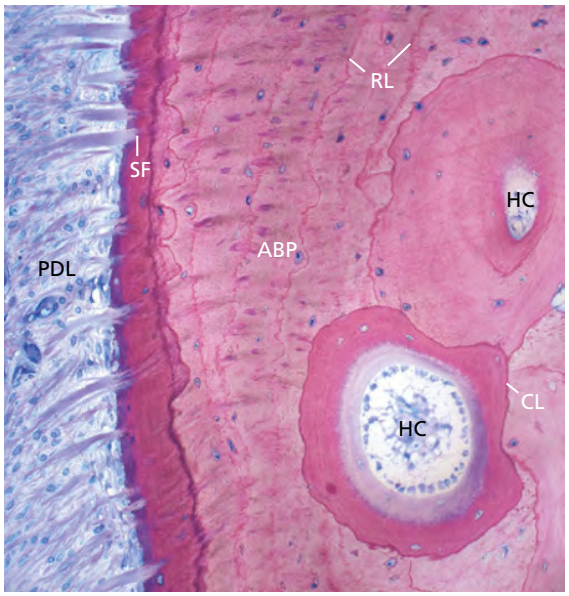

Fig. 1-82 Micrograph showing the borderline between the alveolar bone proper (ABP), the bundle bone, and the alveolar bone that includes an old and a new osteon. A Haversian canal (HC) is in the center of the osteons. The alveolar bone proper contains Sharpey's fibers (SF, striations), which in the lateral direction extend into the periodontal ligament (PDL). CL, cement line; RL, reversal lines.

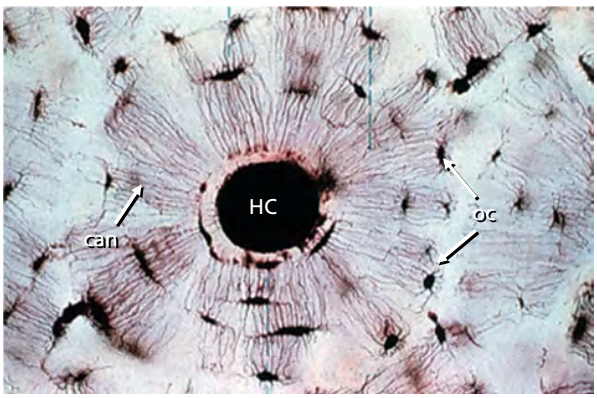

Fig. 1-83 Histologic sections showing numerous osteocytes (OC) that reside in lacunae in an osteon within the lamellar bone. The osteocytes connect via canaliculi (can) that contain cytoplasmic protrusions of the osteocytes. HC, Haversian canal.

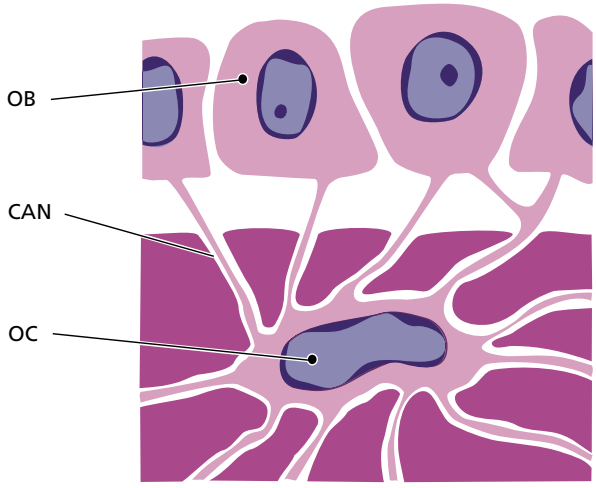

Fig. 1-84 How osteocytes (OC), present in lacunae in the mineralized bone matrix, also communicate with osteoblasts (OB) on the bone surface through canaliculi (CAN).

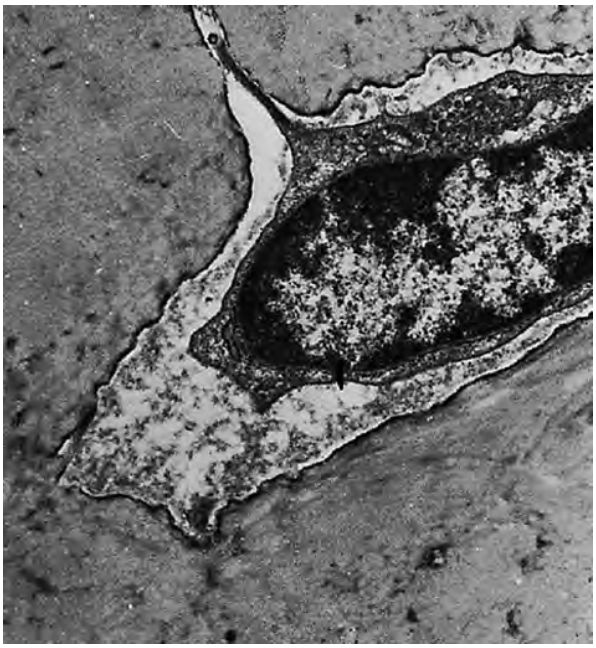

Fig. 1-85 Transmission electron micrograph showing an osteocyte residing in its lacuna, which is surrounded by the mineralized bone matrix.

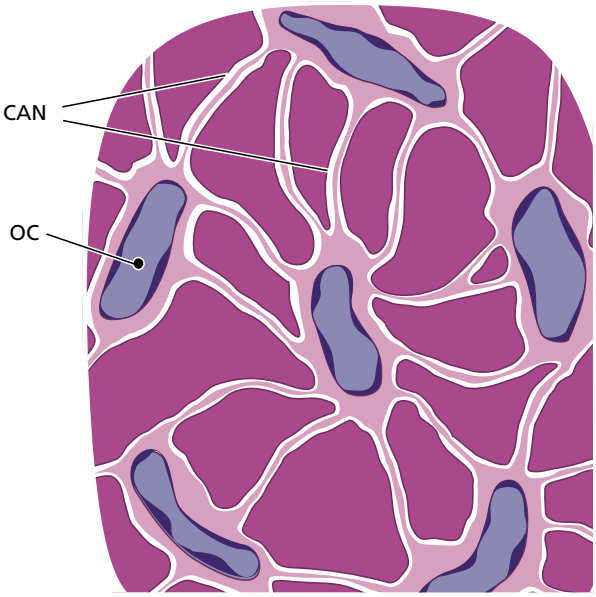

Fig. 1-86 How neighboring osteocytes (OC) communicate with each other via their cytoplasmic processes within the canaliculi (CAN) in bone.

communicate with each other (Fig. 1-86) and with osteoblasts or bone lining cells on the bone surface (Fig. 1-84) via long and delicate cytoplasmic processes situated within the canaliculi. The resulting canalicular–lacunar system is essential for cell metabolism by allowing diffusion of nutrients and waste products. The surface between the osteocytes, with their cytoplasmic processes on one side and the mineralized matrix on the other, is very large. It has been calculated that the interface between cells and matrix in a cube of bone, $10 \times 10 \times 10$ cm, amounts to approximately

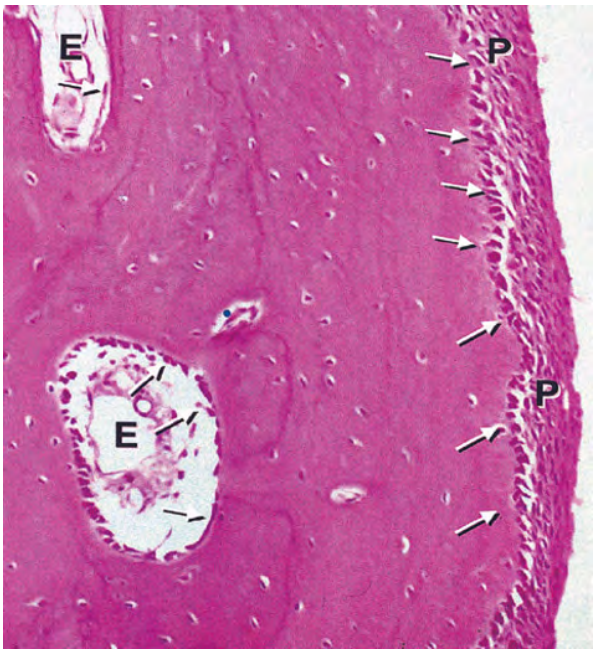

Fig. 1-87 Histologic section illustrating bone. Osteoblasts (arrows) are sandwiched between the bone matrix and the periosteum (P). The inner surface of bone, facing bone marrow, is covered with the endosteum (E).

250 m^2. This enormous surface of exchange serves as a regulator for, for example, serum calcium and serum phosphate levels via hormonal control mechanisms.

All active bone-forming sites harbor osteoblasts, which are sandwiched between the bone matrix and the periosteum (Fig. 1-87). On the "inner surface" of the bone, that is in the bone marrow space, there is an endosteum, which has features similar to those of the periosteum.

The alveolar bone is constantly renewed in response to functional demands. The teeth erupt and migrate in a mesial direction throughout life to compensate for attrition. Such movement of the teeth implies remodeling of the alveolar bone. During the process of remodeling, the bone trabeculae are continuously resorbed and reformed, and the cortical bone mass is removed and replaced by new bone. The resting line in the mineralized bone matrix documents phases of bone formation and rest (Fig. 1-88). During breakdown of the cortical bone, resorption canals are formed by osteoclasts. Such canals, which contain a blood vessel in the center, are subsequently refilled with new bone by the formation of lamellae arranged in concentric layers around the blood vessel (Fig. 1-88).

The resorption of bone is always associated with *osteoclasts* (Fig. 1-89). These cells are large, multinucleated cells specialized in the breakdown of matrix and minerals. The osteoclasts are hematopoetic cells (derived from monocytes in the bone marrow). Hard tissue resorption occurs by the release of acid products (lactic acid, etc.), which form an acidic environment in which the mineral salts become dissolved. Remaining organic substances are eliminated by

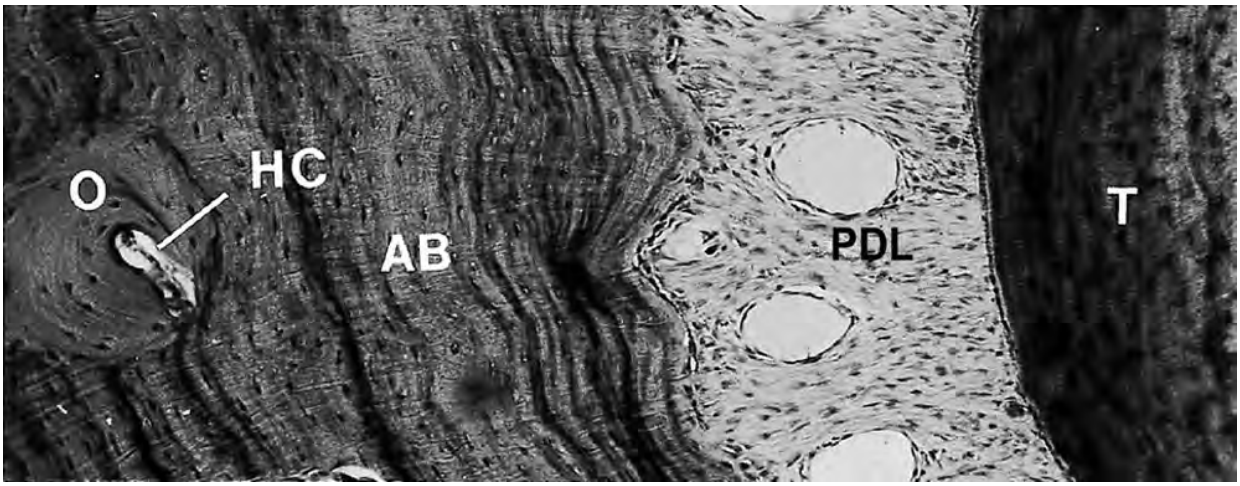

Fig. 1-88 Micrograph of a horizontal section illustrating the tooth attachment apparatus consisting of the tooth (T), the periodontal ligament (PDL), and alveolar bone proper (AB). Numerous resting lines in the alveolar bone proper (AB) document phases of active bone formation and rest. A new osteon (O) with a central Haversian canal (HC) demarcates the border to the lamellar alveolar bone.

proteolytic enzymes and osteoclastic phagocytosis. Actively resorbing osteoclasts adhere to the bone surface through receptors and produce lacunar pits called *Howship's lacunae*. The osteoclasts are mobile and capable of migrating over the bone surface.

Bone multicellular units are always present in bone tissue undergoing active remodeling (Fig. 1-90). The bone multicellular unit has one resorption front characterized by the presence of osteoclasts and one formation front characterized by the presence of osteoblasts.

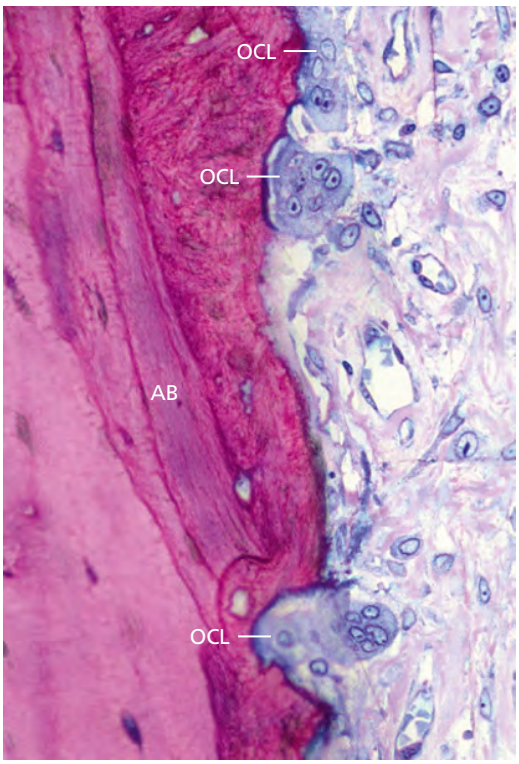

Fig. 1-89 Micrograph illustrating three resorption sites lined with osteoclasts (OCL) on the surface of the alveolar bone (AB).

Both the cortical and cancellous alveolar bone are constantly undergoing remodeling (i.e. resorption followed by formation) in response to tooth drifting and changes in functional forces acting on the teeth. Figure 1-91 illustrates the remodeling sequence. Remodeling of the trabecular bone starts with resorption of the bone surface by osteoclasts (Fig. 1-91a). After a short period, osteoblasts start depositing new bone (Fig. 1-91b) and finally a new bone multicellular unit is formed, clearly delineated by a reversal line (Fig. 1-91c).

Collagen fibers of the periodontal ligament insert in the mineralized bone which lines the wall of the tooth socket (Fig. 1-92). This bone, called alveolar bone proper or bundle bone, has a high turnover rate. The portions of the collagen fibers which are inserted inside the bundle bone are called Sharpey's fibers. These fibers are mineralized at their periphery, but often have a non-mineralized central core. The collagen fiber bundles inserting in the bundle bone generally have a larger diameter and are less numerous than the corresponding fiber bundles in the cementum on the opposite side of the periodontal ligament. Individual bundles of fibers can be followed all the way from the alveolar bone to the cementum. However, despite being in the same bundle of fibers, the collagen adjacent to the bone is always less mature than that adjacent to the cementum. The collagen on the tooth side has a low turnover rate. Thus, while the collagen adjacent to the bone is renewed relatively rapidly, the collagen adjacent to the root surface is renewed slowly or not at all.

Blood supply of the periodontium

The blood supply of the teeth and the periodontal tissues is illustrated in Fig. 1-93. The *dental artery* (arteria dentalis), which is a branch of the *superior* or *inferior* alveolar artery (arteria alveolaris inferior), dismisses

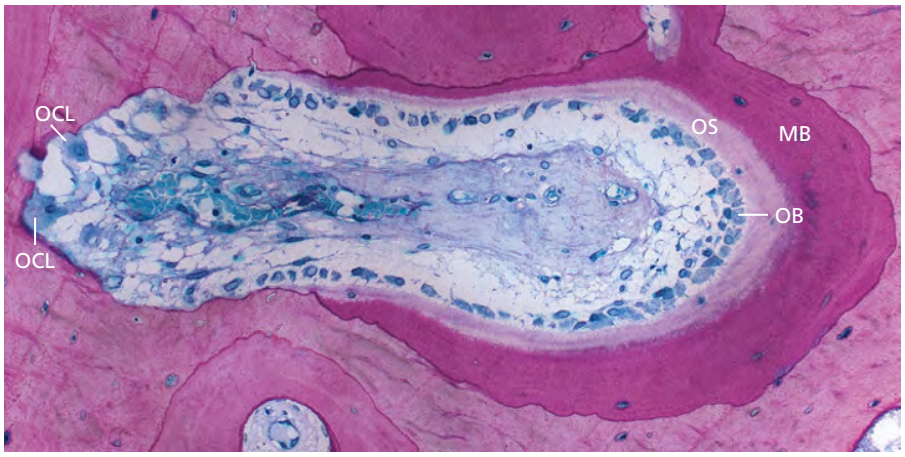

Fig. 1-90 Histologic section of compact bone illustrating a bone multicellular unit characterized by the presence of osteoclasts (OCL) at the resorption front and osteoblasts (OB) at the formation front. MB, mineralized bone matrix; OS, osteoid.

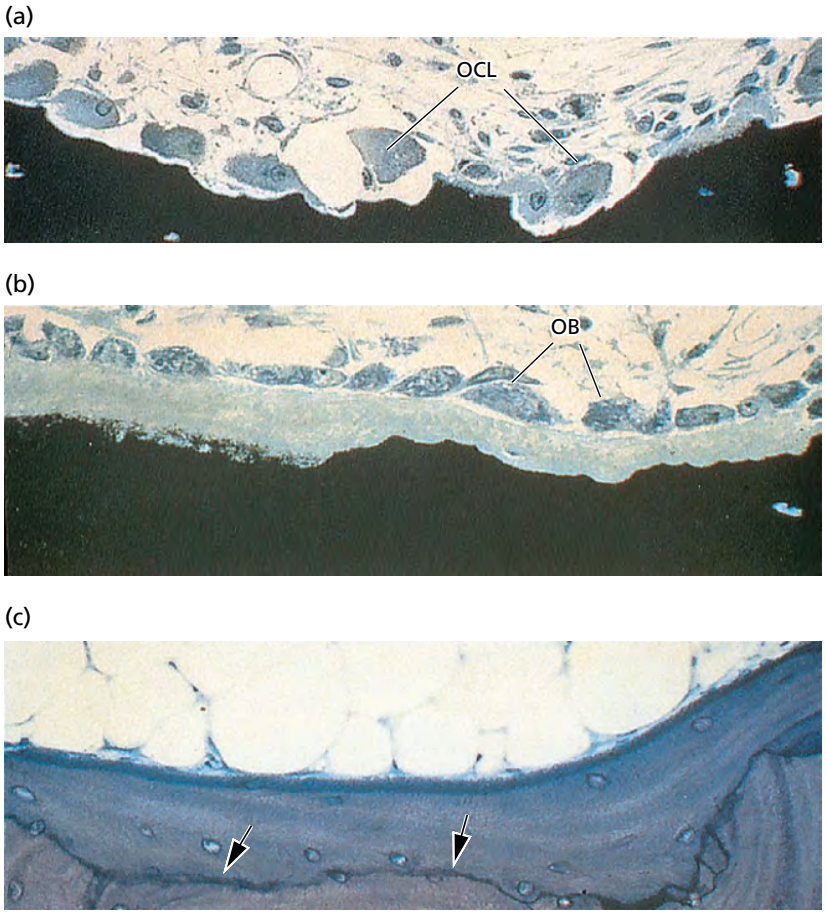

Fig. 1-91 Histologic sections illustrating the sequence of bone remodeling with (a) bone resorption by osteoclasts (OCL), (b) bone matrix deposition and mineralization by osteoblasts (OB), and (c) rest. A reversal line (cement line) (arrows) demarcates the new from the old bone.

the *intraseptal artery* (arteria interseptalis) before it enters the tooth socket. The terminal branches of the *intraseptal artery* (*rami perforantes*) penetrate the alveolar bone proper in canals at all levels of the socket (see Fig. 1-77). They anastomose in the periodontal ligament space, together with blood vessels originating from the apical portion of the periodontal ligament and with other terminal branches from the intraseptal artery. Before the dental artery enters the root canal it puts out branches which supply the apical portion of the periodontal ligament.

The blood supply of the teeth and the periodontal tissues is illustrated in Fig. 1-94. The gingiva receives its blood supply mainly through *supraperiosteal* blood vessels which are terminal branches of the *sublingual artery* (arteria sublingualis), the *mental artery* (arteria mentalis), the *buccal artery* (arteria buccalis), the *facial artery* (arteria facialis), the *greater palatine artery*

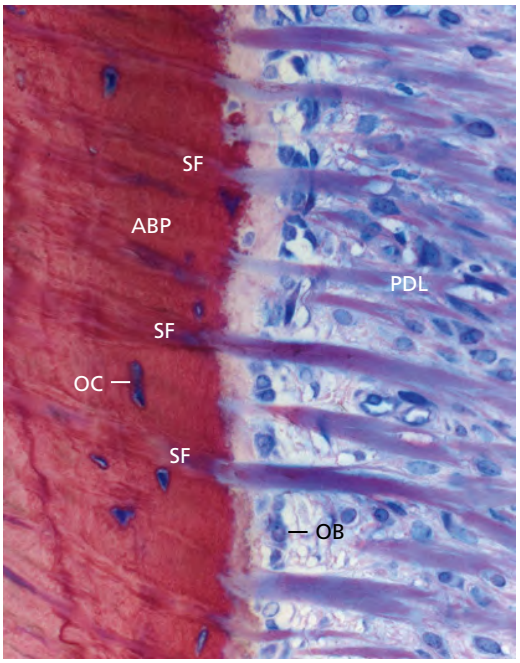

Fig. 1-92 Micrograph illustrating the insertion of periodontal ligament (PDL) fibers in the alveolar bone proper (ABP) or bundle bone that lines the wall of the tooth socket. Sharpey's fibers (SF) traverse the bundle bone, osteoblasts (OB) line the bone surface, and osteocytes (OC) are present in their lacunae surrounded by the mineralized bone matrix.

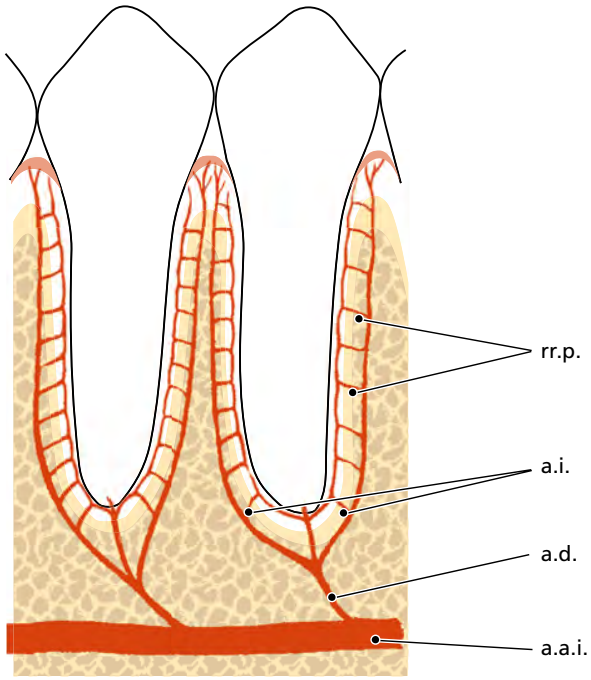

Fig. 1-93 The blood supply to the teeth and the periodontal tissues. a.a.i., superior or inferior alveolar artery; a.d., dental artery; a.i., intraseptal artery; rr.p., terminal branches of the intraseptal artery.

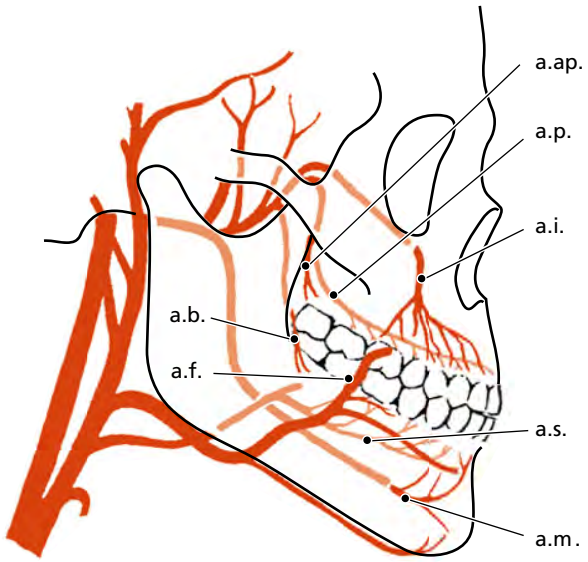

Fig. 1-94 The blood supply to the gingivae. a.ap., posterior superior dental artery; a.b., buccal artery; a.f., facial artery; a.i., infraorbital artery; a.m., mental artery; a.p., greater palatine artery; a.s., sublingual artery.

(arteria palatina major), the *infraorbital artery* (arteria infraorbitalis), and the *posterior superior dental artery* (arteria dentalis superior posterioris). The greater palatine artery, which is a terminal branch of the *ascending palatine artery* (from the *maxillary*, "internal maxillary", artery), runs through the *greater palatine canal* to the palate (Fig. 1-95). As this artery runs in a frontal direction, it puts out branches which supply the gingiva and the masticatory mucosa of the palate.

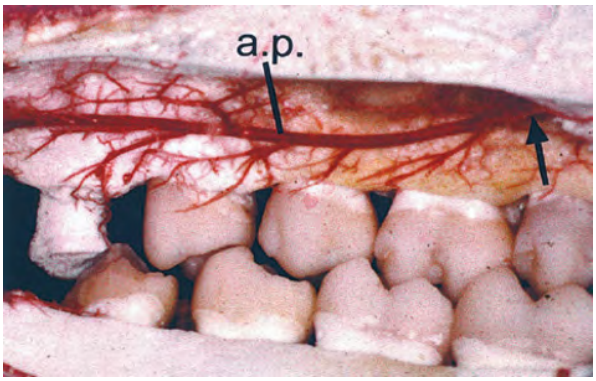

Fig. 1-95 The course of the greater palatine artery (a.p.) in a monkey specimen that was perfused with plastic at sacrifice. Subsequently, the soft tissue was dissolved. The arrow indicates the greater palatine canal.

The various arteries are often considered to supply certain well-defined regions of the dentition. In reality, however, there are numerous anastomoses present between the different arteries (Fig. 1-96). Thus, the *entire system of blood vessels*, rather than individual groups of vessels, should be regarded as the unit supplying the soft and hard tissues of the maxilla and the mandible.

The blood supply of the vestibular gingiva is mainly through *supraperiosteal* blood vessels (Fig. 1-97). Another sample preparation demonstrates that blood vessels originating from vessels in the periodontal ligament pass the alveolar bone crest and contribute to the blood supply of the free gingiva (Fig. 1-98).

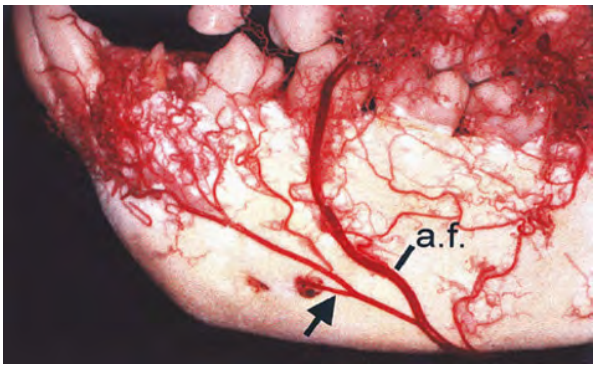

Fig. 1-96 An anastomosis (arrow) between the facial artery (a.f.) and the blood vessels of the mandible.

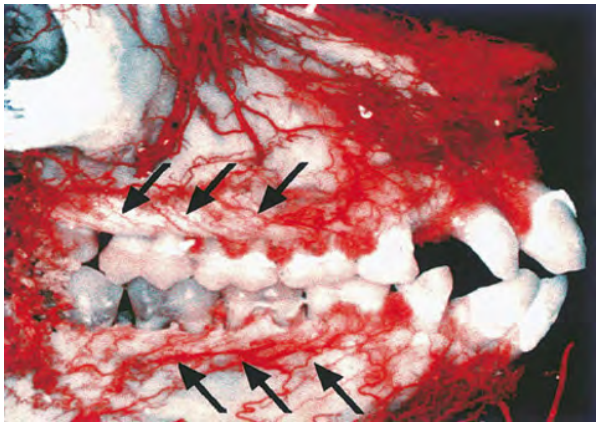

Fig. 1-97 Illustration of a vestibular segment of the maxilla and mandible from a monkey that was perfused with plastic at sacrifice. Note that the blood supply of the vestibular gingiva is mainly through supraperiosteal blood vessels (arrows).

In a cleared specimen (Fig. 1-99), the blood vessel distribution is clearly visible. During their course towards the free gingiva, the supraperiosteal blood vessels put forth numerous branches to the *subepithelial plexus*, located immediately beneath the oral gingival epithelium of the free and attached gingiva. This subepithelial plexus in turn yields thin *capillary loops* to each of the connective tissue papillae projecting into the oral gingival epithelium (seen at higher magnification in Fig. 1-100). The number of such capillary loops is constant over a very long time and is not altered by application of epinephrine or histamine to the gingival margin. This implies that the blood vessels of the lateral portions of the gingiva, even under normal circumstances, are fully utilized and that the blood flow to the free gingiva is regulated entirely by velocity alterations. In the free gingiva, the supraperiosteal blood vessels anastomose with blood vessels from the periodontal ligament and the bone. Beneath the junctional epithelium is a plexus of blood vessels termed the *dentogingival plexus*. The blood vessels in this plexus have a thickness of approximately 40 µm, which means that they are mainly venules. In healthy gingiva, no capillary loops occur in the dentogingival plexus. When cut parallel to the subsurface of the

Fig. 1-98 Blood vessels (arrows) originating from vessels in the periodontal ligament pass the alveolar bone crest and contribute to the blood supply of the free gingiva.

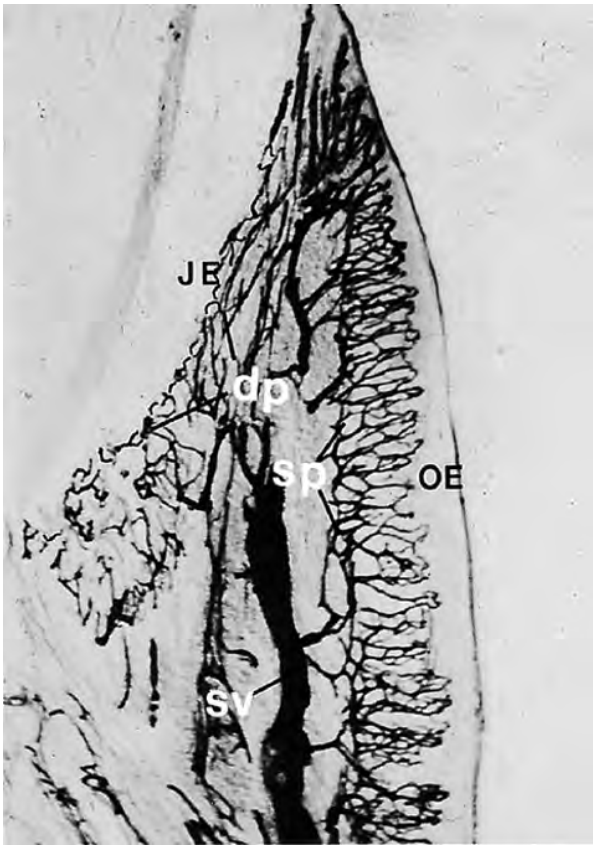

Fig. 1-99 Blood vessels in the gingiva in a specimen from a monkey perfused with ink at the time of sacrifice. Subsequently, the specimen was treated to make the tissue transparent (cleared specimen). The tooth is to the left. dp, dentogingival plexus; JE, junctional epithelium; OE, oral gingival epithelium; sp, subepithelial plexus; sv, supraperiosteal blood vessels.

junctional epithelium, it can be seen that the dentogingival plexus consists of a fine-meshed network of blood vessels (Fig. 1-101).

A summary of the blood vessels in the free gingiva is shown in a three-dimensional schematic drawing

Fig. 1-100 Higher magnification of a cleared specimen illustrating how the subepithelial plexus (s.p.), beneath the oral gingival epithelium of the free and attached gingiva, yields thin capillary loops to each connective tissue papilla. These capillary loops have a diameter of approximately 7 µm, which means they are the size of true capillaries.

Fig. 1-101 Higher magnification of a cleared specimen illustrating the dentogingival plexus in a section parallel to the subsurface of the junctional epithelium. The dentogingival plexus consists of a fine-meshed network of blood vessels. In the upper portion of the image, capillary loops belonging to the subepithelial plexus can be seen beneath the oral sulcular epithelium.

(Fig. 1-102). As stated earlier, the main blood supply of the free gingiva derives from the *supraperiosteal* blood vessels which, in the gingiva, anastomose with blood vessels from the *alveolar bone* and *periodontal ligament*. The subepithelial plexus of vessels adjacent to the oral gingival epithelium can be clearly seen. Likewise, the dentogingival plexus can be seen beneath the junctional epithelium. Under normal conditions, the dentogingival plexus comprises a fine-meshed network without capillary loops.

The blood vessels of the periodontal ligament derive from (1) branches of the dental artery, (2) branches of the interalveolar and interradicular arteries, and (3) the supraperiosteal arteries. Figure 1-103 illustrates how the vessels arising from the intraseptal artery in the alveolar bone run through the Volkmann's canals into the periodontal ligament, where they anastomose. In a section cut parallel to the root surface (Fig. 1-104), it can be seen that, after entering the periodontal ligament, the blood vessels anastomose and form a polyhedral network which surrounds the root like a stocking. The majority of the blood vessels in the periodontal ligament are found close to the alveolar bone. In the coronal portion of the periodontal ligament, blood vessels run in a coronal direction, passing the alveolar bone crest, into the free gingiva (see also Fig. 1-98).

The blood supply of the periodontium is summarized in a schematic drawing (Fig. 1-105). The blood

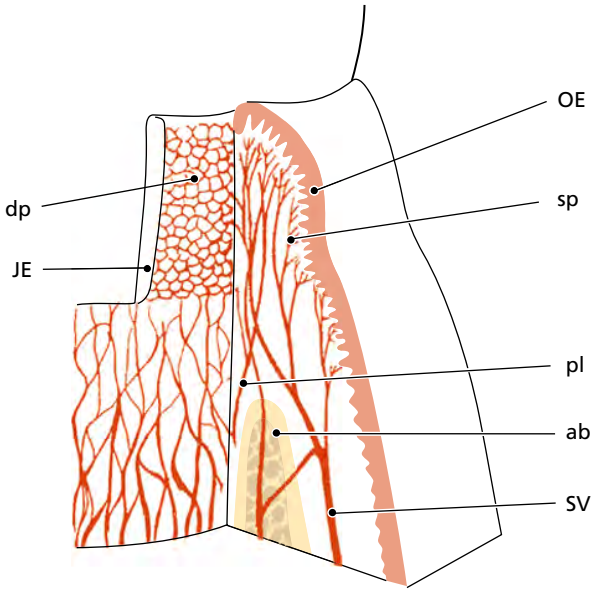

Fig. 1-102 The blood supply to the free gingiva. The main blood supply to the free gingiva derives from the supraperiosteal blood vessels (SV). To the right, the oral gingival epithelium (OE) is depicted with its underlying subepithelial plexus of vessels (sp). To the left, beneath the junctional epithelium (JE), the dentogingival plexus (dp) can be seen, which, under normal conditions, comprises a fine-meshed network without capillary loops. ab, alveolar bone; pdl, periodontal ligament.

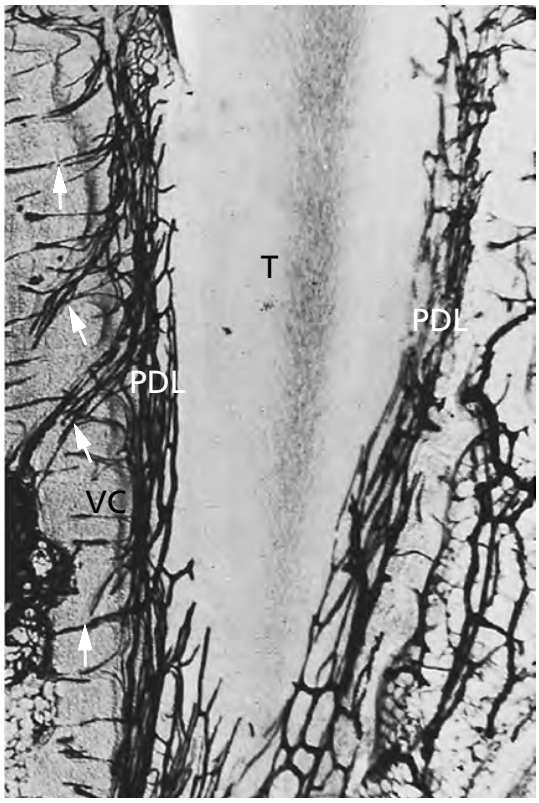

Fig. 1-103 Cleared specimen through a tooth (T) with its periodontium. Blood vessels (perforating rami; arrows) arising from the intraseptal artery in the alveolar bone run through canals in the socket wall, called Volkmann's canals (VC), into the periodontal ligament (PDL), where they anastomose.

Fig. 1-104 Cleared specimen illustrating the blood vessels in the periodontal ligament in a tissue section cut parallel to the root surface. After entering the periodontal ligament, the blood vessels (perforating rami; arrows) anastomose and form a polyhedral network which surrounds the root like a stocking.

vessels in the periodontal ligament form a polyhedral network surrounding the root. The free gingiva receives its blood supply from supraperiosteal blood vessels, the blood vessels of the periodontal ligament, and the blood vessels of the alveolar bone.

The circulatory system (blood vessels and lymphatic vessels) is key to the transport of cells and vital biomolecules and nutrients throughout the body. Beside transport inside vessels, there is the so-called *extravascular* circulation through which nutrients and other substances are carried to the individual cells and metabolic waste products are removed from the tissue (Fig. 1-106). In the arterial end of the capillary a hydraulic pressure of approximately 35 mmHg is maintained as a result of the pumping function of the heart. Since the hydraulic pressure is higher than the osmotic pressure in the tissue (approximately 30 mmHg), transportation of substances will occur from the blood vessels to the extravascular space. In the venous end of the capillary system, the hydraulic pressure has decreased to approximately 25 mmHg (i.e. 5 mmHg lower than the osmotic pressure in the tissue). This allows transportation of substances from the extravascular space to the blood vessels. Thus, the difference between the hydraulic pressure and the osmotic pressure results in transportation of substances from the blood vessels to the extravascular space in the arterial part of the capillary, while in the venous part, transportation of substances occurs from the extravascular space to the blood vessels. An extravascular circulation is hereby established.

Lymphatic system of the periodontium

The smallest lymph vessels, the *lymph capillaries*, form an extensive network in the connective tissue. The wall of the lymph capillary consists of a single layer of endothelial cells. For this reason, such capillaries are difficult to identify in an ordinary histologic section. The lymph is absorbed from the tissue fluid through the thin walls into the lymph capillaries. From the capillaries, the lymph passes into larger lymph vessels which are often in the vicinity of corresponding blood vessels. Before the lymph enters the blood stream, it passes through one or more *lymph nodes* in which the lymph is filtered and supplied with lymphocytes. The lymph vessels are like veins in that they have valves. The lymphatic system of the periodontium is illustrated in Fig. 1-107. The lymph from the periodontal tissues drains to the lymph nodes of the head and neck. The labial and lingual gingiva of the mandibular incisor region is drained to the *submental lymph nodes*. The palatal gingiva of the maxilla is drained to the *deep cervical lymph nodes*. The buccal

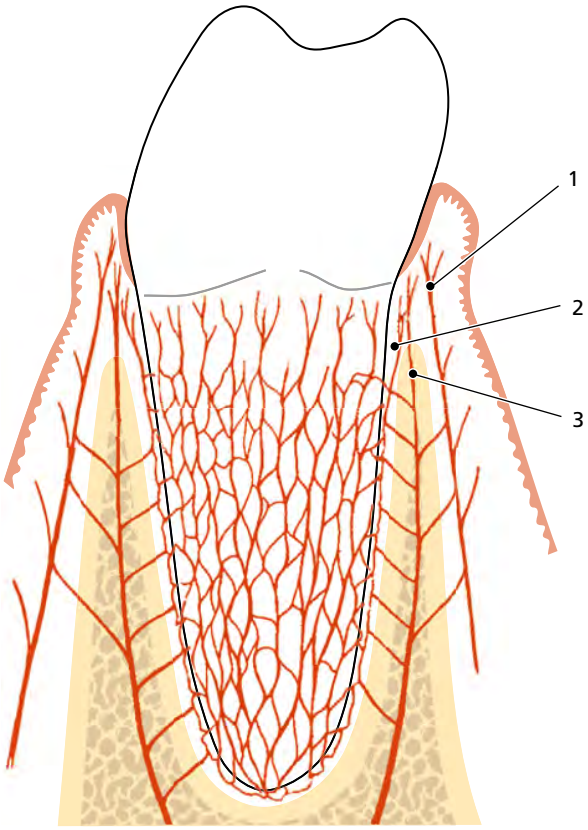

Fig. 1-105 The blood supply of the periodontium. The blood vessels in the periodontal ligament form a polyhedral network surrounding the root. Note that the free gingiva receives its blood supply from (1) supraperiosteal blood vessels, (2) the blood vessels of the periodontal ligament, and (3) the blood vessels of the alveolar bone.

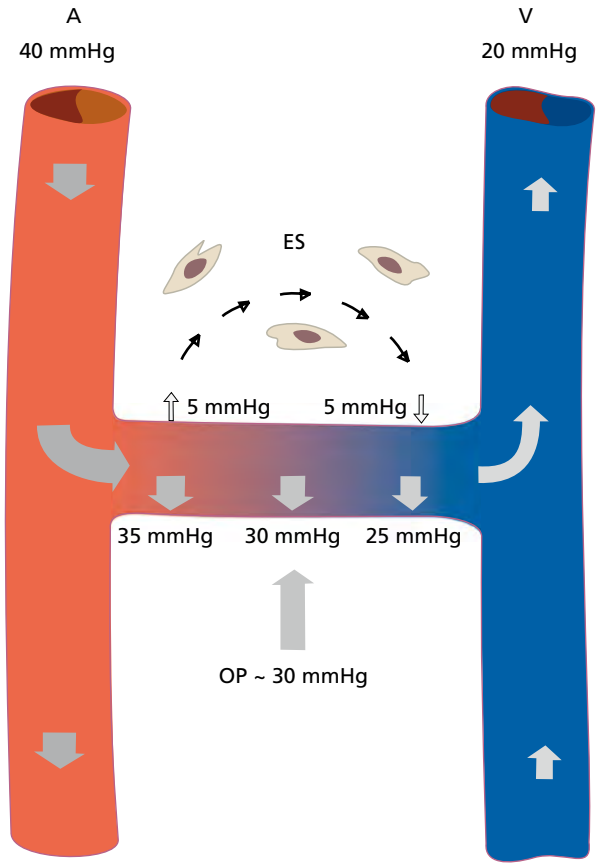

Fig. 1-106 The so-called extravascular circulation (small arrows) through which nutrients and other substances are carried to the individual cells and metabolic waste products are removed from the tissue. A, arterial end of capillary; ES, extracellular space; OP, osmotic pressure; V, venous end of capillary.

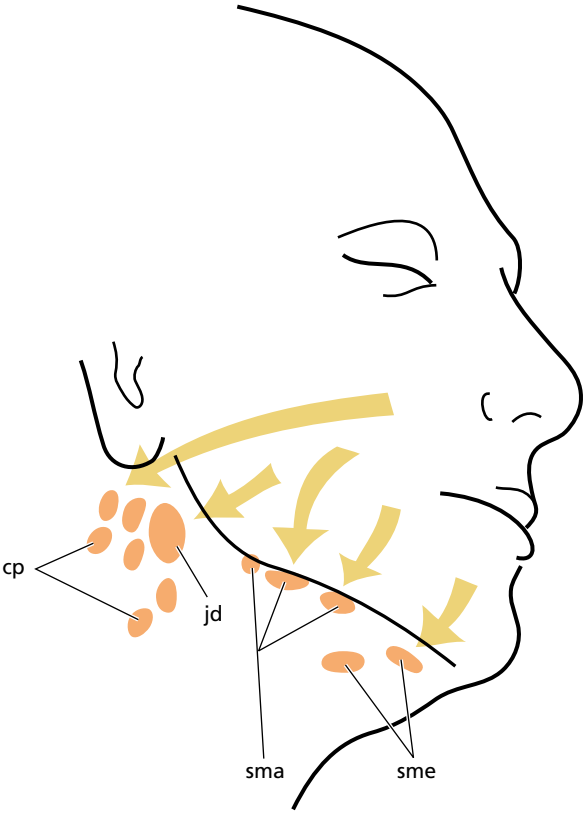

Fig. 1-107 The lymph system in the periodontium. cp, deep cervical lymph nodes; jd, jugulodigastric lymph node; sma, submandibular lymph nodes; sme, submental lymph nodes.

gingiva of the maxilla and the buccal and lingual gingiva in the mandibular premolar–molar region are drained to *submandibular lymph nodes*. Except for the third molars and mandibular incisors, all teeth with their adjacent periodontal tissues are drained to the submandibular lymph nodes. The third molars are drained to the *jugulodigastric lymph node* and the mandibular incisors to the *submental lymph nodes*.

Nerves of the periodontium

Like other tissues in the body, the periodontium contains receptors which record pain, touch, and pressure (*nociceptors* and *mechanoreceptors*). In addition to the different types of sensory receptors, nerve components are found innervating the blood vessels of the periodontium. Nerves recording pain, touch, and pressure have their trophic center in the *semilunar ganglion* and are brought to the periodontium via the *trigeminal nerve* and its end branches. Owing to the presence of receptors in the periodontal ligament, small forces applied on the teeth may be identified. For example, the presence of a very thin (10–30 µm) metal foil strip placed between the teeth during occlusion can readily be identified. It is also well known that a movement which brings the teeth of the mandible in contact with the occlusal surfaces of the maxillary teeth is arrested reflexively and altered into

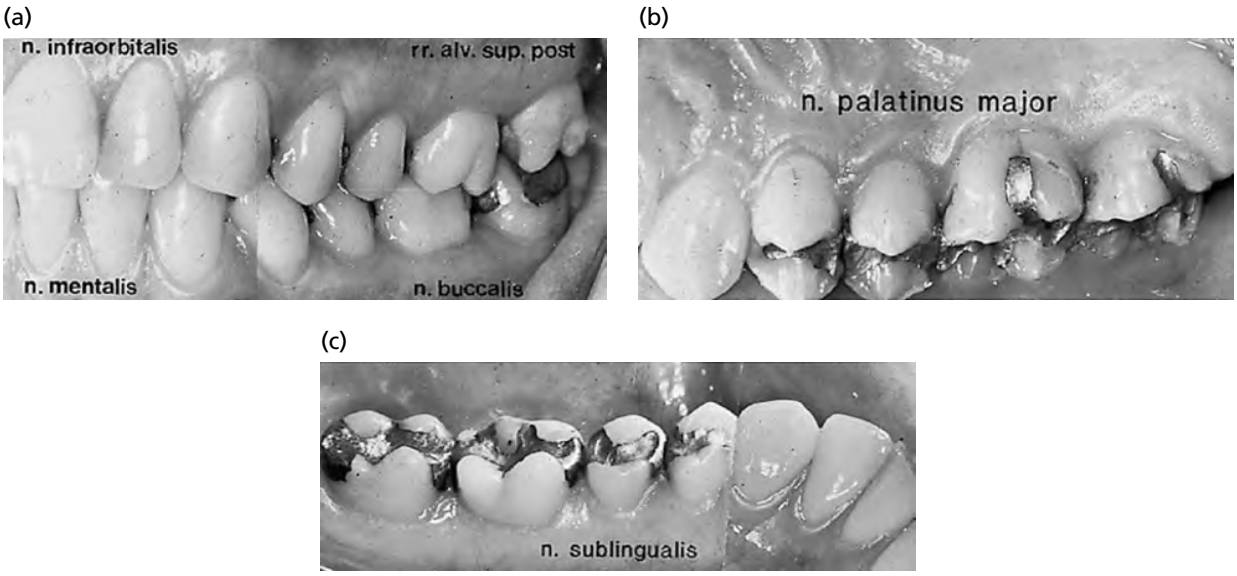

Fig. 1-108 The various regions of the gingiva that are innervated by end branches of the trigeminal nerve. (a) Innervation of the gingiva on the labial aspect of maxillary incisors, canines, and premolars by superior labial branches from the infraorbital nerve (n. infraorbitalis), innervation of the buccal gingiva in the maxillary molar region by branches from the posterior superior dental nerve (rr. alv. sup. post), innervation of the gingiva at the labial aspect of mandibular incisors and canines by the mental nerve (n. mentalis), and innervation of the gingiva at the buccal aspect of the molars by the buccal nerve (n. buccalis). (b) Innervation of the palatal gingiva by the greater palatal nerve (n. palatinus major), except for the area of the incisors, which is innervated by the long sphenopalatine nerve (n. pterygopalatini). (c) Innervation of the lingual gingiva in the mandible by the sublingual nerve (n. sublingualis), which is an end branch of the lingual nerve.

an opening movement if a hard object is detected in the chew. Thus, the receptors in the periodontal ligament, together with the proprioceptors in muscles and tendons, play an essential role in the regulation of chewing movements and chewing forces.

The various regions of the gingiva that are innervated by end branches of the trigeminal nerve are illustrated in Fig. 1-108. The gingiva on the labial aspect of maxillary incisors, canines, and premolars is innervated by *superior labial branches* from the *infraorbital nerve* (Fig. 1-108a). The buccal gingiva in the maxillary molar region is innervated by branches from the *posterior superior dental nerve* (Fig. 1-108a). The palatal gingiva is innervated by the *greater palatal nerve* (Fig. 1-108b), except for the area of the incisors, which is innervated by the *long sphenopalatine nerve*. The lingual gingiva in the mandible is innervated by the *sublingual nerve* (Fig. 1-108c), which is an end branch of the *lingual nerve*. The gingiva at the labial aspect of mandibular incisors and canines is innervated by the *mental nerve*, and the gingiva at the buccal aspect of the molars by the *buccal nerve* (Fig. 1-108a). The innervation areas of these two nerves frequently overlap in the premolar region. The teeth in the mandible, including their periodontal ligaments, are innervated by the *inferior alveolar nerve*, while the teeth in the maxilla are innervated by the *superior alveolar plexus*.

The small nerves of the periodontium follow almost the same course as the blood vessels. The nerves to the gingiva run in the tissue superficial to the periosteum and put out several branches to the oral gingival epithelium on their way towards the free gingiva. The nerves enter the periodontal ligament apically through branches of the dental nerve and laterally through the perforations in the socket wall (Volkmann's canals) (see Fig. 1-103). In the periodontal ligament, the nerves join larger bundles that take a course parallel to the long axis of the tooth. Figure 1-109 shows small nerves

Fig. 1-109 Photomicrograph showing small nerves (arrows) that have emerged from larger bundles of ascending nerves in order to supply certain parts of the periodontal ligament tissue.

that have emerged from larger bundles of ascending nerves in order to supply certain parts of the periodontal ligament tissue. Various types of neural terminations, such as free nerve endings and Ruffini's corpuscles, have been identified in the periodontal ligament.

Acknowledgment

We thank the following for contributing to the illustrations in Chapter 1: M. Listgarten, R.K. Schenk, H.E. Schroeder, K.A. Selvig, K. Josephsen, A. Sculean, T. Karring, and L. Furquim.

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Chapter 2

Bone as a Living Organ

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Introduction

Bone is a complex organ composed of multiple specialized tissues (osseous, periosteum/endosteum, and bone marrow) that act synergistically and serve multiple functions (Fig. 2-1). Its composition allows the bone tissue to: (1) provide structural and mechanical stability, (2) protect highly sensitive organs from external forces, and (3) participate as a reservoir of cells and minerals that contribute to systemic homeostasis of the body. Therefore, the concept of "bone as a living organ", integrates the structurally dynamic nature of bone with its capacity to orchestrate multiple mechanical and metabolic functions; these characteristics have important local and systemic implications (McCauley & Somerman 2012). The structural and functional properties of bone are modulated by many factors (e.g. biochemical, hormonal, cellular, biomechanical) and ultimately, it is these influences that determine bone quality in a given context (Ammann & Rizzoli 2003; Marotti & Palumbo 2007; Bonewald & Johnson 2008; Ma *et al*. 2008). The purpose of this chapter is to provide foundational knowledge of bone development, structure, function, and homeostasis.

Development

During embryogenesis, the skeleton forms by either a direct or indirect ossification process. In direct ossification, termed *intramembranous osteogenesis*, mesenchymal progenitor cells condensate and undergo direct differentiation into osteoblasts (Nanci & Moffat 2012). This process occurs to form the mandible, maxilla, flat bones of the skull, and clavicles.

In contrast, in indirect ossification, termed *endochondral osteogenesis*, bone formation is initiated through a cartilage template, which serves as an anlage that is gradually replaced by bone. The mandibular condyle, long bones of the skeleton, and vertebrae form through this cartilage-dependent growth process (Ranly 2000) (Fig. 2-2).

Intramembranous bone formation

During intramembranous osteogenesis, an ossification center develops through mesenchymal condensation. As the collagen-rich extracellular matrix (ECM) develops and matures, osteoprogenitor cells undergo further osteoblastic differentiation. On the outer surfaces of the ossification center, a fibrous

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

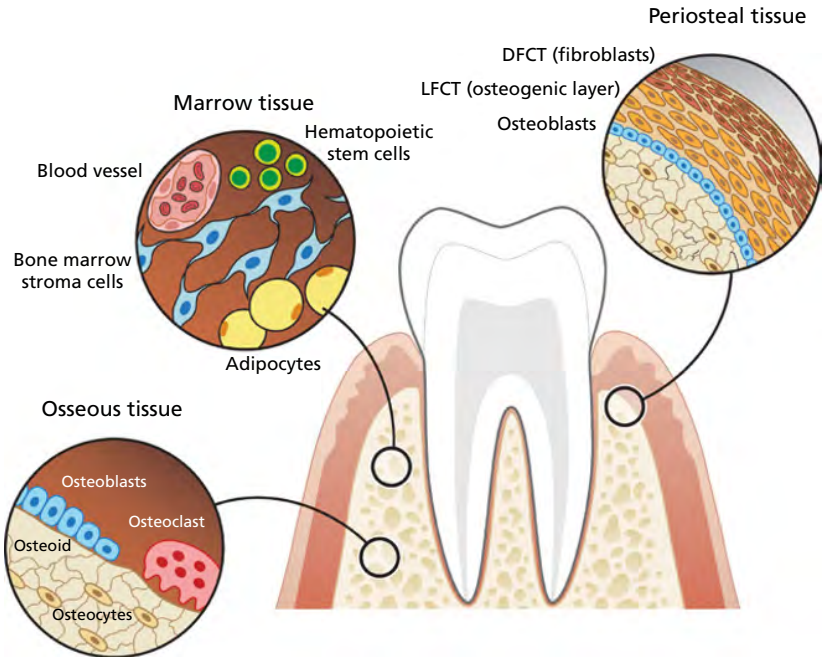


Fig. 2-1 Bone as an organ. The bone organ encompasses a number of complex tissues that synergize during health to execute a number of functions. It serves as a source of stem cells and a reservoir of minerals and other nutrients; it protects a number delicate organs; and it acts as a mechanosensoring unit that adapts to the environment and individual demands. This figure highlights three main tissues and their respective cells that are involved in these roles and the maintenance of the structure and function of bone as an organ. DFCT, dense fibrous connective tissue; LFCT, loose fibrous connective tissue.

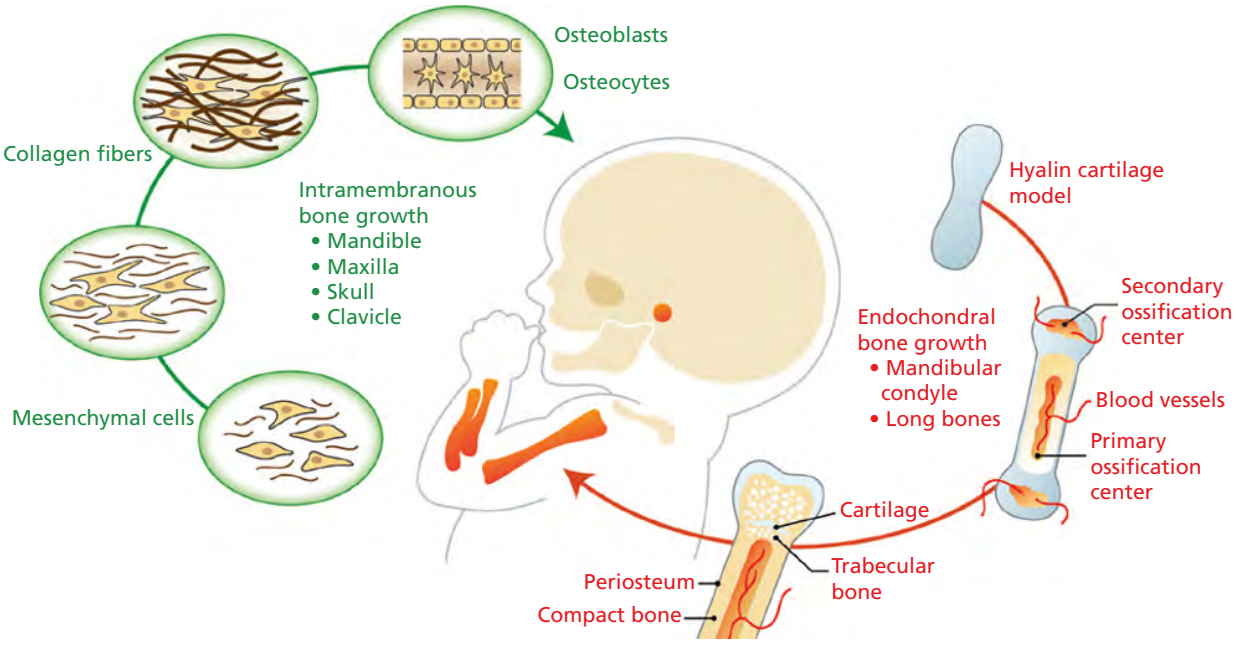


Fig. 2-2 Bone development. There are two types of process involved in bone development: intramembranous ossification (green arrow) and endochondral ossification (orange arrow). They primarily differ in the presence of a cartilaginous template during endochondral bone growth. During intramembranous osteogenesis, an ossification center develops through mesenchymal condensation. As the collagen-rich extracellular matrix develops and matures, osteoprogenitor cells undergo further osteoblastic differentiation. A subpopulation of osteoblasts become embedded in the mineralizing matrix and gives rise to the osteocyte lacuno-canalicular network. Within the craniofacial complex, most bones develop and grow through this mechanism. On the other hand, long bones within the skeleton and the mandibular condyle initially develop through the formation of a cartilaginous template that mineralizes and is later resorbed by osteoclasts and replaced by bone. The endochondral bone growth process leads to the formation of primary and secondary ossification centers that are separated by a cartilaginous structure known as the growth plate. As bone develops and matures through these two processes, structurally distinct areas of compact bone and trabecular bone are formed and maintained through similar bone remodeling mechanisms.

periosteum forms over a layer of osteoblasts. As new osteoblasts form from the underside of the periosteum, appositional growth occurs. A subpopulation of osteoblasts becomes embedded in the mineralizing matrix and gives rise to the osteocyte lacunocanalicular network. Within the craniofacial complex, most bones develop and grow through this mechanism.

Endochondral bone formation

During endochondral osteogenesis, bones develop through the formation of a cartilaginous template (hyaline cartilage model) that mineralizes and is later resorbed by osteoclasts and replaced by bone that is laid down afterwards. This process begins during the third month of gestation. The endochondral bone growth process leads to the formation of primary and secondary ossification centers that are separated by a cartilaginous structure known as the growth plate. Following the formation of the primary ossification center, bone formation extends towards both ends of the bone from the center of the shaft. The cartilage cells on the leading edges of ossification die. Osteoblasts cover the cartilagenous trabeculae with woven, spongy bone. Behind the advancing front of ossification, osteoclasts absorb the spongy bone and enlarge the primary marrow cavity. The periosteal collar thickens and extends toward the epiphyses to compensate for the continued hollowing of the primary cavity.

The processes of osteogenesis and resorption occur in all directions. The spaces between the trabeculae become filled with marrow tissue. As the new bone matrix remodels, osteoclasts assist in the formation of primary medullary cavities which rapidly fill with bone marrow hematopoietic tissue. The fibrous, non-mineralized lining of the medullary cavity is the endosteum. Osteoblasts form in the endosteum and begin the formation of endosteal bone. The appositional growth of endosteal bone is closely regulated to prevent closure of the primary marrow cavities and destruction of bone marrow.

Structure

Osseous tissue

Osseous tissue is a specialized connective tissue composed of organic and inorganic elements that mineralizes and is populated by highly specialized cells that regulate its stability (Fig. 2-3a).

Matrix

The organic matrix of bone makes up approximately 30–35% of the total bone weight and is formed of 90% collagen type I and 10% non-collagenous proteins, proteoglycans, glycoproteins, carbohydrates, and lipids. The organic matrix is synthesized by osteoblasts, and while it is still unmineralized, is known as osteoid. Within the collagen fibers, mineral nucleation occurs as calcium and phosphate ions are laid down and ultimately form hydroxyapatite crystals. Non-collagenous proteins along the surface of the collagen fibers assist in the propagation of the mineral and the complete mineralization of the matrix.

Inorganic components

Hydrated calcium and phosphate in the form of hydroxyapatite crystals [$3Ca_3(PO_4)_2(OH)_2$] are the principal inorganic constituent of the osseous matrix. Mineralization is clearly depicted in backscatter scanning electron microscopy images (Fig. 2-3b). Different degrees of mineralization are noticeable within the mature bone. Specific elements within the mineral can be further identified by energy-dispersive X-ray spectroscopy (EDS). In Fig. 2-3b, characteristic peaks of calcium and phosphorus are significantly pronounced in bone due to their high content within the hydroxyapatite crystals.

Organic components

Bone is initially laid down as a purely organic matrix rich in collagen as well as in other non-collagenous molecules (Fig. 2-3c). Chemical analysis of bone by Raman spectroscopy clearly highlights this organic counterpart in the matrix. The transition from a purely organic matrix to a mineralized matrix is clearly depicted in the transmission electron micrograph in Fig. 2-3a as an osteocyte becomes embedded within the mineralized mature matrix. As the matrix matures, mineral nucleation and propagation is mediated by the organic components in the ECM. Figure 2-3a shows the aggregation of mineral crystals, forming circular structures. As the mineral propagates along the collagen fibrils, a clear mineralization front forms and clearly demarcates the transition between the osteoid area and the mature bone.

Mineralization

The initiation of the mineralization process within the osteoid matrix typically occurs within a few days of secretion. However, maturation of the mineralized matrix through the propagation of the hydroxyapatite crystals occurs over the course of several months (Fig. 2-3a). In addition to providing the bone with its strength and rigidity to resist load and protect highly sensitive organs, the mineralization of the osteoid allows the storage of minerals that contribute to systemic homeostasis.

Cells

Within the bone tissue, different and distinct cellular components can be identified. These specific cell populations include osteogenic precursor cells, osteoblasts, osteoclasts, osteocytes, mesenchymal stem cells, and hematopoietic elements of bone marrow. This chapter will focus on the three main functional

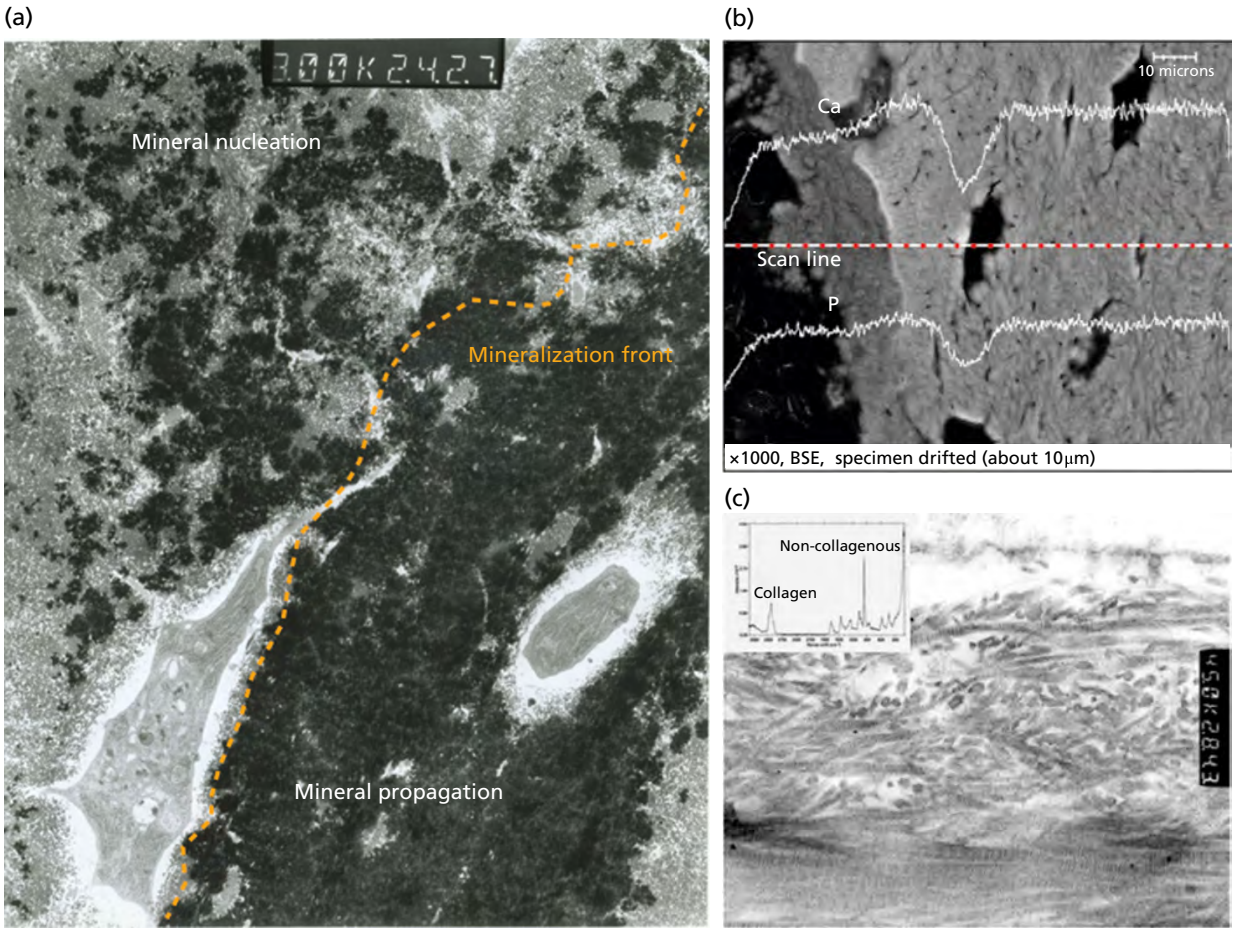


Fig. 2-3 Osseous matrix. The extracellular matrix in bone is particularly abundant compared with its cellular counterpart. (a) The osseous matrix has the unique ability to mineralize: a process that requires the support of organic components and the assistance of highly specialized cells. (b) Calcium and phosphorus are present in the form of hydroxyapatite crystals. These crystals tend to follow the organic scaffold in the bone matrix. The orange dashed line represents a linear scan that emphasizes the high content of calcium and phosphorus in the mature bone, as shown by the energy dispersive X-ray spectroscopy analysis. (c) Collagen fibers as well as non-collagenous proteins are abundant in the matrix and are often found to be arranged in a preferential direction, as shown by the Raman spectroscopy.

cells ultimately responsible for establishing and sustaining skeletal homeostasis.

Osteoblasts (Fig. 2-4)

Osteoblasts are the primary cells responsible for the formation of bone; they synthesize the organic ECM components and control the mineralization of the matrix (Fig. 2-4a, b). Osteoblasts are located on bone surfaces exhibiting active matrix deposition and may eventually differentiate into two different types of cells: bone lining cells and osteocytes. Bone lining cells are elongated cells that cover a surface of bone tissue and exhibit no synthetic activity. The osteoblasts are fully differentiated cells and lack the capacity for migration and proliferation. Thus, for bone formation at a given site, undifferentiated mesenchymal progenitor cells driven by the expression of a gene known as Indian hedgehog (*Ihh*) and later by *RUNX2* (*osteoprogenitor cells*), migrate to the site and proliferate to become osteoblasts (Fig. 2-4c). The determined osteoprogenitor cells are present in the bone marrow, in the endosteum, and in the periosteum that covers the bone surface. Such cells possess an intrinsic capacity to proliferate and differentiate into osteoblasts. The differentiation and development of osteoblasts from osteoprogenitor cells are dependent on the release of osteoinductive or osteopromotive growth factors, such as bone morphogenetic proteins (BMP), and other growth factors, such as insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), and fibroblast growth factor-2 (FGF-2).

Osteocytes (Fig. 2-5)

Osteocytes are stellate-shaped cells and are embedded within the mineralized bone matrix in compartments known as lacunae (Fig. 2-5a, b) with many similarities to cementocytes (also see Chapter 1; Zhao *et al.* 2016). These cells maintain a network of cytoplasmic processes known as dendrites (Fig. 2-5c). These osteocyte cytoplasmic projections extend through cylindrical encased compartments commonly referred to as canaliculi (Robling & Bonewald 2020). They extend to different areas and contact blood vessels and other osteocytes (Fig. 2-5d, e). The osteocyte network is therefore an extracellular and intracellular

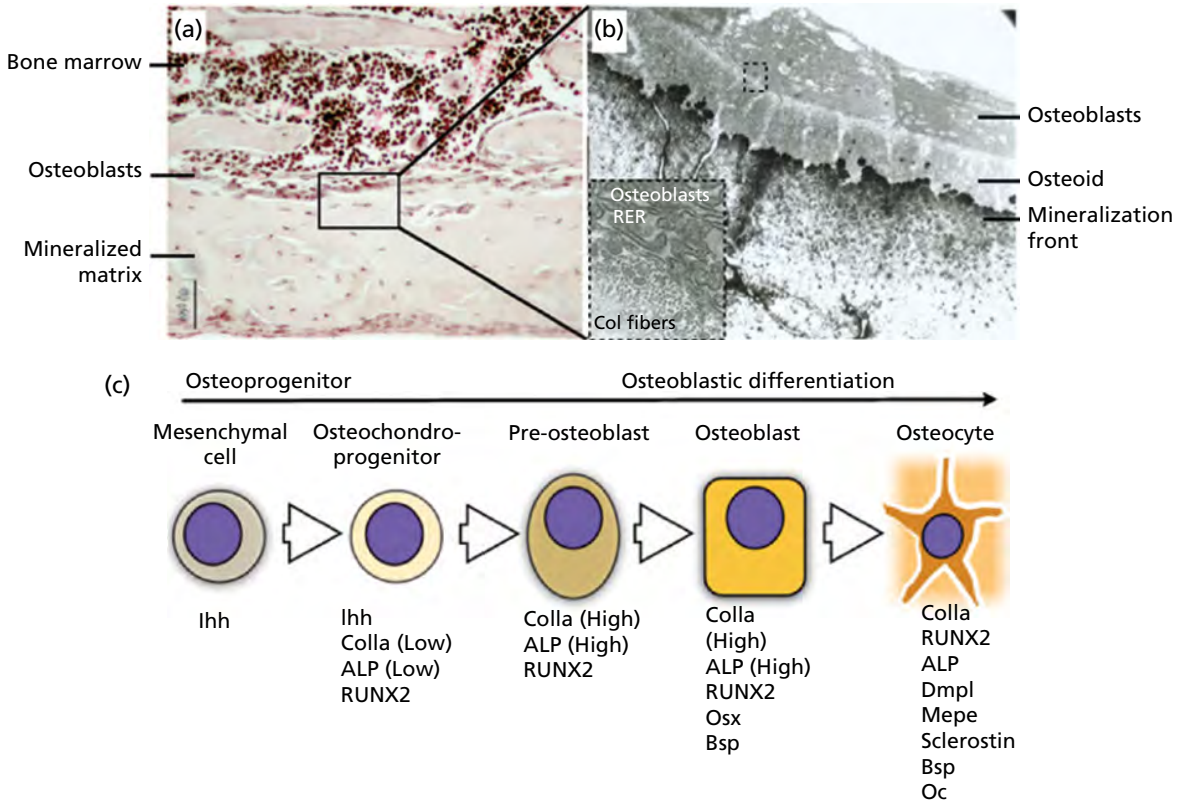


Fig. 2-4 Osteoblast. Osteoblasts are derived from bone marrow osteoprogenitor cells and are responsible for the synthesis of the immature bone matrix known as osteoid. (a) The arrow depicts a group of osteoblasts that line the mature bone that contains cells embedded within the mineralized matrix. (b) Further detail of the osteoblasts lining the mature bone is clearly visualized with transmission electron microscopy (TEM). The abundant rough endoplasmic reticulum (RER) and Golgi apparatus within these cells reflects their high metabolic activity. (c) The key molecules involved in the differentiation of an osteoprogenitor cell through to a mature terminally differentiated osteocyte.

communication channel that is sensitive at the membrane level to shear stress caused by the flow of fluid within the canaliculi space as the result of mechanical stimuli and bone deformation. Osteocytes convert mechanical signals into biochemical mediators that ultimately assist in modulating anabolic and catabolic events within bone. Their organization within the matrix enables them to (1) participate in the regulation of blood calcium homeostasis and (2) sense mechanical loading and transmit this information to other cells within the bone to further orchestrate osteoblast and osteoclast function (Burger *et al*. 1995; Marotti 2000). Different bone diseases and disorders affect the arrangement of the osteocyte lacuno-canalicular system, causing significant disruption of this important cellular organizational network (Fig. 2-6).

Osteoclasts (Fig. 2-7)

Bone formation is closely coupled to bone resorption which is initiated and maintained by osteoclasts (Biosse-Duplan *et al*. 2012). Osteoclasts have the capacity to develop and adhere to bone matrix where they secrete acid and lytic enzymes that degrade and break down the mineral and organic components of bone and cartilage (Fig. 2-7a, b, c). The degradation process of bone matrix results in the formation of a specialized extracellular compartment known as *Howship's lacuna* (Rodan 1992; Vaananen & Laitala-Leinonen 2008). Osteoclasts are specialized multinucleated cells that originate from the monocyte/macrophage hematopoietic lineage. This differentiation process is driven initially by the expression of the transcription factor PU-1. Macrophage colony-stimulating factor (M-CSF) engages osteoclasts in the differentiation pathway and promotes their proliferation and expression of RANKL. At this stage, RANKL-expressing stromal cells interact with pre-osteoclasts and further commit them to differentiation along the osteoclast lineage (Fig. 2-7d, Fig. 2-8).

Periosteal tissue

The periosteum is a fibrous sheath that covers the outer surface of a long bone's shaft (diaphysis), but does not overlay the articulating surfaces. The periosteum consists of dense irregular connective tissue and is divided into a dense, fibrous, vascular layer (the "fibrous layer") and an inner, more loosely arranged, connective tissue inner layer (the "osteogenic layer") (see Fig. 2-1). The fibrous layer is mainly formed of fibroblasts, while the inner layer contains osteoprogenitor cells and mesenchymal stem cells. This layer is also very important in regeneration of osseous tissues (Lin *et al*. 2014).

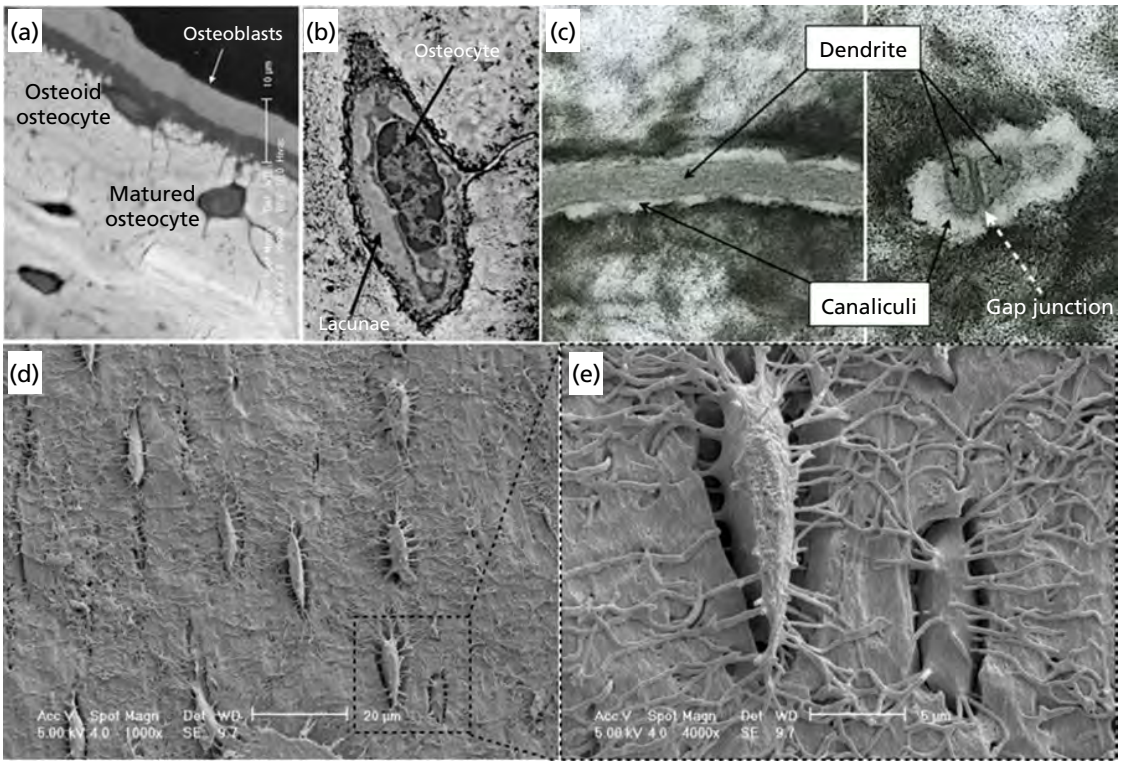


Fig. 2-5 Osteocytes. The osteocyte can be defined as the orchestrator of the remodeling process within bone. (a) As bone matrix is synthesized, a number of osteoblasts become embedded within the osteoid, which later mineralizes and resides in the mature matrix as osteocytes as shown in this backscatter scanning electron micrograph (SEM) treated with osmium to allow the visualization of the cell. (b) The osteocytes reside within a well-defined space in bone known as the osteocyte lacuna. (c) A transmission electron micrograph of a dendrite within a canaliculi, showing the space through which fluid flows; the shear stress from this stimulates the surface of the osteocyte cell membrane. This unique biologic architectural characteristic of the osteocyte and the lacunocanalicular network represent the foundation that allows the conversion of mechanical stimuli into the biochemical signals necessary for bone homeostasis. (d, e) SEM of a casted lacunocanalicular network allow the visualization of the degree of connectivity between osteocytes and the regular diameter of the canalicular structures.

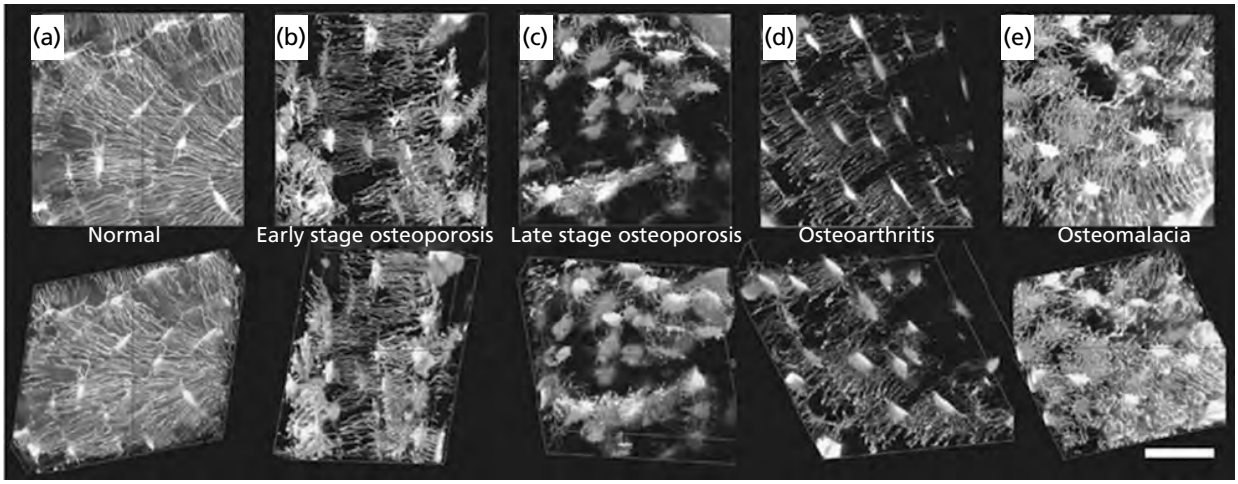


Fig. 2-6 Osteocytes: lacunocanalicular system in disease. (a) In healthy bone, a high density osteocyte system is established throughout the mature matrix and is characterized by high cellular interconnectivity. With disease, the system is significantly disrupted, leading to important functional alterations. (b, c) In osteoporosis, osteocytic density changes and an apparent decrease in cellular interconnectivity is observed. (d) In osteoarthritis, the canalicular system is altered, but with no major lacunar changes. (e) In osteomalacia, the entire osteocyte lacunocanalicular system appears disrupted due to the altered mineralization pattern.

Osteoblasts derived from the "osteogenic layer" are responsible for increasing the width of long bones and the overall size of the other bone types. In the context of a fracture, progenitor and stem cells from the periosteum differentiate into osteoblasts and chondroblasts, which are essential in the process of stabilizing the wound.

In contrast to the osseous tissue, the periosteum has nociceptive nerve endings, making it very sensitive to mechanical stimuli. It also allows the passage

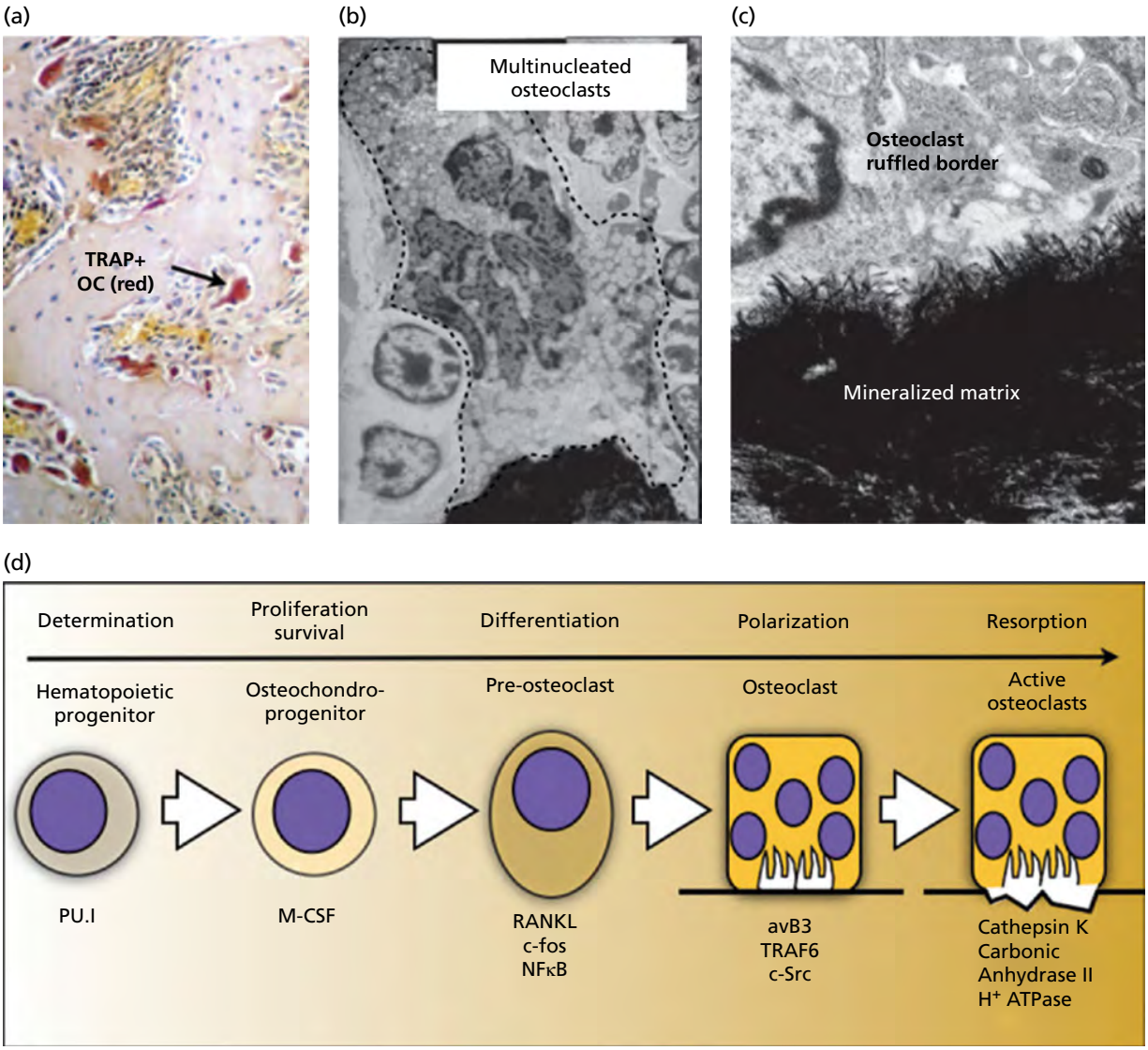


Fig. 2-7 Osteoclasts. (a) Histologically, osteoclasts can be depicted morphologically as multinucleated cells attached to bone matrix using special staining such as the tartrate-resistant acid phosphatase (TRAP) stain (arrow). OC, osteoclast. (b) A transmission electron micrograph of a multinucleated osteoclast attached to the mineralized bone matrix. (c) Ruffled border at the resorbing end of the cells. (d) Osteoclasts are derived from cells of the macrophage/monocyte lineage and represent the bone resorbing units within the skeleton. The key molecules involved in the early events of differentiation of a hematopoietic progenitor through to a mature functional osteoclast are shown.

of lymphatics and blood vessels into and out of bone, providing nourishment. The periosteum anchors tendons and ligaments to bone by strong collagenous fibers in the "osteogenic layer", called Sharpey's fibers, which extend to the outer circumferential and interstitial lamellae. It also provides an attachment for muscles and tendons.

Bone marrow

The bone marrow consists of hematopoietic tissue islands, stromal cells, and adipose cells surrounded by vascular sinuses interspersed within a meshwork of trabecular bone (see Fig. 2-1). The bone marrow is the major hematopoietic organ, a primary lymphoid tissue (responsible for the production of erythrocytes, granulocytes, monocytes, lymphocytes, and platelets) and an important source of mesenchymal stem cells.

Types

There are two types of bone marrow: red marrow, which consists mainly of hematopoietic tissue, and yellow marrow, which is mainly made up of adipocytes. Erythrocytes, leukocytes, and platelets arise in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries. At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type; only around half of adult bone marrow is red. In cases of severe blood loss, the body can convert yellow marrow back to red marrow to increase blood cell production.

Cells

The stroma of the bone marrow is not directly involved in the primary function of hematopoiesis. However, it serves an indirect role by indirectly providing the

ideal hematopoietic microenvironment. For instance, it generates colony stimulating factors, which have a significant effect on hematopoiesis. Cells that constitute the bone marrow stroma are:

- Fibroblasts
- Macrophages
- Adipocytes
- Osteoblasts
- Osteoclasts
- Endothelial cells.

Stem cells

Mesenchymal stem cells (MSC), also called *marrow stromal cells*, were first identified following their isolation and characterization from the bone marrow stroma. MSC are multipotent stem cells that can differentiate into a variety of cell types. They have demonstrated the capacity to differentiate, *in vitro* or *in vivo*, into osteoblasts, chondrocytes, myocytes, adipocytes, vascular cells, and beta-pancreatic islet cells and evidence of their transdifferentiation into neuronal cells has also been reported. In addition, the bone marrow contains hematopoietic stem cells, which give rise to the three classes of blood cells that are found in the circulation: leukocytes, erythrocytes, and platelets (Polymeri *et al*. 2016).

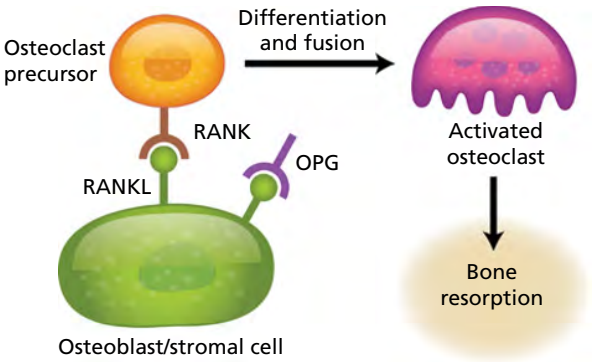


Fig. 2-8 Bone formation/resorption coupling. Bone formation and resorption processes are intimately linked. The osteoblastic/stromal cells provide an osteoclastogenic microenvironment by presenting RANKL to the osteoclast precursor, triggering their further differentiation and fusion, leading to the formation of multinucleated and active osteoclasts. This process is modulated by inhibitors of these interactions such as osteoprotegerin (OPG). In addition, bone formation by osteoblasts depends on the preceding resorption by osteoclasts.

Function

The main functions of bone are to provide locomotion, organ protection, and mineral homeostasis. Mechanical tension, local environment factors, and systemic hormones influence the balance between bone resorption and deposition. The distinct mechanical properties of bone contribute to its strength and ability to allow movement. In addition, an intricate series of interactions between cells, matrix, and signaling molecules maintain calcium and phosphorus homeostasis within the body, which also contributes to mechanical strength.

Mechanical properties

Bone is a highly dynamic tissue that has the capacity to adapt based on physiological needs. Hence, bone adjusts its mechanical properties according to metabolic and mechanical requirements (Burr *et al*. 1985; Lerner 2006). As discussed previously, calcium and phosphorus comprise the main mineral components of bone in the form of calcium hydroxyapatite crystals. Hydroxyapatite regulates both the elastic stiffness and tensile strength of bone. The skeletal adaptation mechanism is regulated primarily by the processes of bone resorption and bone formation, these processes collectively referred to as bone remodeling (Fig. 2-9). Bone is resorbed by osteoclasts,

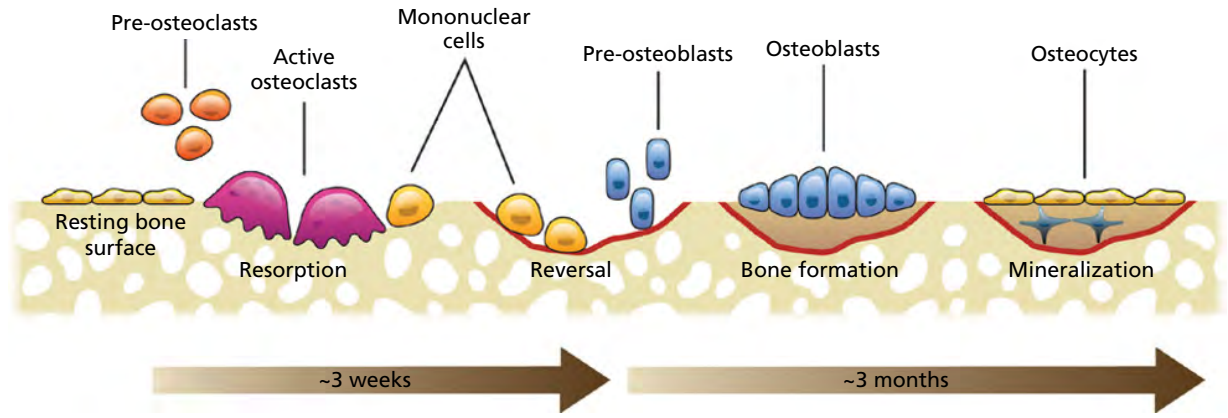


Fig. 2-9 Bone remodeling. The bone remodeling cycle involves a complex series of sequential steps that are highly regulated. The "activation" phase of remodeling is dependent on the effects of local and systemic factors on mesenchymal cells of the osteoblast lineage. These cells interact with hematopoietic precursors to form osteoclasts in the "resorption" phase. Subsequently, there is a "reversal" phase during which mononuclear cells are present on the bone surface. They may complete the resorption process and produce the signals that initiate bone formation. Finally, successive waves of mesenchymal cells differentiate into functional osteoblasts, which lay down matrix in the "formation" phase. (Source: McCauley & Nohutcu (2002). Reproduced from American Academy of Periodontology.)

after which new bone is deposited by osteoblasts (Raisz 2005). From the perspective of bone remodeling, it has been proposed that osteoclasts recognize and 'home' to skeletal sites of compromised mechanical integrity, and once there, initiate bone remodeling inducing new bone formation that is mechanically competent (Parfitt 1995, 2002).

In general, bone tissue responds to patterns of loading by increasing matrix synthesis, and altering composition, organization, and mechanical properties (Hadjidakis & Androulakis 2006). Evidence indicates that the same holds true for bone under repair. When bone experiences mechanical loading, osteoclast mechanoreceptors are directly stimulated, which begins the bone turnover process to regenerate and repair bone in the area. In addition, pressure increases M-CSF expression, increasing osteoclast differentiation in the bone marrow (Schepetkin 1997). Osteoclasts are also indirectly stimulated through osteoblasts and chondrocytes secreting prostaglandins in response to mechanical pressure. The ECM can also promote bone turnover through signaling. Mechanical deformation of the matrix induces electric potentials that stimulate osteoclastic resorption.

Bone strength is determined by a combination of bone quality, quantity, and turnover rate. It is well established that a loss of bone density, or quantity, decreases bone strength and results in increased fracture incidence. However, several pathologic conditions characterized by increased bone density, such as Paget's disease, are also associated with decreased bone strength and increased fracture incidence, so quality of bone is also an important factor in determining bone strength.

Metabolic properties

Calcium homeostasis is of major importance for many physiologic processes that maintain health (Bonewald 2002; Harkness & Bonny 2005). Osteoblasts deposit calcium by mechanisms including phosphate and calcium transport with alkalinization to absorb acid produced by mineral deposition; cartilage calcium mineralization occurs by passive diffusion and phosphate production. Calcium mobilization by osteoclasts is mediated by acid secretion. Both bone-forming and bone-resorbing cells use calcium signals as regulators of differentiation and activity (Sims & Gooi 2008). This has been studied in more detail in osteoclasts: both osteoclast differentiation and motility are regulated by calcium.

Despite calcium being an important mineral acquired exogenously from the diet, bone serves as the major reservoir of calcium and a key regulatory organ for calcium homeostasis. Bone, in major part, responds to calcium-dependent signals from the parathyroid glands and via vitamin D metabolites, although it responds directly to extracellular calcium if parathyroid regulation is lost. Serum calcium homeostasis is achieved through a complex regulatory process whereby a balance between bone resorption, absorption, and secretion in the intestine, and reabsorption and excretion by the kidneys is tightly regulated by osteotropic hormones (Schepetkin 1997). The balance of serum ionized calcium blood concentrations results from a complex interaction between parathyroid hormone (PTH), vitamin D, and calcitonin. Other osteotropic endocrine hormones that influence bone metabolism include thyroid hormones, sex hormones, and retinoic acids. In addition, fibroblast growth factor aids in phosphate homeostasis. Fig. 2-10 reflects how input from the diet and from the bones and excretion via the gastrointestinal tract and urine maintain homeostasis.

Vitamin D is involved in the absorption of calcium, while PTH stimulates calcium release from the bone, reduces its excretion from the kidney, and assists in the conversion of vitamin D into its biologically active form (1,25-dihydroxycholecalciferol) (Holick 2007). Decreased intake of calcium and vitamin D and estrogen deficiency may also contribute to calcium deficiency (Lips *et al*. 2006). Hormonal factors such as retinoids, thyroid and steroid hormones are capable of passing through biologic membranes and interacting with intracellular receptors to have a major impact on the rate of bone resorption. Lack of estrogen increases bone resorption as well as decreases the formation of new bone (Harkness & Bonny 2005). Osteocyte apoptosis has also been documented in estrogen deficiency. In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition.

Circulating PTH regulates serum calcium and is released in conditions of hypocalcemia. PTH binds to osteoblast receptors, increasing the expression of RANKL and the binding of RANKL to RANK on osteoclasts (McCauley & Nohutcu 2002). This signaling stimulates bone remodeling by activating osteoclasts with the final goal of promoting calcium release from bone. A secondary function of PTH is to increase calcium reabsorption from the kidney. When administered therapeutically at low, intermittent doses, PTH can act as an anabolic agent to promote bone formation, although the mechanism of this action is not well understood.

T cells produce calcitonin, a 32 amino acid peptide whose main physiologic role is the suppression of bone resorption. Calcitonin receptors are present in high numbers on osteoclasts and their precursors (Schepetkin 1997). Thus, calcitonin is able to act directly on osteoclast cells at all stages of their development to reduce bone resorption through preventing fusion of mononuclear preosteoclasts, inhibiting differentiation, and preventing resorption by mature osteoclasts (McCauley & Nohutcu 2002). The concentration and phosphorylation of calcitonin receptors decreases in the presence of calcitonin. As a result, the effect of calcitonin on osteoclasts is transient and thus is not used for clinical therapeutic applications.

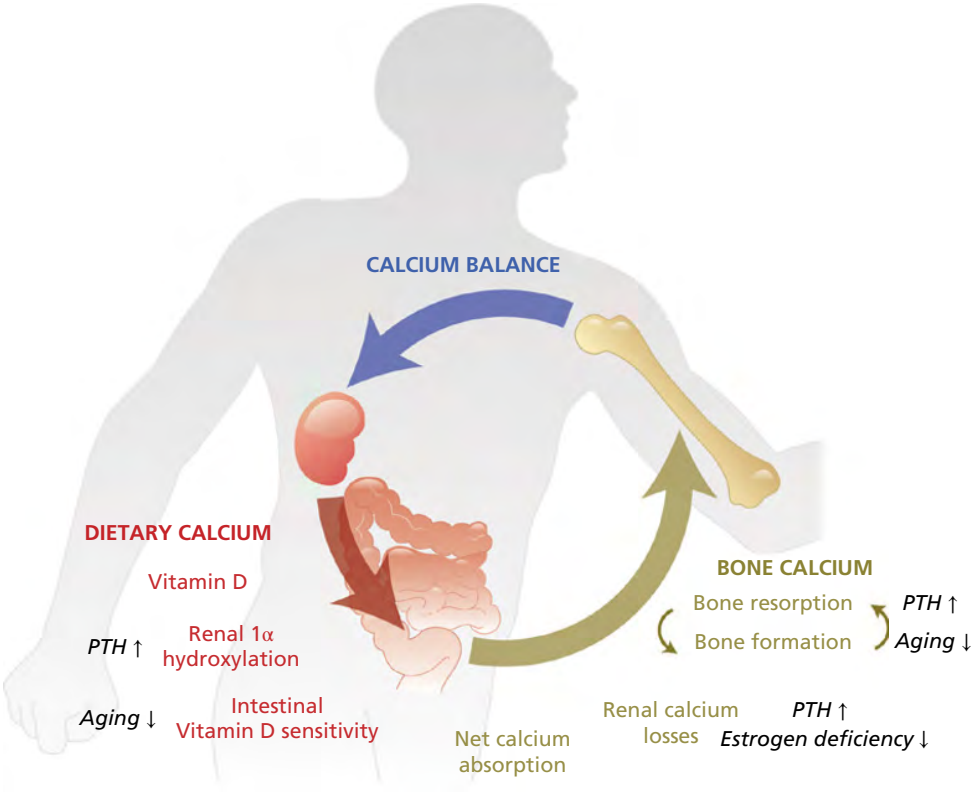


Fig. 2-10 Calcium and bone metabolism. Calcium homeostasis is of major importance for many physiologic processes that maintain health. The balance of serum ionized calcium blood concentrations results from a complex interaction between parathyroid hormone (PTH), vitamin D, and calcitonin. The figure reflects how input from the diet and from the bones and excretion via the gastrointestinal tract and urine maintain homeostasis. Vitamin D is involved in the absorption of calcium, while PTH stimulates calcium release from the bone, reduces its excretion from the kidney, and assists in the conversion of vitamin D into its biologically active form (1,25-dihydroxycholecalciferol). Decreased intake of calcium and vitamin D and estrogen deficiency may also contribute to calcium deficiency.

Skeletal homeostasis

Healing

In most situations where tissue injury occurs, healing of the injured site leads to the formation of a tissue that differs in morphology, composition, or function of the original tissue. This type of healing is termed *repair*. Tissue *regeneration*, on the other hand, is a term used to describe a healing process that results in complete restoration of morphology, composition, and function. The healing of bone tissue includes both regenerative and repair phenomena, depending on the nature of the injury.

Repair

Trauma to bone tissue, whether repeated stress or a single, traumatic episode, most commonly results in fracture. When bone is damaged, a complex and multistage healing process is immediately initiated in order to facilitate repair. Tissue and cell proliferation are mediated at different stages by carious growth factors, inflammatory cytokines, and signaling molecules. Although it is a continuous process, bone repair can be roughly divided into three phases – inflammation, reparative, and remodeling (Hadjidakis & Androulakis 2006).

The inflammation phase begins immediately after tissue injury and lasts for approximately 2 weeks (Fazzalari 2011). The initial step in the repair process is the formation of a blood clot. Cytokine release from injured cells then recruits inflammatory cells into the area, where macrophages begin phagocytosis of damaged tissue and cells. Osteoclasts begin the process of resorbing damaged bone in the area to recycle mineral components. In addition, cells from myeloid and mesenchymal cell lineages are recruited to the area where they begin to differentiate into osteoblasts and chondroblasts. At this point, the RANKL:osteoprotegerin (OPG) ratio is reduced.

The reparative phase is characterized by the formation of a soft callous where new bone matrix and cartilage scaffolding begins to form. Osteoblasts and chondroblasts produce a protein scaffold to create this callus, which is slowly mineralized to form a hard callus. The hard callus is composed of immature woven bone. The initiation of cartilage and periosteal woven bone formation is primarily mediated through early up-regulation of interleukin 6 (IL-6), OPG, vascular endothelial growth factor (VEGF), and BMPs (Fazzalari 2011). The process of soft to hard callus formation occurs approximately 6–12 weeks from the time of bone fracture.

In the final stage of repair, known as the remodeling phase, the bone matrix and cartilage are remodeled into mature bone. Woven bone is eventually converted into mature lamellar bone through normal bone turnover mediated by osteoblast/osteoclast coupling. Adequate vitamin D and calcium are critical for proper bone repair and their levels may, in part, dictate the rate of repair. The time for the remodeling stage usually requires months from the time of injury; however, it varies depending upon individual variability in bone metabolism.

Regeneration

Optimum bone healing promotes tissue formation in such a way that the original structure and function of bone is preserved. This process is in contrast to tissue repair, which merely replaces lost tissue with immature tissue and does not completely restore form or function.

Over time, bone sustains damage from mechanical strain, overloading, and other forms of tissue injury that results in microfractures and other defects in the bony architecture. In order to prevent greater injury, the bone undergoes a natural remodeling process to regenerate or renew itself. The turnover rates of individual bones is unique, although the average turnover rate is 10% (McCauley & Nohutcu 2002).

Regeneration of bone tissue involves the coupling of bone formation and resorption in a basic multicellular unit (BMU) (Sims & Gooi 2008) (Fig. 2-11). In this process, bone resorption by osteoclasts occurs first over a period of 3–4 weeks, along with cellular signaling to promote osteoblast recruitment to the area. Osteoblasts then form bone for a period of 3–4 months, with a quiescent period between bone resorption and formation, called the reversal phase. Trabecular bone undergoes a significantly higher degree of bone turnover than cortical bone (McCauley & Nohutcu 2002). In a rodent alveolar bone healing model, this process occurs more rapidly, allowing appreciation of the cellular and molecular events that occur during the maturation of the newly regenerated bone (Figs. 2-12, 2-13) (Lin *et al*. 2011).

Bone regeneration is a normal process yet in some scenarios there is a need to regenerate bone at either an accelerated rate or in order to overcome the effects of pathologic bone disorders. Therapeutic strategies to promote bone regeneration include the use of: bone grafts from various sources, epithelial–occlusive barrier membranes, antiresorptive agents, anabolic agents, and growth factors which promote osteoblast differentiation and proliferation (Giannobile *et al*. 2019).

When alterations in bone turnover occur, skeletal homeostasis is disrupted, resulting in conditions of increased or decreased bone mineral density (BMD), or bone necrosis, and often accompanied by a decrease in bone strength. A wide variety of conditions can alter bone homeostasis and these include cancer, menopause, medications, genetic conditions, nutritional deficiencies, or infection. Some of these etiologies, such as vitamin D deficiency, are easily treatable, whereas

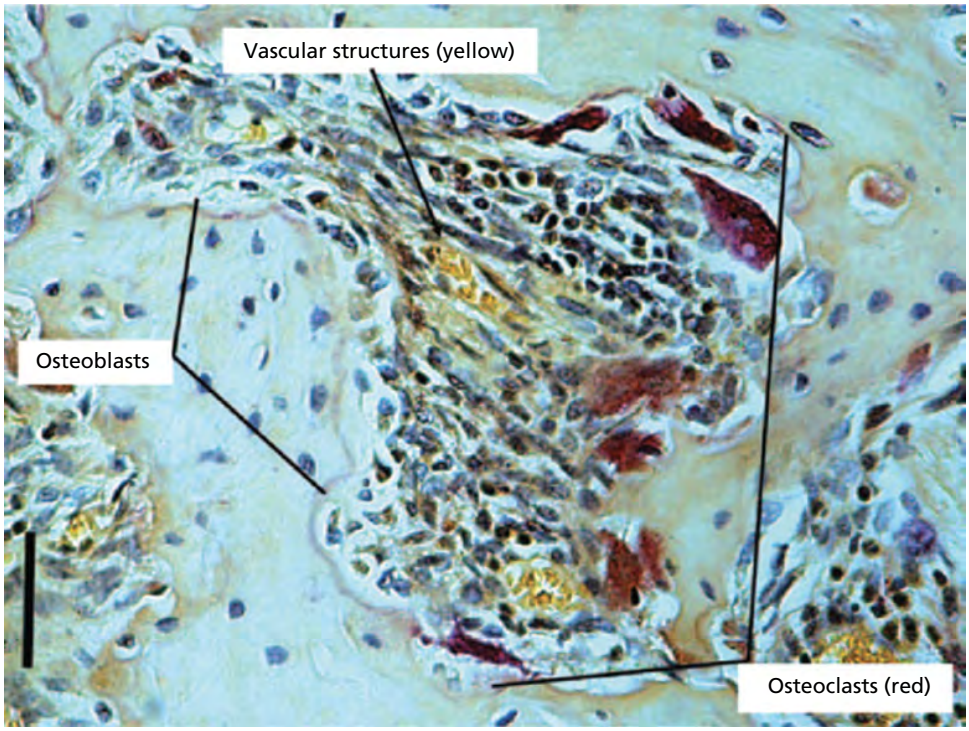


Fig. 2-11 Bone multicellular units (BMU). Bone remodeling occurs in local groups of osteoblasts and osteoclasts called BMU; each unit is organized into an osteoclast reabsorbing front, followed by a trail of osteoblasts reforming the bone to fill the defect left by osteoclasts. The red staining (tartrate acid phosphatase) highlights the resorption front. Note the increased number of multinucleated osteoclasts in this area.

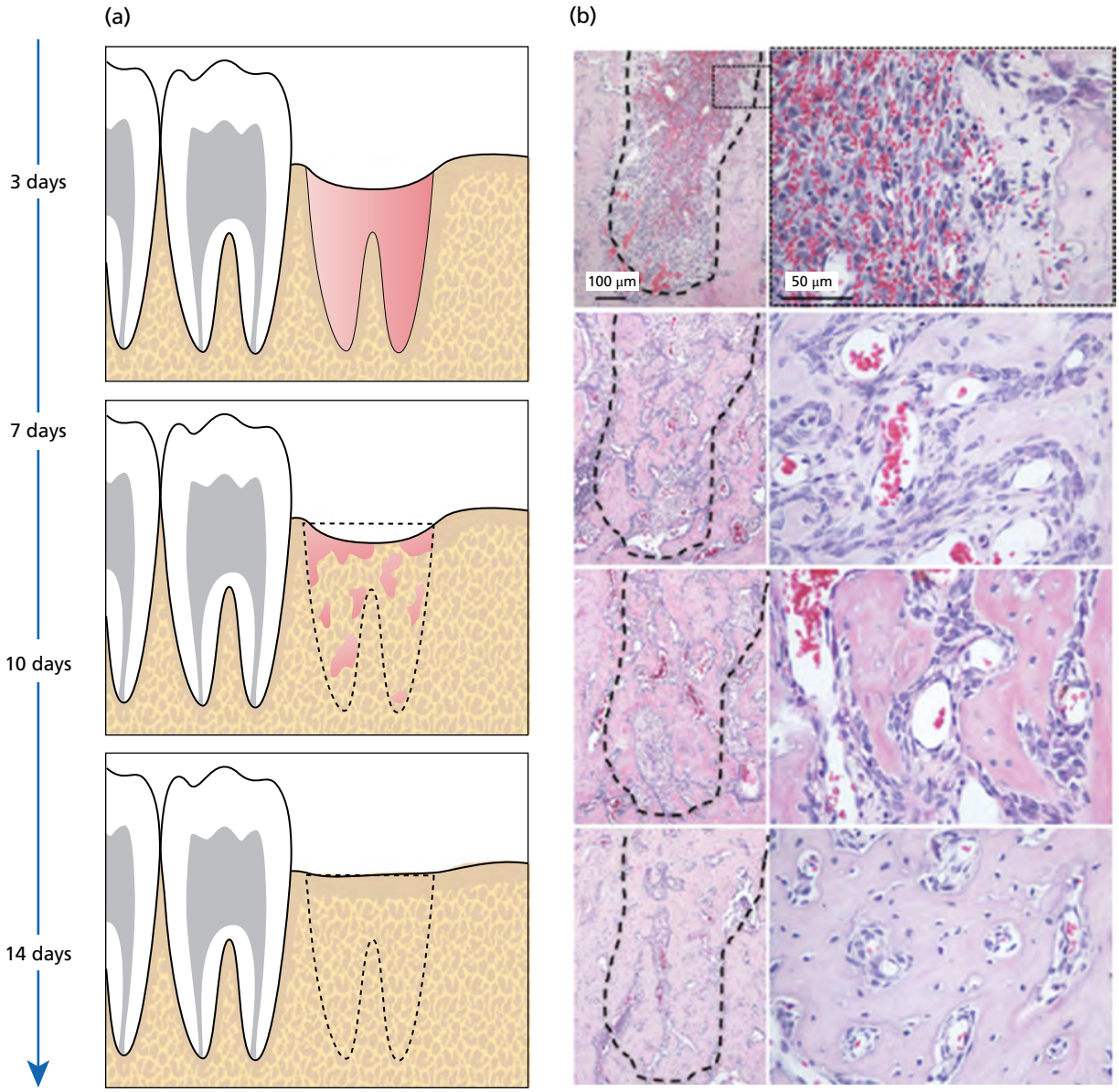


Fig. 2-12 Alveolar socket healing sites over time. (a) Rodent extraction model. Sequence of events that characterize healing during the initial 14 days. (b) Hematoxylin and eosin (H&E) staining for tooth extraction site healing. The histologic images to the right of the healing area (black dashed lines) clearly capture the regeneration of the bone within the alveolar process. Note the clearly visible blood clot at day 3. At day 7, the cell density in the defect area is higher. At day 10, the defect site appears to be filled by a condensed mesenchymal tissue. Finally, by day 14, an integration of the newly formed bone to the original socket walls is noted.

others, such as genetic mutations, are typically treated through managing symptoms. Alterations in bone homeostasis cause a wide array of symptoms, including increased fracture incidence, bone pain, and other skeletal deformities that result in a high degree of morbidity and in some cases mortality. A brief review of the more common conditions is given below.

Disorders

Osteoporosis

Osteoporosis is a common condition characterized by both alterations in the macro- and microarchitecture of the bone (Fig. 2-14). There are multiple etiologies of this systemic disease, including postmenopausal, age-associated, glucocorticoid-induced, secondary to cancer, androgen ablation, and aromatase inhibitors (Kanis 2002). All forms result in reduced bone strength and increased fracture risk, accompanied by a high degree of morbidity and mortality.

Postmenopausal osteoporosis is the most common form of the disease and results from a decline in gonadal hormone secretion following menopause. Rapid loss of trabecular BMD and, to a lesser extent, cortical loss are common in this condition (Kanis 2002).

Diagnosis is made by comparing the BMD of a patient to that of a healthy 20–29-year-old adult of the same gender. Systemic BMD at least 2.5 standard deviations below the average, referred to as a T-score, is used by the World Health Organization (WHO) to define

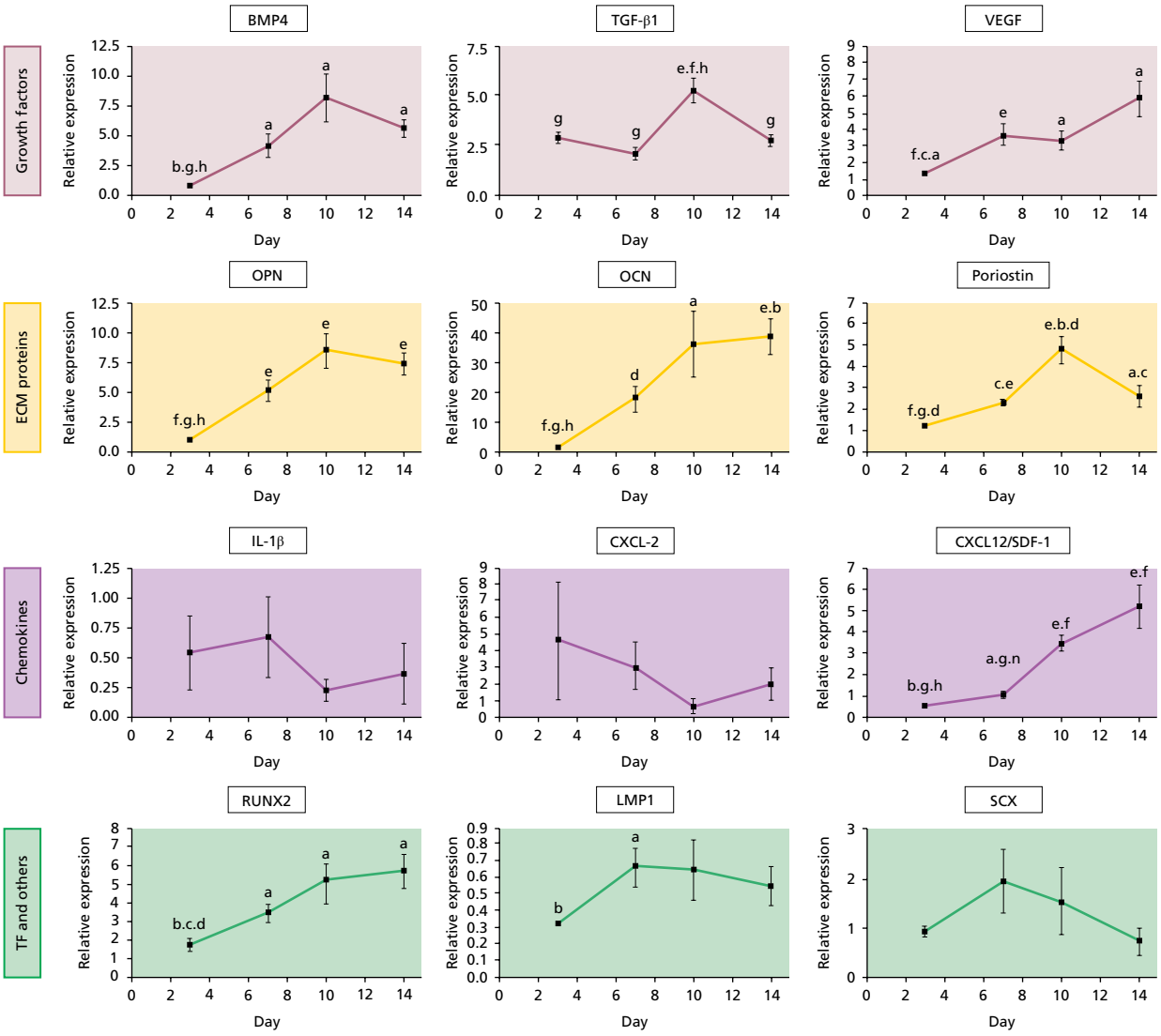


Fig. 2-13 Gene expression pattern of tooth extraction healing sites. Laser capture microdissection (LCM) analysis of genes associated with wound healing categorized them into three different groups: those for growth factors/chemokines, extracellular matrix proteins (ECM), and transcription factors (TF). Three expression patterns were evident. (1) Genes whose expression was slowly increased during the healing process: those for growth factors (*BMP4*, *BMP7*, *Wnt10b*, and *VEGF*), transcription factors (*RUNX2*), and extracellular matrix proteins related to mineralized tissue (*OPN* and *OCN*) were in this group; very interestingly, CXCL12 (SDF-1) gradually increased during extraction socket healing. Transforming growth factor beta 1 (TGF-β1) increased at the midstage of healing (day 10) and then decreased, and periostin (*POSTN*), a target gene of TGF-β1, had the same expression pattern. (2) Genes that were highly expressed at early time points and are downregulated at later stages. Genes for chemokines IL-1β, CXCL2, and CXCL5 belong to this category, although no statistical difference was seen due to the limited number of animals analyzed. Expression of *Wnt5a* and *Wnt4* also seemed to decrease during healing. (3) Genes that were constitutively expressed. LIM domain mineralization protein (LMP-1) and tendon-specific transcription factor SCX were in this group.

osteoporosis (WHO 1994; McCauley 2020). Osteopenia, a less severe form of the disease, is diagnosed when T-scores are between –1.0 and –2.5 (Fig. 2-15).

Osteopetrosis

Osteopetrosis is a group of related diseases in which there is a pronounced increase in BMD due to abnormal bone turnover, and in some ways this is the opposite of osteoporosis. These conditions are inherited and the mode of transmission varies from autosomal dominant to autosomal recessive. Increases in BMD in this patient population are due to a variety of defects in osteoclastic bone resorption. These include higher or lower osteoclast numbers, impaired differentiation, deficiencies in carbonic anhydrase, the ability to form a ruffled border, and alterations in signaling pathways (Stark & Savarirayan 2009). In most cases, it is the ability of the osteoclast to create an acidic environment in the lacunae to resorb bone that is in some way compromised, ultimately resulting in a net increase in bone formation (Fig. 2-16).

Osteomalacia

Vitamin D is essential for the metabolism of calcium and phosphorus in the body, which are the key minerals required for bone formation (Holick 2007).

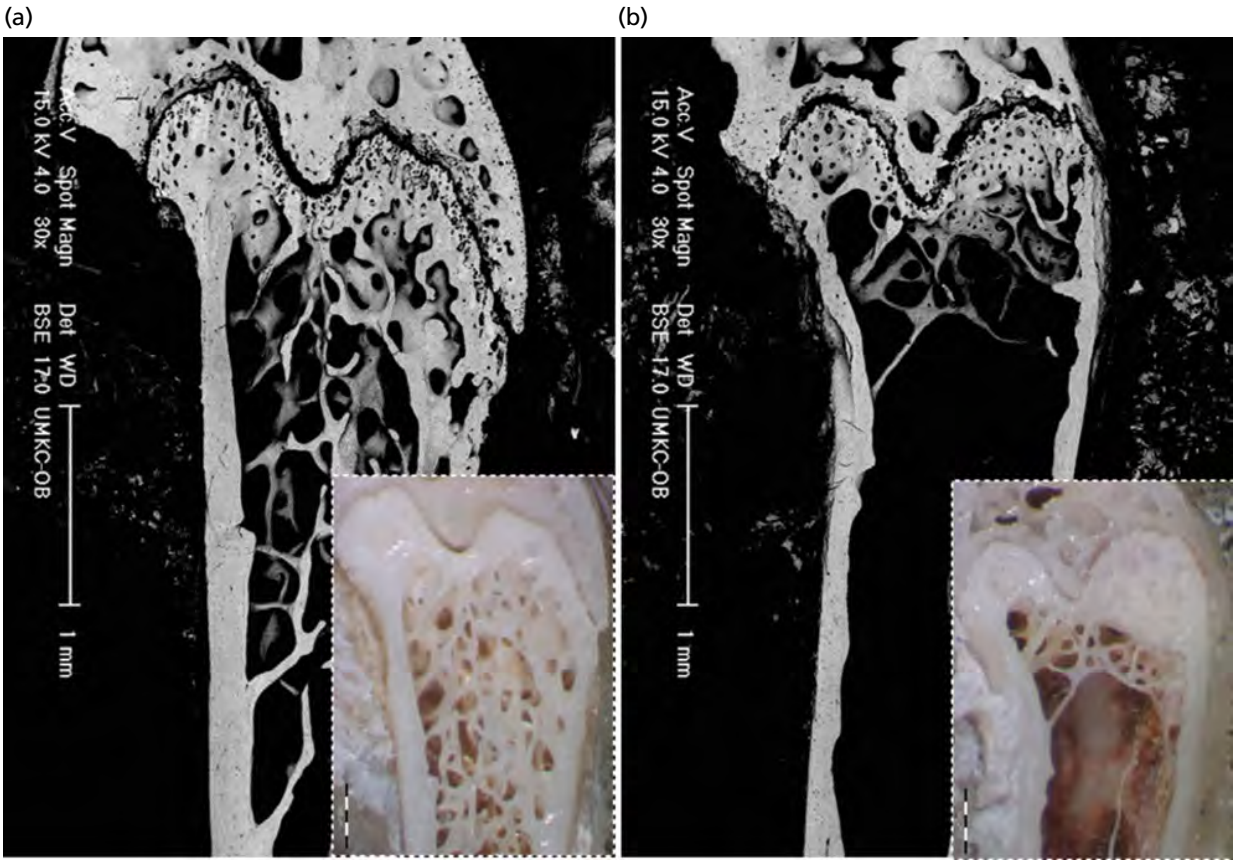
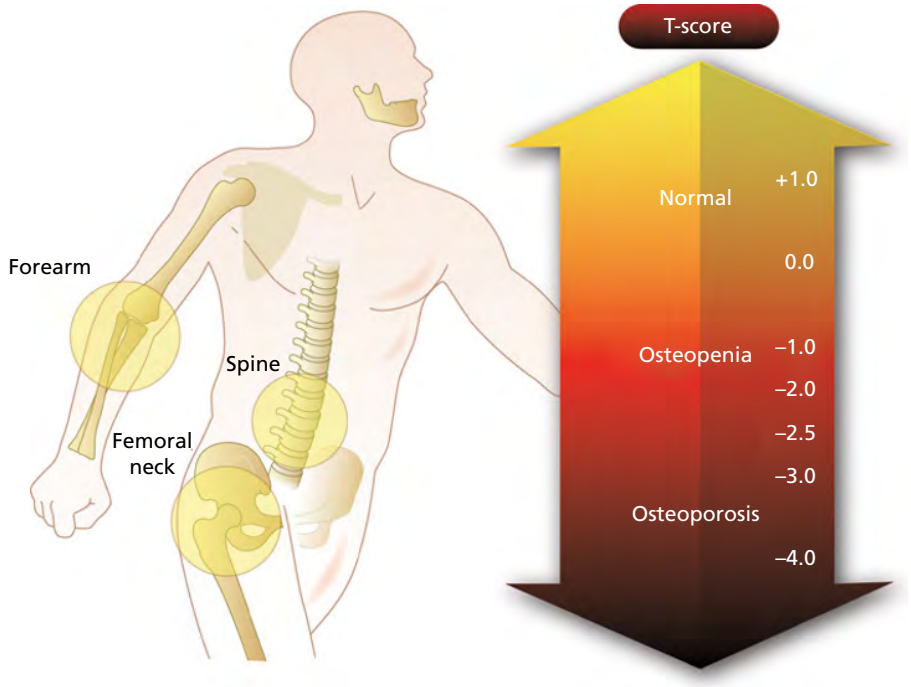


Fig. 2-14 Osteoporosis. In osteoporosis, there is decreased cortical thickness in addition to a marked decrease in trabecular number and connectivity. As this process continues over time, there is further deterioration of the internal architecture with a significant impact on the ability of the bone to sustain compressive forces without failure.



$$\text{T-Score} = \frac{\text{Measured BMD} - \text{young adult mean BMD}}{\text{Young adult standard deviation}}$$

Fig. 2-15 Bone mineral density (BMD). Dual-energy X-ray absorptiometry (DEXA) is considered the preferred technique for measurement of BMD. The sites most often used for DEXA measurement of BMD are the spine, femoral neck, and forearm. The World Health Organization defines osteoporosis based on "T-scores". T-scores refer to the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex as the patient.

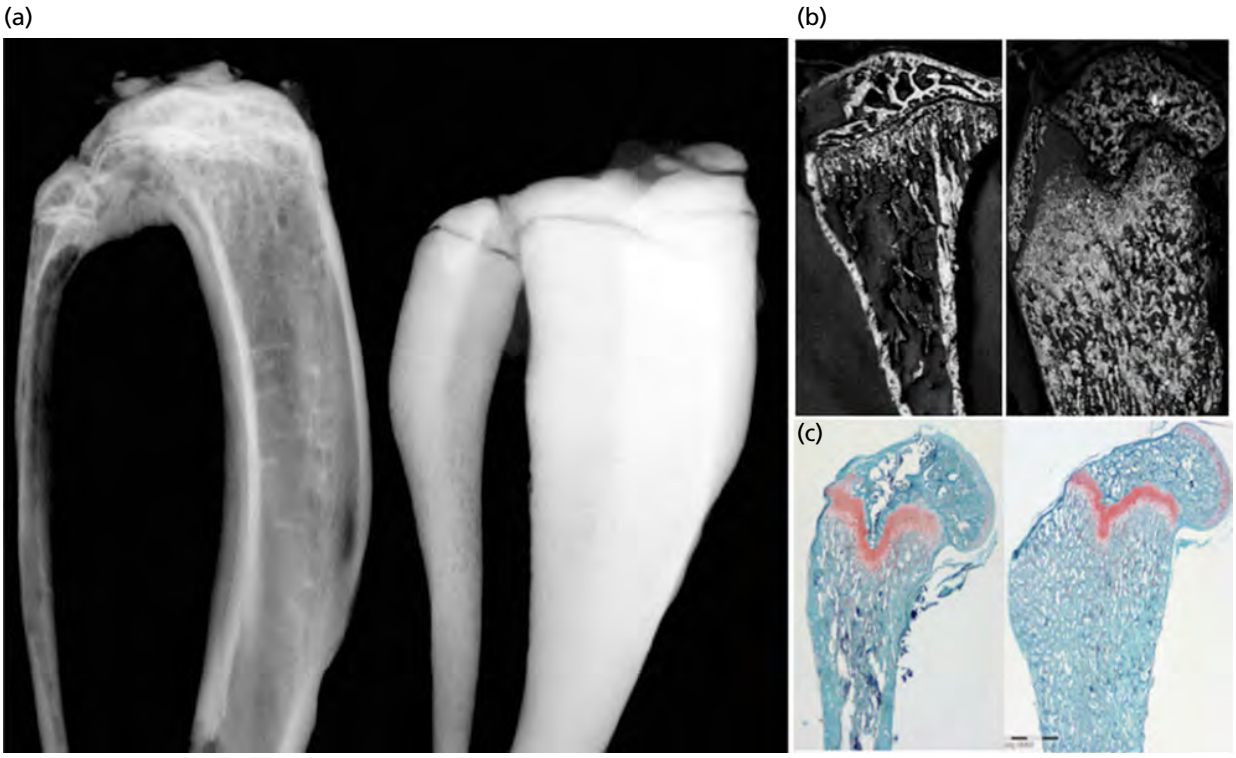


Fig. 2-16 Osteopetrosis. Increased density and deposits of mineralized bone matrix are a common finding in those with osteopetrosis. (a) Obliteration of the bone marrow cavity. (b) Backscatter SEM. (c) Staining with safranin-O.

Vitamin D deficiency, or the inability to absorb the vitamin, is a common condition, especially in Northern climates since vitamin D is obtained primarily through sunlight exposure and diet. Other conditions may also predispose to vitamin D deficiency, such as oncogenic or benign tumors and liver disease.

When inadequate vitamin D is available, mineralization of the bones is impaired, resulting in a condition referred to as osteomalacia. When the disease occurs in children, it is referred to as rickets. The key features of osteomalacia are bones that contain a normal collagen matrix and osteoid structure, but lack proper mineralization, resulting in the softening of bones (Russell 2010). Osteomalacia differs from osteoporosis in that osteomalacia alters bone as it is developing, whereas osteoporosis weakens bones that have already formed (Fig. 2-17).

Severity ranges widely from an asymptomatic presentation to death in early childhood. Despite the increase in bone density, the newly formed bone is of poor quality and symptoms include increased fracture incidence, neuropathy, and short stature. Treatment of osteomalacia involves reversing the vitamin D deficiency status, usually through dietary supplementation combined with removing the cause of the deficiency. In severe cases, early management of this condition may involve a bone marrow transplant. Vitamin D deficiency is also associated with poor regenerative outcomes following periodontal surgical procedures (Bashutski *et al*. 2011).

Osteonecrosis

When ischemia occurs in bone for an extended period of time, often due to an interruption in blood supply, cell death occurs. Cells from a hematopoietic lineage are most prone to the negative effects of ischemia and cannot survive longer than 12 hours without an adequate blood supply (Steinberg 1991). Cells directly responsible for bone mineralization and turnover – osteoblasts, osteoclasts, and osteocytes – are less prone to anoxia, although cell death occurs in these cells after 48 hours of anoxia. If the blood supply resumes quickly, healing may occur and the bone may recover. However, after this critical time period passes, the bone in question will necrose, requiring partial or total resection, followed by reconstruction.

Osteonecrosis has multiple etiologies including radiation, bisphosphonate use, steroid use, hypertension, and in some cases arthritis or lupus. Bisphosphonate-related osteonecrosis of the jaw (ONJ) is of growing concern in the dental field. ONJ is defined as an area of exposed bone that does not heal within 8 weeks after identification by a healthcare provider (Khosla *et al*. 2008). Patients diagnosed with bisphosphonate-related ONJ include only those who have not had prior radiation to the craniofacial regions. Oral bisphosphonate use is associated with lower risk and has an incidence of 0.01–0.04%; this is in contrast to patients taking intravenous bisphosphonates who have a higher incidence of ONJ at 0.8–12% (Vescovi & Nammour 2011). This higher incidence is likely due to the higher dosing regimen given intravenously

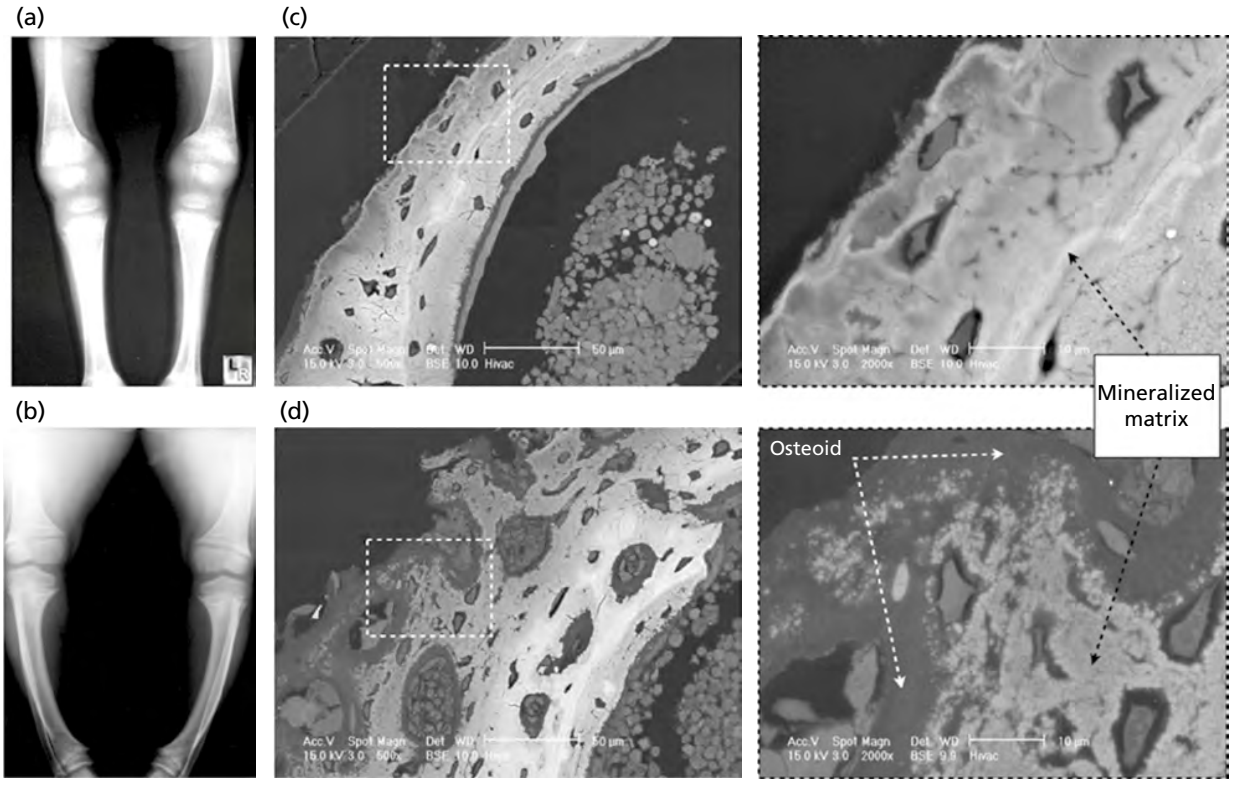


Fig. 2-17 Osteomalacia. (a, c) Normal matrix mineralization and maturation. (b, d) In osteomalacia, large hypomineralized zones accompanied by an increase in osteoid/immature matrix deposits are present.

and the severity and extent of the disease entity being treated. Oral bisphosphonates are typically used to treat osteoporosis, whereas intravenous bisphosphonates are given for the treatment of Paget's disease, multiple myeloma, and other conditions.

Osteomyelitis

Osteomyelitis is an infection of the bone and can be classified according to the source of infection, prognosis, bone anatomy, host factors, and clinical presentation (Calhoun & Manring 2005). Open fractures, surgery, and conditions such as diabetes mellitus and peripheral vascular disease increase the risk of developing osteomyelitis. Osteomyelitis from a hematogenous source is much more common in the pediatric population.

A definitive diagnosis of osteomyelitis is made by isolation of the bacteria in conjunction with diagnostic imaging, but can be challenging. Treatment involves antibiotic therapy in conjunction with drainage, debridement, and other appropriate surgical management, including bone stabilization and skin grafting (Conterno & da Silva Filho 2009).

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a group of genetic disorders of impaired collagen formation leading to decreased bone quality. Fractures, bone fragility, and osteopenia are common features of the disease. OI is relatively rare, with an incidence of 1 in 10 000 births. Autosomal dominant and recessive forms exist, although the autosomal dominant form is more common (Michou & Brown 2011).

The clinical presentation of OI has features in common with other diseases of bone metabolism, including fractures, bone deformities, and joint laxity. In addition, distinct features of OI include hearing loss, vascular fragility, blue sclerae, and dentinogenesis imperfecta. Type I collagen defects, including interruptions in interactions between collagen and noncollagenous proteins, weakened matrix, defective cell–cell and cell–matrix relationships, and defective tissue mineralization contribute to the etiology of the autosomal dominant form (Forlino *et al*. 2011). In the recessive form, deficiency of any of the three components of the collagen prolyl 3-hydroxylation complex results in a reduced ability of type I procollagen to undergo post-translational modification or folding. The severity of the disease, as well as the presence of defining features, varies widely.

Multiple therapeutic options are employed to treat the symptoms of OI, including surgery, collaboration with hearing, dental, and pulmonary specialists, and medication such as bisphosphonates and recombinant human growth hormone.

Other disorders

Several other conditions can affect bone homeostasis, including primary and secondary hyperparathyroidism, Paget's disease, and fibrous dysplasia.

Hyperparathyroidism is an overproduction of PTH, which promotes resorption of calcium and phosphorus from bone to increase serum calcium to normal levels (Unnanuntana *et al*. 2011). Primary hyperparathyroidism is most commonly caused by a parathyroid gland adenoma, whereas secondary hyperparathyroidism occurs when PTH production is overstimulated in response to low serum calcium. Hyperparathyroidism often presents with no symptoms and is discovered at routine screenings. The clinical presentation is very similar to that of rickets. Treatment includes identifying and eliminating the initiating cause.

Paget's disease is a condition where bone metabolism is significantly higher than normal, with bone formation exceeding that of resorption (Noor & Shoback 2000). This results in excessive bone formation and may affect one or multiple bones. The pelvic bone is most commonly affected. The affected bones, despite having increased bone formation, are weak and deformed. This is due to irregular collagen fiber formation within the bones. Bisphosphonate therapy is effective at decreasing bone turnover in this patient population, although this carries with it an increased risk of developing ONJ. Approximately 0.01–0.04% of patients taking bisphosphonates for the treatment of Paget's disease develop ONJ (Vescovi & Nammour 2011).

Fibrous dysplasia may affect multiple bones, but in 60% of cases, only one bone is affected (Michou & Brown 2011). It most commonly presents in childhood. Fibrous dysplasia lesions form in the medullary cavity extending to the cortical bone and are comprised of hyaline cartilage, immature woven bone, and osteoblast progenitor cells. Symptoms of this condition include fractures and bone pain. Notably, this condition has other craniofacial symptoms, including craniofacial bone deformities, exophthalmos, and dental abnormalities.

Conclusion

It can be appreciated that the dynamic nature of bone and its associated structures serves as an important organ system that supports form and function of the skeleton including the bones of the jaws. This chapter provides the overview of the highly complex and coordinated developmental processes of bone formation and homeostasis during health and disease.

Acknowledgments

The authors appreciate the assistance of Drs. Hector Rios and Jill Bashutski on the previous edition of this chapter. We thank Mr. Chris Jung for his assistance with the figures.

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Chapter 3

The Edentulous Ridge

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Clinical considerations

The alveolar process extends from the basal bone of the maxilla or the mandible and forms a boundary between the outer portion of the maxilla and the inner portion of the mandible (Pietrokovski *et al*. 2007). The alveolar process forms in harmony with the development and eruption of the teeth, and gradually regresses when the teeth are lost. In other words, the formation as well as the preservation of the alveolar process is dependent on the continued presence of teeth. Furthermore, the morphologic characteristics of the alveolar process are related to the size and shape of the teeth, events occurring during tooth eruption, as well as the inclination of the erupted teeth. Thus, subjects with long and narrow teeth, compared with subjects who have short and wide teeth, appear to have a more delicate alveolar process and, in particular in the front tooth regions, a thin, sometimes fenestrated, buccal bone plate (Fig. 3-1).

The tooth and its surrounding attachment tissues – the root cementum, the periodontal ligament, and the bundle bone – establish a functional unit (Fig. 3-2). Hence, forces elicited, for example during mastication, are transmitted from the crown of the tooth via the root and the attachment tissues to the load-carrying hard tissue structures in the alveolar process, where they are dispersed.

The loss of teeth and the loss or change of function within and around the socket will result in a series of adaptive alterations of the now edentulous portion of the ridge. Thus, it is well documented that following *multiple tooth* extractions and the subsequent restoration with removable dentures, the size of the ridge will become markedly reduced, not only in the horizontal but also in the vertical dimension (Figs. 3-3, 3-4). An important long-term study of dimensional ridge alterations in 42 complete denture wearers was presented by Bergman and Carlsson (1985). Cephalometric radiographic examinations were performed in a cephalostat and profiles of the edentulous mandible and maxilla were depicted 2 days after tooth extraction, and subsequently after 5 years and 21 years (Fig. 3-5). The authors concluded that during the observation interval most of the hard tissue component of the ridge was lost. However, there was wide variation in the degree of bone resorption and amount of remaining bone among the patients (Tallgren 1957, 1966; Atwood 1962, 1963; Johnson 1963, 1969; Carlsson *et al*. 1967).

Also, following the removal of *single* teeth, the ridge at the site will be markedly diminished (Fig. 3-6). The magnitude of this change was studied and reported by Pietrokovski and Massler (1967). The authors had access to 149 dental cast models (72 maxillary and 77 mandibular) in which one tooth was missing on one side of the jaw. The outer contours of the buccal and lingual (palatal) portions of the ridge at a tooth site and at the contralateral edentulous site were determined by the use of a profile stylus and

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

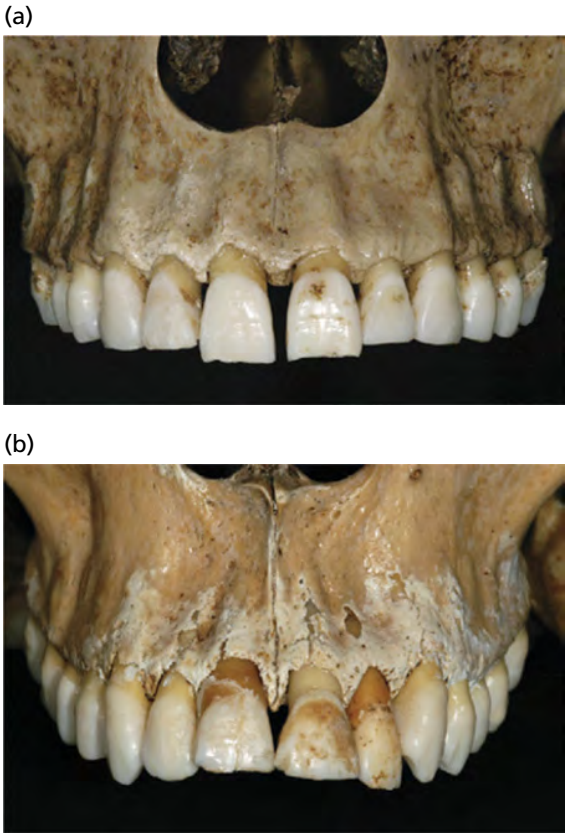

Fig. 3-1 Buccal aspect of adult skull preparations illustrating a dentate maxilla of one subject with a relatively thick (a) and another subject with a relatively thin (b) phenotype.

an imaging technique. Their findings are reported in Table 3-1.

It was concluded that the amount of tissue resorption (hard and soft tissues combined) following the loss of a single tooth was substantial and that the reduction of the ridge was twice as large at the buccal aspect as along the lingual and palatal aspect in all teeth groups examined. The absolute amounts of tissue loss varied from one group of teeth to the next. As a result of this tissue modeling, the center of the edentulous site shifted toward the lingual or palatal aspect of the ridge. The observations made by Pietrokovski and Massler (1967) were supported by findings presented by Schropp *et al*. (2003). They studied bone and soft tissue volume changes that took place during a 12-month period following the extraction of single premolars and molars. Clinical as well as cast model measurements were made immediately after tooth extraction and subsequently after 3, 6, and 12 months of healing. It was observed that the buccolingual/-palatal dimension during the first 3 months was reduced by about 30%, and after 12 months the edentulous site had lost at least 50% of its original width. Furthermore, the height of the buccal bone plate was reduced and after 12 months of healing the buccal prominence was located 1.2 mm apical of its lingual/palatal counterpart.

Misawa *et al*. (2016) evaluated the hard tissue changes that occurred in the alveolar process of

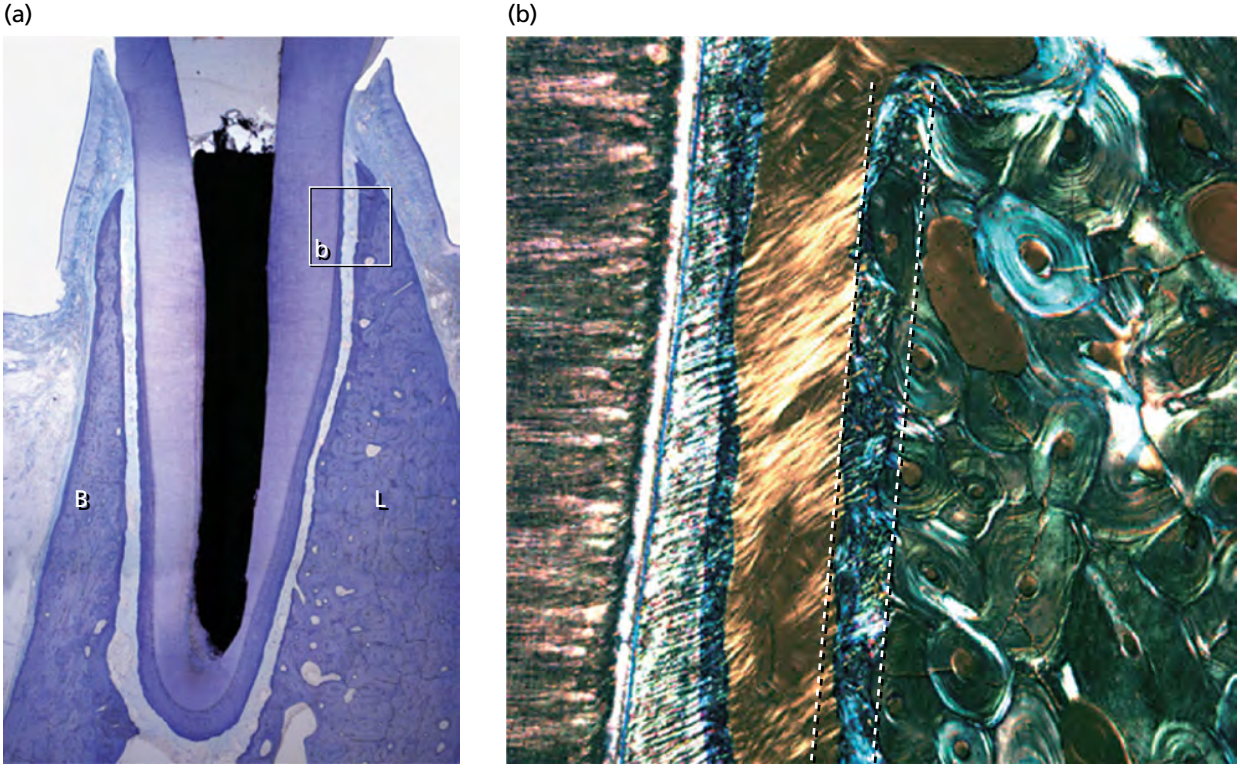

Fig. 3-2 Buccolingual histologic section of the alveolar process. (a) Tooth is surrounded by its attachment tissues (cementum, periodontal ligament, alveolar bone proper). B, buccal aspect; L, lateral aspect. (b) Higher magnification of the attachment tissues. Note that the dentin is connected to the alveolar bone via the root cementum, and the periodontal ligament. The alveolar bone is characterized by its content of circumferential lamellae. The portion of the bone that is facing the periodontal ligament (between the dotted lines) is called the alveolar bone proper or the bundle bone.

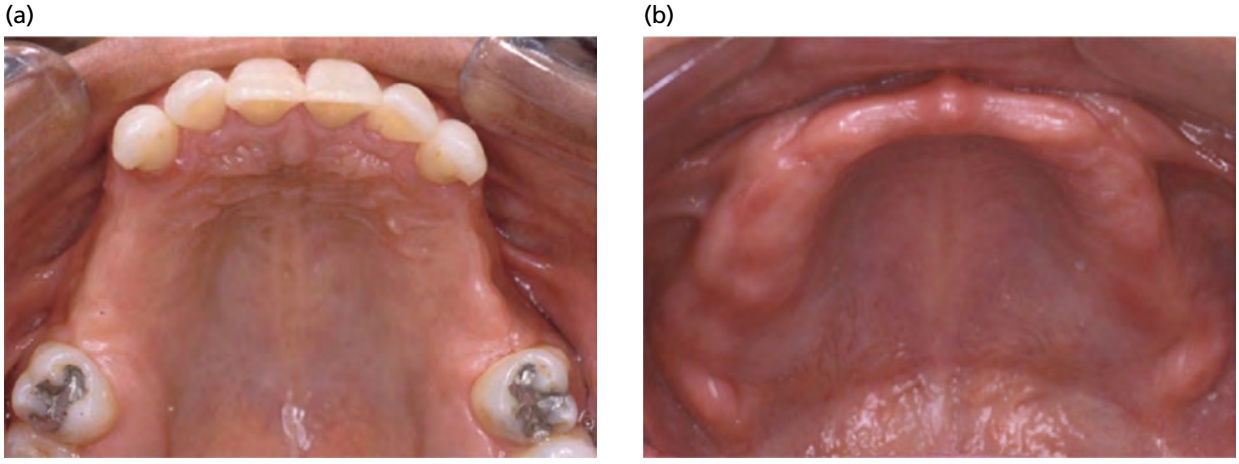

Fig. 3-3 (a) Clinical view of a partially edentulous maxilla. Note that the crest of the edentulous portions of the ridge is narrow in the buccopalatal direction. (b) Clinical view of a fully edentulous and markedly resorbed maxilla. Note that *papilla incisiva* is located in the center of the ridge. This indicates that the entire buccal and also a substantial portion of the palatal ridge are missing.

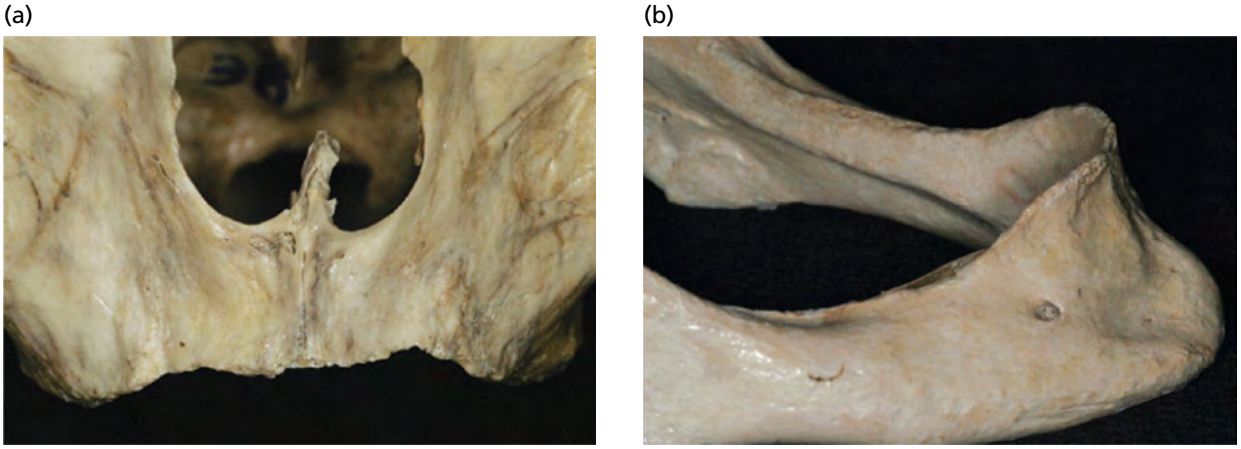

Fig. 3-4 Buccal aspect of a skull preparation illustrating a fully edentulous maxilla (a) and mandible (b). The small segments of the alveolar ridge that still remain are extremely thin in the buccopalatal/-lingual direction.

incisor and premolar sites of the maxilla following tooth removal. The authors obtained cone-beam computed tomograms from fully healed extraction sites (>1 year) and compared such scans with the contralateral pristine tooth sites. The study disclosed that all parameters had been significantly reduced following tooth removal. Thus, the overall (1) cross-sectional area was reduced from 99 to 65 mm^2, (2) the height from 11.5 to 9.5 mm, and (3) the width from about 9 to 3 mm (marginal third), 9 to 5 mm (middle portion), and 9 to 6 mm (apical portion).

The information provided by Pietrokovski and Massler (1967), Schropp *et al*. (2003) and Misawa *et al*. (2016) suggest that if an alveolar process includes a tooth that has a horizontal width of, for example, 12 mm, the edentulous site will be only 6 mm wide 12 months after healing following tooth extraction. During this 12-month interval, 4 mm of tissue will be lost from the buccal and 2 mm from the lingual aspect of the site.

In a clinical study (Sanz *et al*. 2010; Tomasi *et al*. 2010) it was observed that the degree of early (4 months) resorption of the buccal bone plate following tooth extraction was dependent on its original dimension. Thus, bone plates that were <1 mm wide lost substantially more dimension (width and height) than plates that were >1 mm wide.

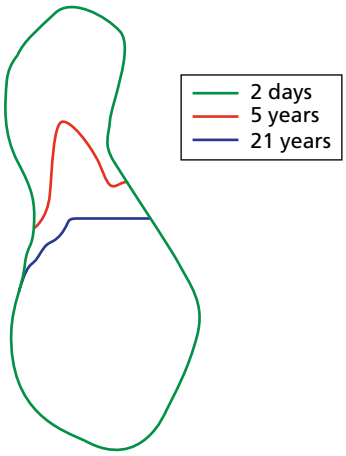

Fig. 3-5 Profile of the mandibular bone following tooth extraction at 2 days, 5 years, and 21 years after tooth removal. (Source: Bergman & Carlsson 1985. Reproduced with permission from Elsevier.)

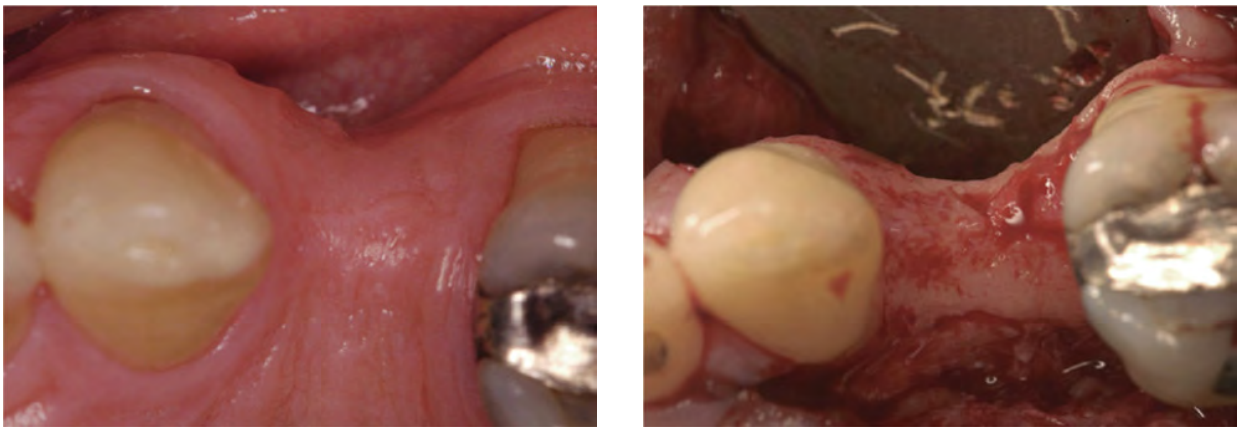

Fig. 3-6 Clinical view of an edentulous ridge in the maxillary premolar region. The premolar was extracted several years before the clinical documentation was made. (a) Note the presence of a buccal invagination of the ridge. (b) Following flap elevation, the crest region of the severely resorbed buccal portion of the alveolar process is disclosed.

Table. 3-1 Average amount of resorption of tooth extraction in different tooth areas.[a]

Tooth	Average amount of resorption (mm)		Difference
	Buccal surface	Lingual/ palatal surface	
Mandibular teeth			
Central incisor	2.08	0.91	1.17
Lateral incisor	3.54	1.41	2.13
Canine	3.25	1.59	1.66
First premolar	3.45	1.40	2.05
Second premolar	3.28	0.75	2.53
First molar	4.69	2.79	1.90
Second molar	4.30	3.00	1.30
Maxillary teeth			
Central incisor	3.03	1.46	1.57
Lateral incisor	3.47	0.86	2.61
Canine	3.33	1.91	1.42
First premolar	3.33	2.04	1.29
Second premolar	2.58	1.62	0.96
First molar	5.25	3.12	2.13

[a] "The amount of resorption was greater along the buccal surface than along the lingual or palatal surface in every specimen examined, although the absolute amounts and differences varied very widely. This caused a shift in the center of the edentulous ridge toward the lingual or palatal side of the ridge with a concomitant *decrease* in arch length in the mandible as well as the maxillae" (Pietrokovski & Massler 1967).

In this context it is important to acknowledge that the buccal bone plate in the frontal tooth region in humans is frequently (>80% of sites) <1 mm wide (Braut *et al*. 2011; Januário *et al*. 2011; Nowzari *et al*. 2012). Hence, it can be anticipated that tooth loss in this part of the dentition may result in marked dimension alterations (horizontal as well as vertical) of the ridge and that this in turn may cause esthetic concerns.

Conclusion: The extraction of single as well as multiple teeth induces a series of adaptive changes in the soft and hard tissues that result in an overall regression of the edentulous site(s). Resorption appears to be more pronounced at the buccal than at the lingual/palatal aspects of the ridge.

It should be realized that the alveolar process might also undergo change as the result of tooth-related disease processes, such as forms of marginal periodontitis, as well as periapical periodontitis. Furthermore, traumatic injuries (including from improper tooth removal techniques) may cause marked damage to the alveolar process of the maxilla and mandible.

Remaining bone in the edentulous ridge

In the publication by Schropp *et al*. (2003), bone tissue formation in single extraction sockets was studied by means of subtraction radiography. Thus, radiographs of the study sites were obtained using a standardized technique immediately after tooth extraction and then after 3, 6, and 12 months of healing (Fig. 3-7). It was observed that in the first few months, some bone loss (height) took place in the alveolar crest region. Most of the bone gain in the socket occurred in the first 3 months. There was additional gain of bone in the socket between 3 and 6 months. In the interval between 6 and 12 months, the newly formed bone obviously remodeled and the amount of mineralized tissue was reduced. In other words, in the later phases of socket healing, small amounts of mineralized tissue may have remained in the center of the edentulous site.

The bony part of the edentulous ridge in humans was examined in biopsies sampled from the posterior portions of the jaw by Lindhe *et al*. (2012). The peripheral borders of the ridge were consistently lined with dense cortical bone. More central parts harbored cancellous bone and included trabeculae made up mainly of lamellar bone (Fig. 3-8a). The trabeculae

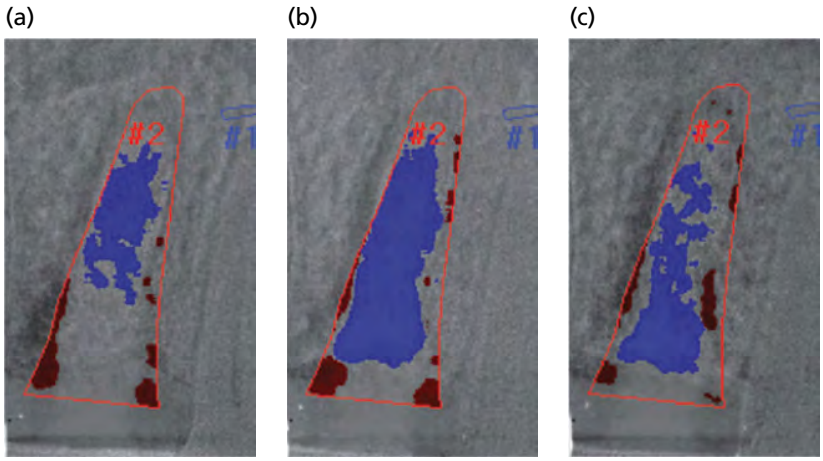

Fig. 3-7 Radiographic (subtraction radiography) images of an extraction site obtained after (a) 3 months, (b) 6 months, and (c) 12 months of healing. The blue color represents areas of new bone formation. During the first 6 months, the deposition of new bone was intense. Between 6 and 12 months, some of the newly formed bone was remodeled. (Source: Courtesy of L. Schropp.)

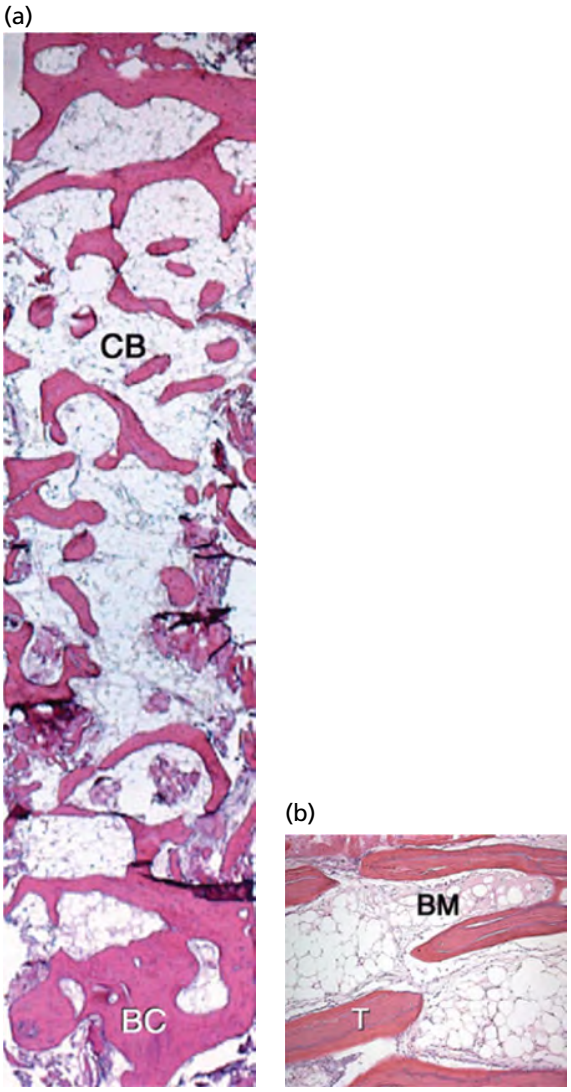

Fig. 3-8 Histologic sections of an edentulous site obtained from the maxillary premolar region in man. (a) The marginal portion of the ridge (BC) is protected by a cortical cap made up of lamellar bone, while more central regions house the cancellous bone (CB). (b) The cancellous bone is characterized by the trabeculae of mineralized bone (T) within the bone marrow (BM) compartment.

that were embedded in bone marrow varied in shape, and frequently had a haphazard orientation. The bone marrow was dominated by adipocytes, vascular structures, and scattered inflammatory cells. The hard tissue component of the ridge was comprised of a mixture of mineralized bone (about 60%), bone marrow (about 20%), and fibrous tissue (about 15%) (Fig. 3-8b).

Classification of remaining bone

Based on the volume of remaining mineralized bone, the edentulous sites may, according to Lekholm and Zarb (1985), be classified into five different groups (Fig. 3-9). In groups A and B, substantial amounts

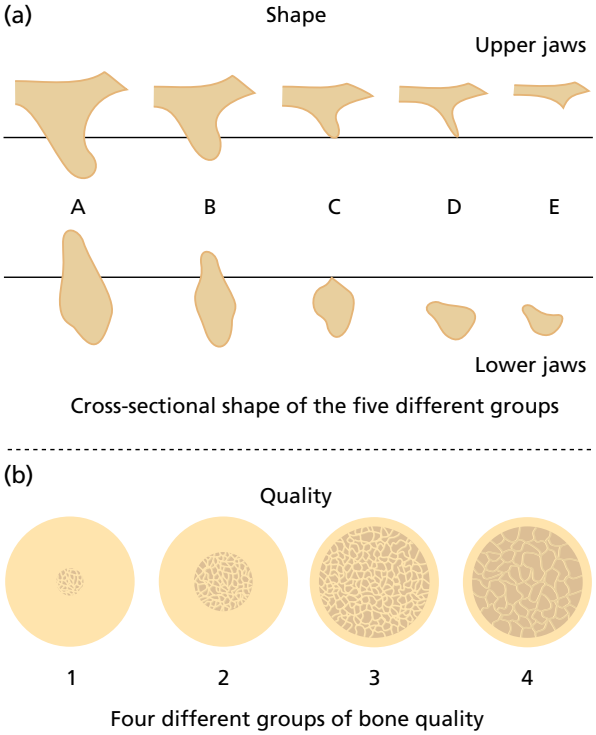

Fig. 3-9 (a) A classification of residual jaw shape and (b) jaw bone quality. (Source: Lekholm & Zarb 1985. Reproduced from Quintessence.)

of the ridge still remain, whereas in groups C, D, and E, only minute amounts of hard tissue remain. Lekholm and Zarb (1985) also classified the "quality" of the bone in the edentulous site. Class 1 and class 2 characterized a location in which the walls – the cortical plates – of the site are thick and the volume of bone marrow is small. Relatively thin walls of cortical bone, however, will border sites that belong to class 3 and class 4, while the amount of cancellous bone (spongiosa), including trabeculae of lamellar bone and marrow, is large.

Topography of the alveolar process

The alveolar process that houses the roots of the teeth extends from the basal bone (Fig. 3-10a) of the maxilla and the mandible. The shape and dimensions (height and width) of the basal bone vary considerably from subject to subject (Figs. 3-10a, b) and from site to site in the same individual. There is no distinct boundary between the alveolar process and the basal bone of the jaws.

At sites of the jaws where the teeth erupt in "normal" orientation in the developing alveolar process, hard tissue will be present on the facial (buccal) as well as on the lingual (palatal) aspect of the roots (Fig. 3-10c). However, at sites where the teeth erupt with a facial orientation, the facial (buccal) bone of the alveolar process will become thin and at times even disappear (dehiscence, fenestration) (Fig. 3-10d).

The outer walls of the alveolar process – facial (buccal), marginal, and lingual (palatal) aspects – are continuous with the outer walls of the basal bone. The walls are comprised of dense cortical bone, while more central portions harbor trabecular bone (radiographic term; spongy bone, anatomic term; cancellous bone, histologic term) that contains bone trabeculae within the bone marrow.

The cortical walls (plates) of the alveolar process are continuous with the bone that lines the sockets, that is the alveolar bone proper or the bundle bone (see Fig. 3-2b). The cortical plates (the outer walls) of the alveolar process meet the alveolar bone proper at

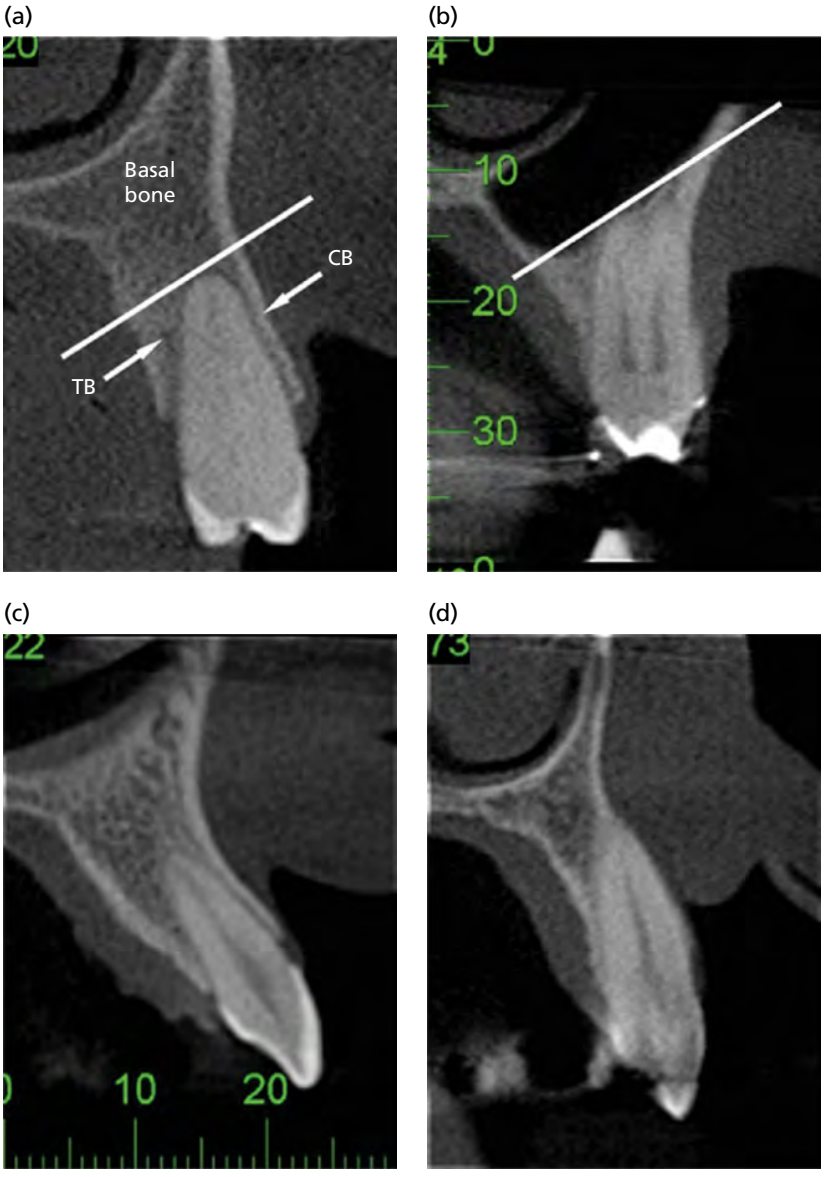

Fig. 3-10 (a) Cone-beam tomogram of the premolar region of the maxilla. The alveolar process is continuous with the voluminous basal bone of the maxilla. CB, cortical bone plate; TB, trabecular bone. (b) Cone-beam tomogram of the premolar region of the maxilla. Note that at this site the dimension of the basal bone is very small. (c) Tomogram of an anterior maxillary tooth with a "normal" direction of eruption. The incisor resides within the bony compartment of the alveolar process. (d) Tomogram of a canine tooth that erupted in a facial orientation. The facial (buccal) bone of the alveolar process is thin or even absent.

the crest of the interdental septum. In subjects (sites) with healthy periodontium, the crest of the septum is located 1–2 mm apical of the cementoenamel junction.

In some portions of the dentition (such as in the symphysis region of the mandible), the trabecular bone component of the alveolar process may be absent.

From an alveolar process to an edentulous ridge

The alterations that occur in the alveolar process following the extraction of a single tooth can, for didactic reasons, be divided in two interrelated series of events, namely *intra-alveolar processes* and *extra-alveolar processes*.

Intra-alveolar processes

The healing of extraction sockets in human volunteers was studied by, for example, Amler (1969) and Evian *et al*. (1982). Although the biopsy technique used by Amler only allowed the study of healing in the marginal portions of the empty socket, his findings are often referred to.

Amler stated that following tooth extraction, the first 24 hours are characterized by the formation of a *blood clot* in the socket. Within 2–3 days the blood clot is gradually replaced with *granulation tissue*. After 4–5 days, the *epithelium* from the margins of the soft tissue starts to proliferate to cover the granulation tissue in the socket. One week after extraction, the socket contains granulation tissue and *young connective tissue*, and *osteoid* formation is ongoing in the apical portion of the socket. After 3 weeks, the socket contains connective tissue and there are signs of mineralization of the osteoid. The *epithelium* covers the wound. After 6 weeks of healing, bone formation in the socket is pronounced and trabeculae of newly formed bone can be seen.

Amler's study was of short duration, so it could only evaluate events that took place in the marginal portion of the healing socket. His experimental data did not include the important later phase of socket healing that involves the processes of modeling and remodeling of the newly formed tissue in various parts of the alveolus. Thus, the tissue composition of the fully healed extraction site was not documented in the study.

In a later and longer-term study, Trombelli *et al*. (2008) examined socket healing in biopsies sampled during a 6-month period from human volunteers. They confirmed most of Amler's findings and reported that in the early healing phase (tissue modeling), the socket was filled with granulation tissue that was subsequently replaced with provisional connective tissue and woven bone. In biopsies sampled in later phases of healing, it was observed that the process by which woven bone was replaced by lamellar bone and marrow, that is remodeling, was slow and exhibited great individual variation. In only a limited number of specimens representing 6 months of healing had woven bone been replaced with bone marrow and trabeculae of lamellar bone. It can be assumed therefore that tissue modeling following tooth extraction in humans is a rather rapid process, while the subsequent remodeling is slow and may take years to be completed.

The results from experiments using the dog model (Cardaropoli *et al*. 2003; Araújo & Lindhe 2005) will be used in this chapter to describe details of the various phases of socket healing, including processes of both modeling and remodeling. It should be remembered that healing of the postextraction sites in these animal studies, including phases of modeling and remodeling, was a rapid process compared to socket healing in humans. Thus, the extraction socket was in most instances completely healed (filled with cancellous bone) after 2–3 months.

The model

Buccal and lingual full-thickness flaps are elevated and the distal roots of mandibular premolars extracted (Fig. 3-11a). The mucosal flaps are subsequently replaced to provide soft tissue coverage of the fresh extraction wound (Fig. 3-11b). Healing of the experimental sites is monitored in biopsy specimens obtained at time intervals varying from 1 day to 6 months (Fig. 3-11c).

Overall pattern of socket healing

Figure 3-12 shows a mesiodistal section of a fresh extraction socket bordered by adjacent roots. The socket walls are continuous with the alveolar bone proper of the neighboring teeth. The tissue inside the interdental (inter-radicular) septa is made up of cancellous bone and includes trabeculae of lamellar bone within bone marrow.

The empty socket is first filled with blood and a *coagulum* (clot) forms (Fig. 3-13a). Inflammatory cells (polymorphonuclear leukocytes and monocytes/macrophages) migrate into the coagulum and start to phagocytose elements of necrotic tissue. The process of wound cleansing is initiated (Fig. 3-13b). Sprouts of newly formed vessels and mesenchymal cells (from the severed periodontal ligament) enter the coagulum and *granulation tissue* is formed. The granulation tissue is gradually replaced with *provisional connective tissue* (Fig. 3-13c) and subsequently immature bone (*woven bone*) is laid down (Fig. 3-13d). The hard tissue walls of the socket – the alveolar bone proper or the bundle bone – are gradually resorbed and the socket becomes filled with immature woven bone (Fig. 3-13e). The initial phase of the healing process (tissue modeling) is now complete. In subsequent phases, the woven

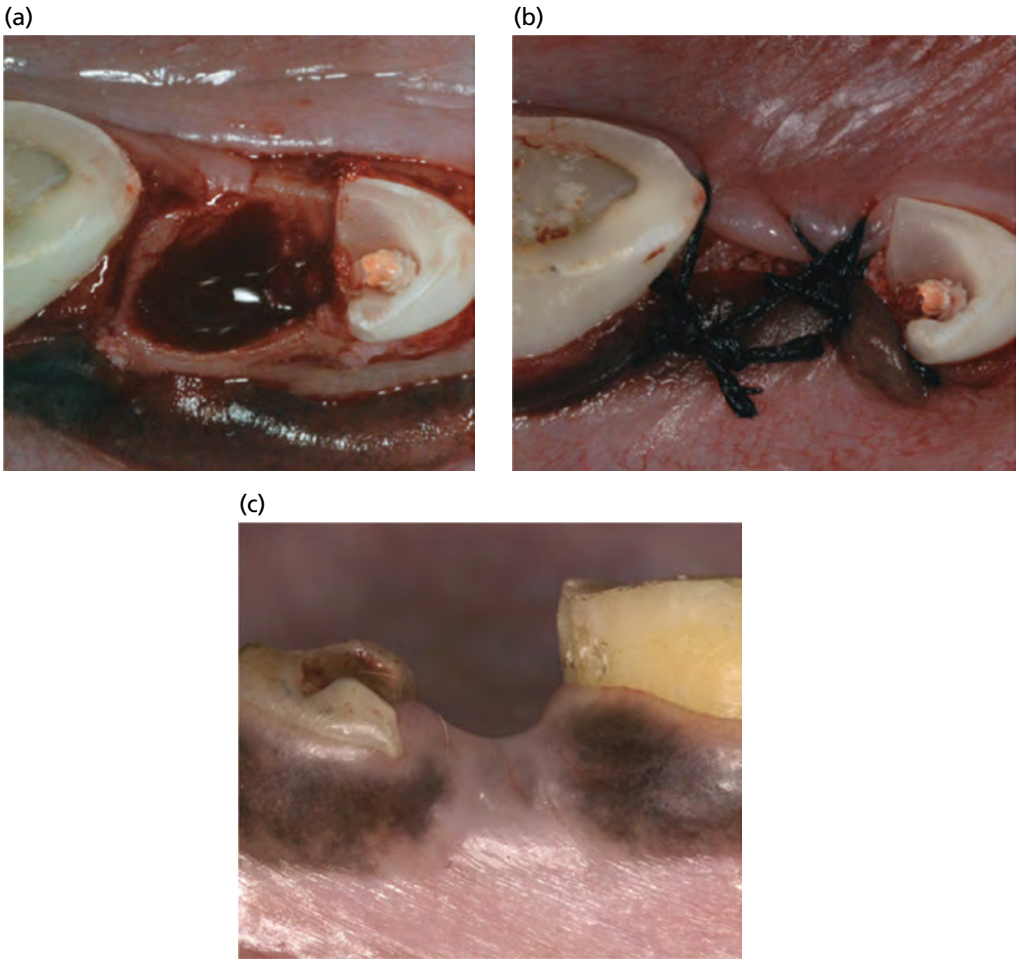

Fig. 3-11 (a) A mandibular premolar site (from a dog model) from which the distal root of the fourth premolar had been removed. (b) Mucosal, full-thickness flaps were replaced and sutured to close the entrance of the socket. (c) Site after 6 months of healing. Note the saddle-shaped outline (loss of tissue) of the alveolar crest region.

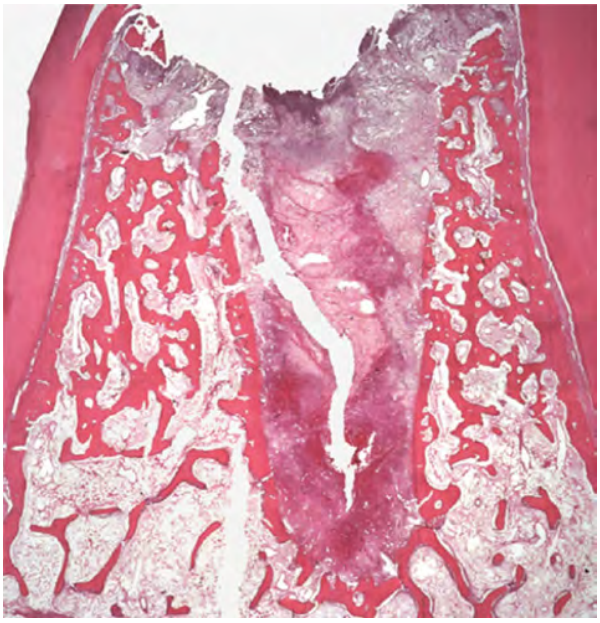

Fig. 3-12 Histologic section showing the mesiodistal aspect of a fresh extraction socket bordered by two neighboring roots. Note that the alveolar bone from the tooth sites is continuous with the walls of the empty socket. The interdental septum contains cancellous bone including trabeculae of lamellar bone and marrow.

bone in the socket will be gradually remodeled into lamellar bone and marrow (Fig. 3-13f–h).

Important events in socket healing

Blood clotting

Immediately after tooth extraction, blood from the severed vessels will fill the socket. Proteins derived from vessels and damaged cells initiate a series of events that lead to the formation of a fibrin network (Fig. 3-14). *Platelets* form aggregates and interact with the fibrin network to produce a *coagulum* (a blood clot) that effectively plugs the severed blood vessels and stops the bleeding. The blood clot acts as a physical matrix that directs cellular movements and it contains substances that are of importance for the forthcoming healing process. Thus, the clot contains substances (i.e. *growth factors*) that (1) influence mesenchymal cells and (2) enhance the activity of inflammatory cells. Such substances will thus induce and amplify the migration of various types of cells into the socket wound, as well as their proliferation, differentiation, and synthetic activity within the coagulum.

Although the blood clot is crucial in the initial phase of wound healing, its removal is mandatory

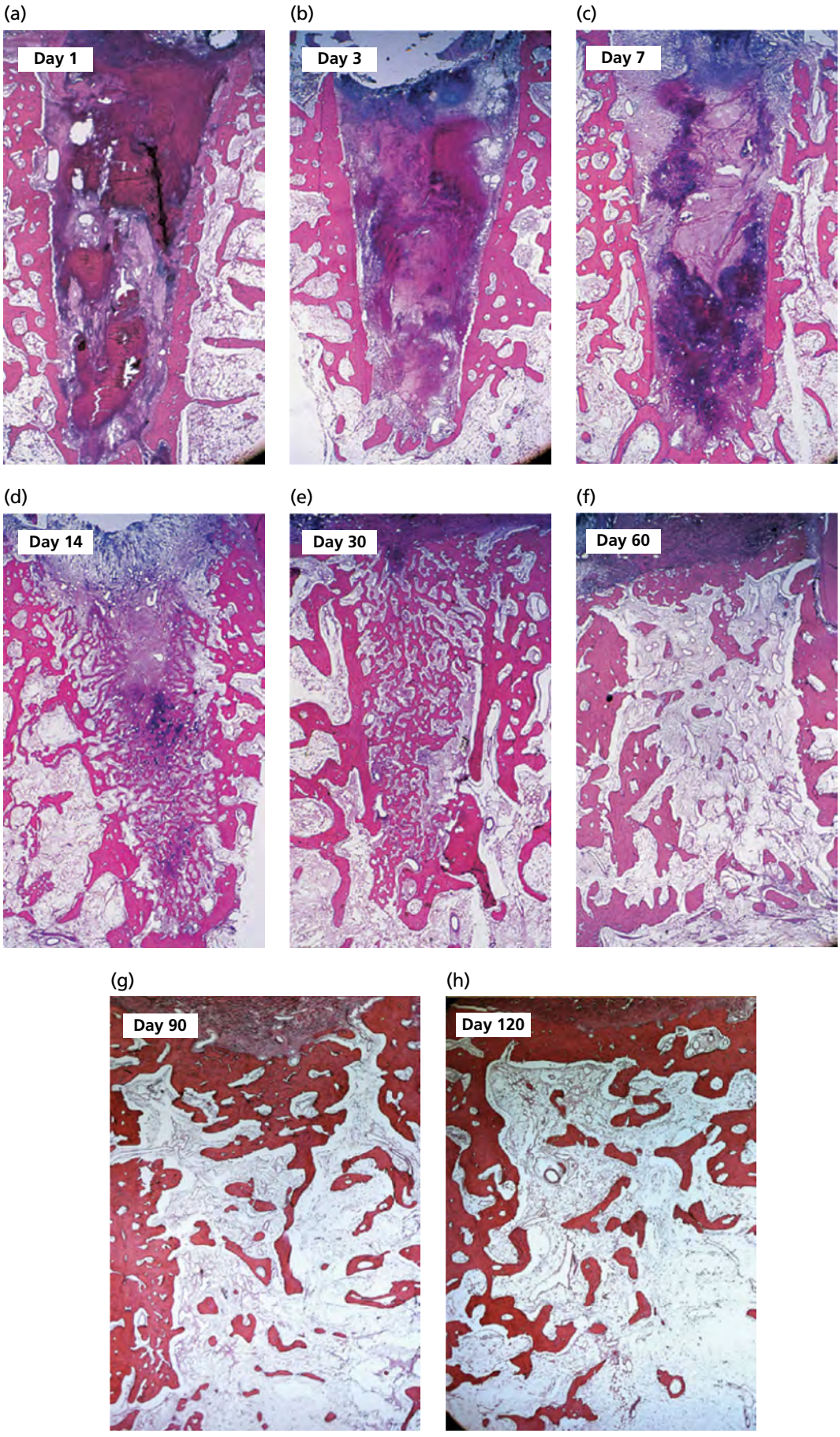

Fig. 3-13 (a–h) Overall pattern of bone formation in an extraction socket. For details see text.

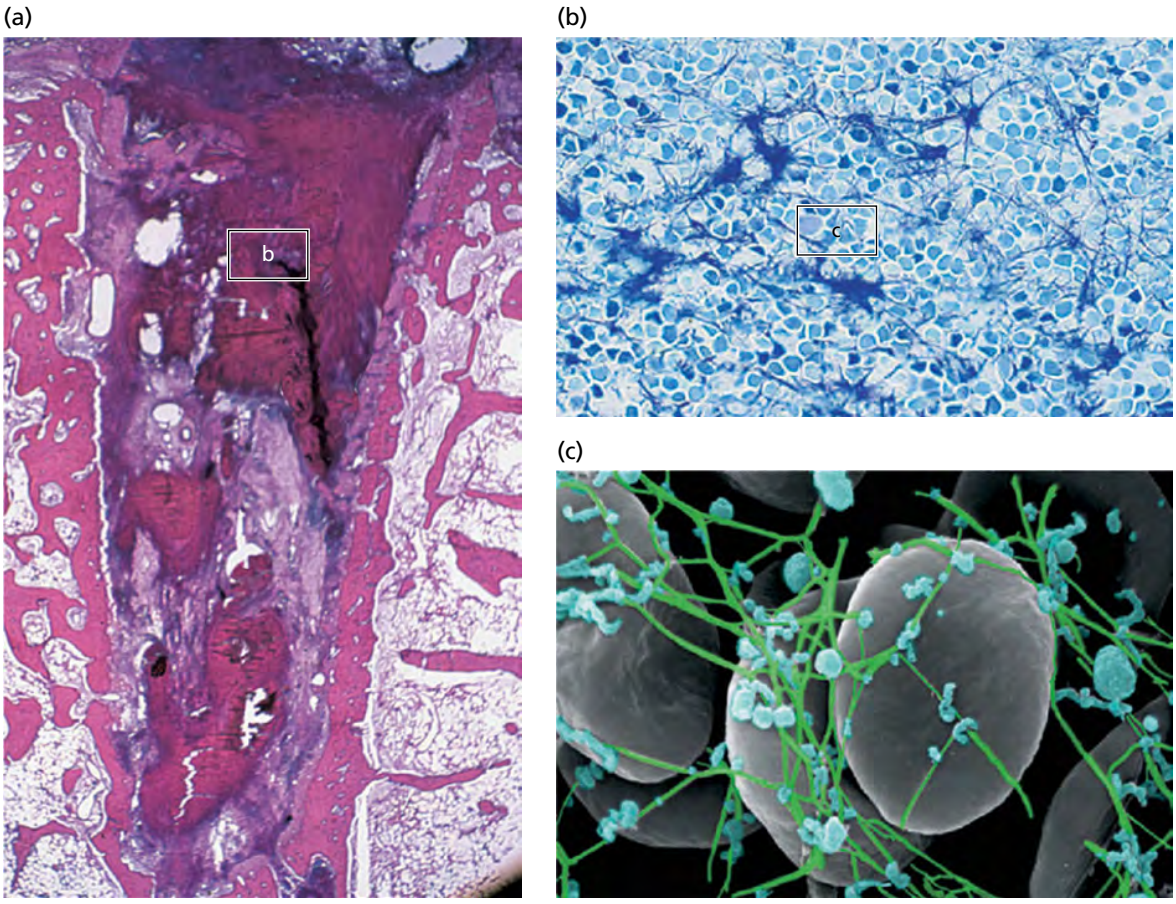

Fig. 3-14 Histologic section (mesiodistal aspect) representing 1 day of healing (a). The socket is occupied with a blood clot that contains large numbers of erythrocytes (b) entrapped in a fibrin network, as well as platelets [blue in (c)].

to allow the formation of new tissue. Thus, within a few days after the tooth extraction, the blood clot will start to break down, that is, the process of "fibrinolysis" is initiated (Fig. 3-15).

Wound cleansing

Neutrophils and macrophages migrate into the wound, engulf bacteria and damaged tissue, and clean the site before the formation of new tissue can start. The neutrophils enter the wound early, while macrophages appear somewhat later. The macrophages are not only involved in the cleaning of the wound but they also release growth factors and cytokines that further promote the migration, proliferation, and differentiation of mesenchymal cells. Once the debris has been removed and the wound has been "sterilized", the neutrophils undergo a programmed cell death (*apoptosis*) and are removed from the site through the action of macrophages. The macrophages subsequently withdraw from the wound.

Tissue formation

Sprouts of vascular structures (from the severed periodontal ligament) as well as mesenchymal, fibroblast-like cells (from the periodontal ligament and from adjacent bone marrow regions) enter the socket. The mesenchymal cells start to proliferate and deposit matrix components in an extracellular location (Fig. 3-16); *granulation tissue* will gradually replace the blood clot. This granulation tissue eventually contains macrophages and a large number of fibroblast-like cells, as well as numerous newly formed blood vessels. The fibroblast-like cells continue to (1) release growth factors, (2) proliferate, and (3) deposit a new extracellular matrix that guides the ingrowth of additional cells and allows the further differentiation of the tissue. The newly formed vessels provide the oxygen and nutrients that are needed for the increasing number of cells that occur in the new tissue. The intense synthesis of matrix components exhibited by the mesenchymal cells is called *fibroplasia*, while the formation of new vessels is called *angiogenesis*. A *provisional connective tissue* is established through the combination of fibroplasia and angiogenesis (Fig. 3-17).

The transition of the provisional connective tissue into bone tissue occurs along the vascular structures. Thus, osteoprogenitor cells (e.g. pericytes) migrate and gather in the vicinity of the vessels. They differentiate into osteoblasts that produce a matrix of collagen fibers, which takes on a woven pattern. The *osteoid* is formed. The process of mineralization is initiated within the osteoid. The osteoblasts continue to lay down osteoid and occasionally such cells are trapped in the matrix and become osteocytes. This newly formed bone is called *woven bone* (Figs. 3-17, 3-18).

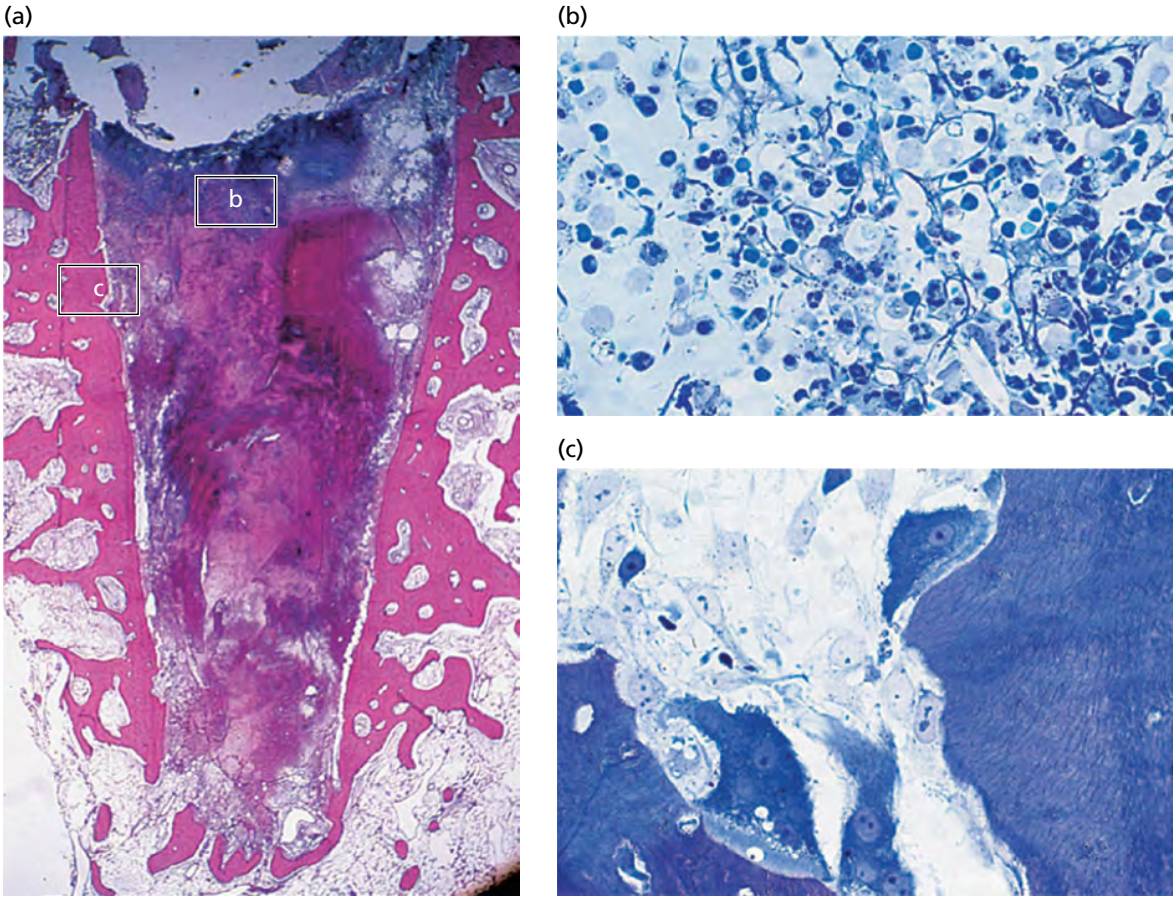

Fig. 3-15 (a) Histologic section (mesiodistal aspect) representing 3 days of healing. (b) Note the presence of neutrophils and macrophages that are engaged in wound cleansing and the breakdown of the blood clot. (c) Osteoclastic activity occurs on the surface of the old bone in the socket walls.

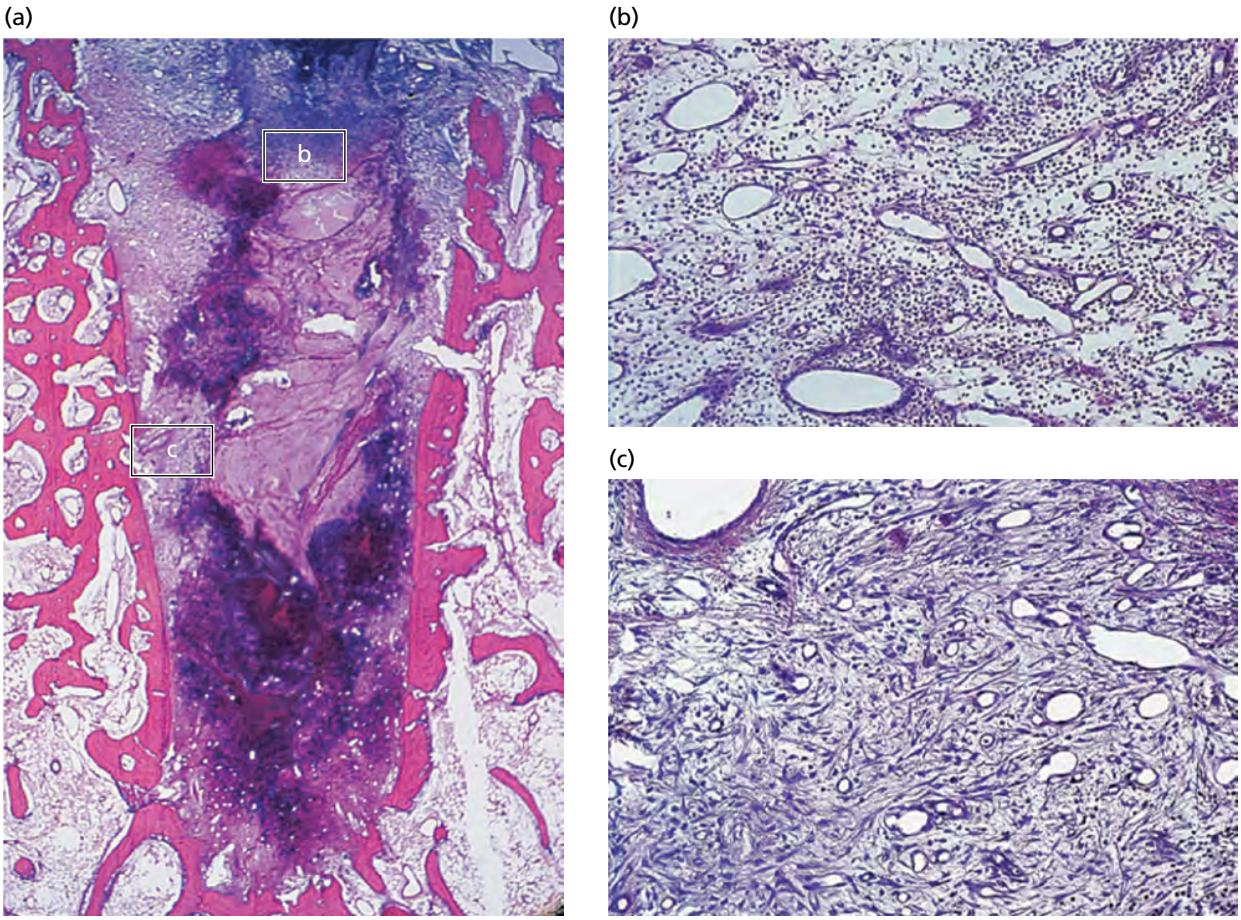

Fig. 3-16 (a) Histologic section (mesiodistal aspect) representing 7 days of healing. (b) Note the presence of a richly vascularized early granulation tissue with large numbers of inflammatory cells in the upper portion of the socket. (c) In more apical areas, a tissue including large numbers of fibroblast-like cells is present (late granulation tissue).

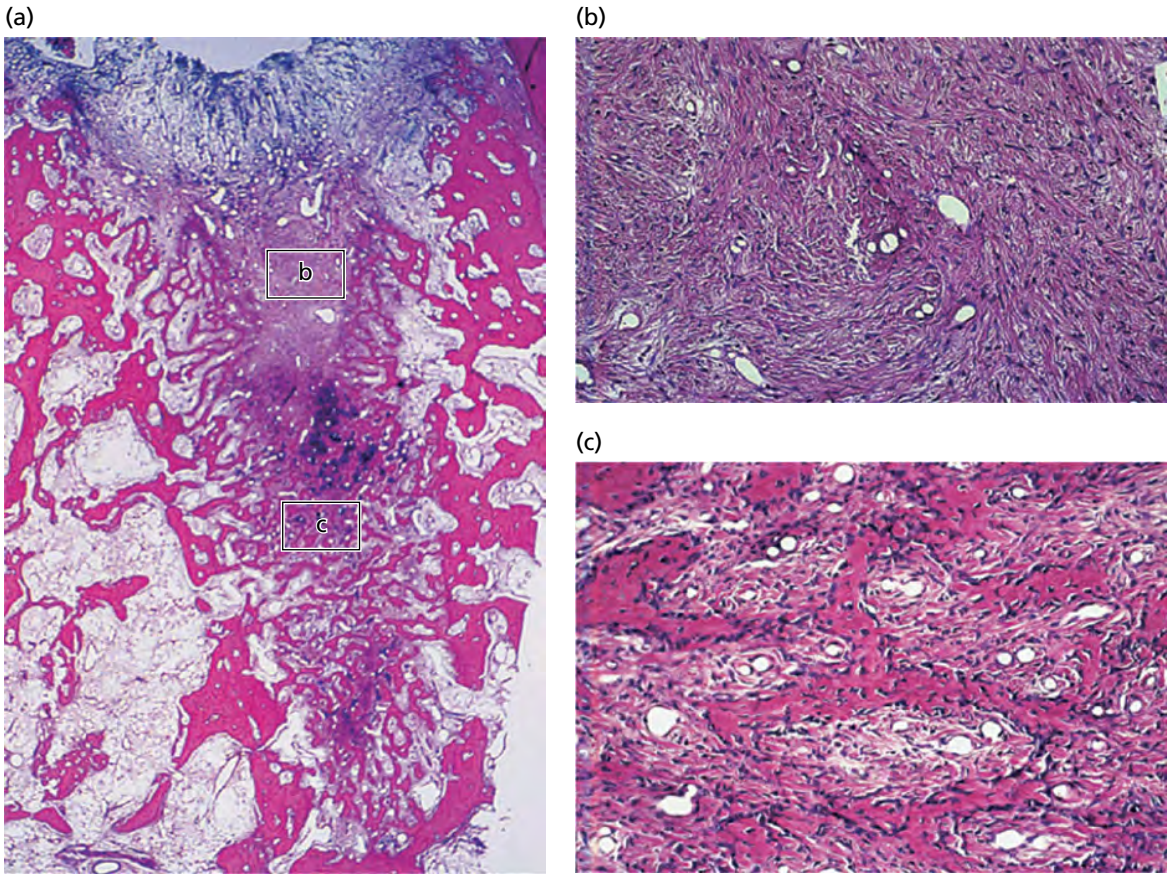

Fig. 3-17 (a) Histologic section (mesiodistal aspect) representing 14 days of healing. (b) In the marginal portion of the wound, a provisional connective tissue rich in fibroblast-like cells is present. (c) The formation of woven bone has at this time interval already begun in the apical and lateral regions of the socket.

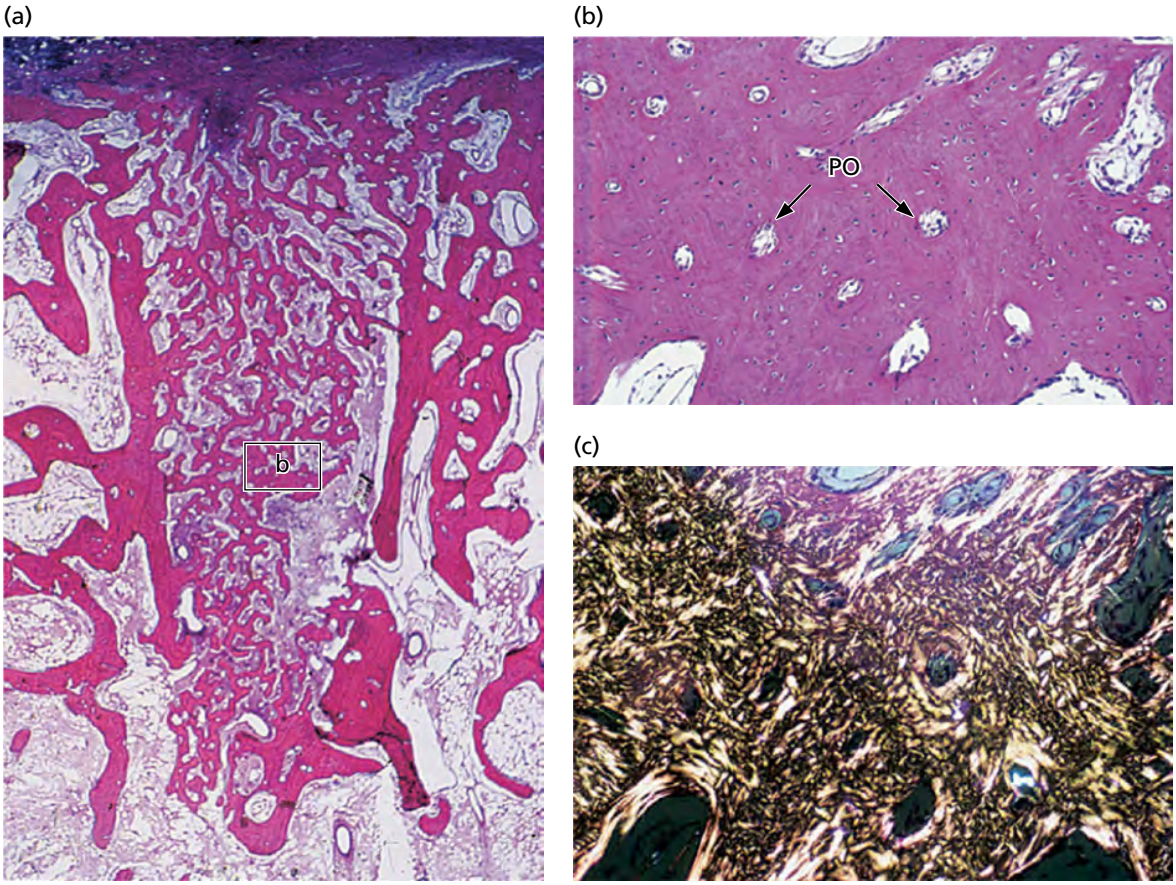

Fig. 3-18 (a) Histologic section (mesiodistal aspect) representing 30 days of healing. The socket is filled with woven bone. (b) Woven bone contains a large number of cells and primary osteons (PO). (c) The woven pattern of the collagen fibers of this type of bone is illustrated (polarized light).

The woven bone is the first type of bone to be formed and is characterized by (1) its rapid deposition as finger-like projections along the route of vessels, (2) the poorly organized collagen matrix, (3) the large number of osteoblasts that are trapped in its mineralized matrix, and (4) its low load-bearing capacity. Trabeculae of woven bone are shaped around and encircle the vessel. The trabeculae become thicker through the deposition of additional woven bone. Cells (osteocytes) become entrapped in the bone tissue and the first set of osteons, the *primary osteons*, are organized. The woven bone is occasionally reinforced by the deposition of so-called *parallel-fibered bone* (collagen fibers organized not in a woven but in a concentric pattern).

It is important to realize that during this early phase of healing most of the bone tissue in the walls of the socket (the bundle bone) is removed.

Tissue modeling and remodeling

The initial bone formation in this dog model is a fast process. Within a few weeks, the entire extraction socket is filled with woven bone or, as this tissue is also called, *primary bone spongiosa*. The woven bone offers (1) a stable scaffold, (2) a solid surface, (3) a source of osteoprogenitor cells, and (4) an ample blood supply for cell function and matrix mineralization.

The woven bone with its primary osteons is gradually replaced with lamellar bone and bone marrow (Fig. 3-19). In this process, the primary osteons are replaced with *secondary osteons*. The woven bone is first resorbed to a certain level. The level of the resorption front will establish a so-called *reversal line*, which is also the level from which new bone with secondary osteons will form (Fig. 3-20). Although this remodeling may start early during socket healing, it will take several months until all woven bone in the extraction socket has been replaced with lamellar bone and marrow.

An important part of socket healing involves the formation of a *hard tissue cap* that will close the marginal entrance to the socket. This cap is initially comprised of woven bone (Fig. 3-21a), but is subsequently remodeled and replaced with lamellar bone that becomes continuous with the cortical plate at the periphery of the edentulous site (Fig. 3-21b). This process is called corticalization.

The wound is now healed, but the tissues in the site will continue to adapt to functional demands.

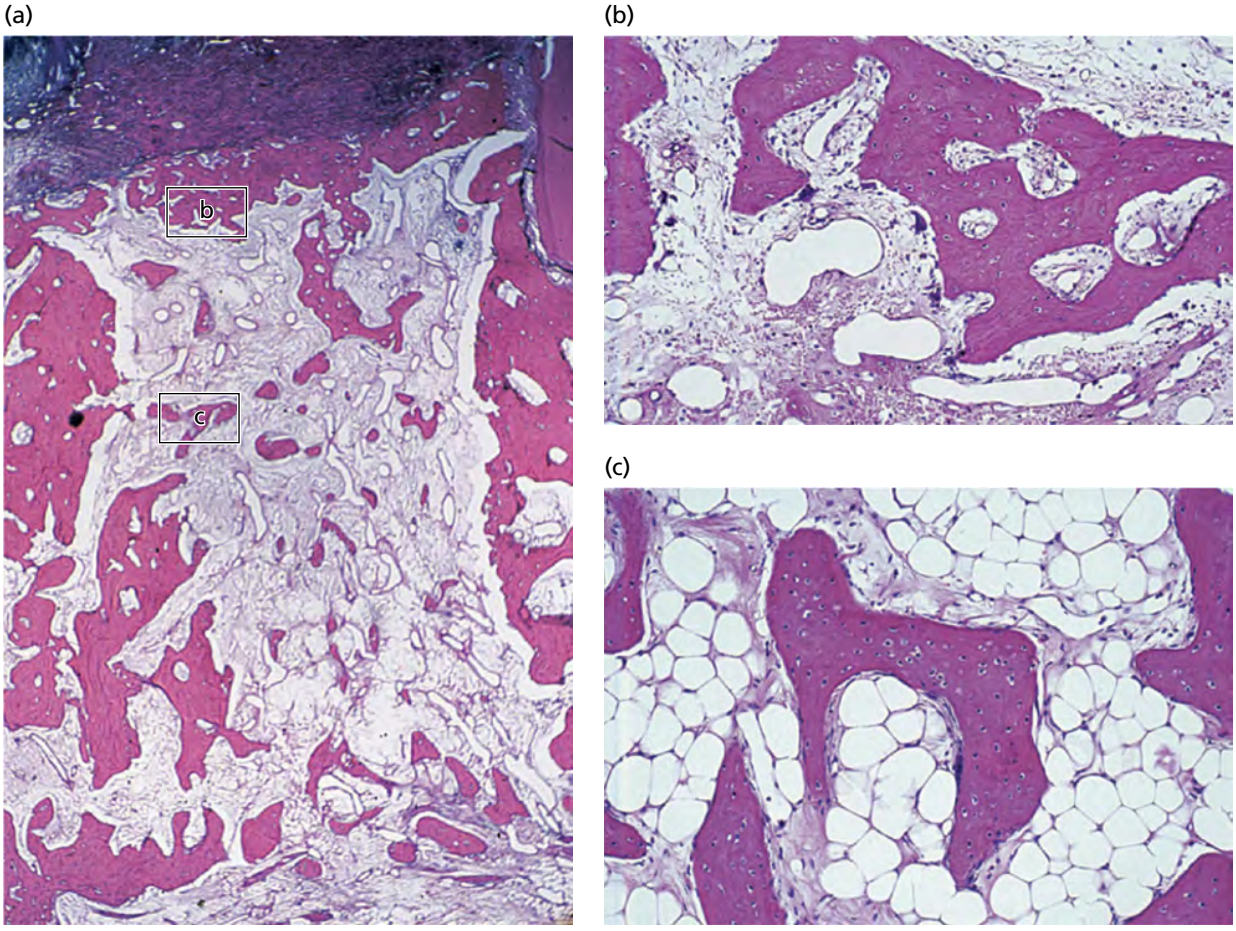

Fig. 3-19 (a) Histologic section (mesiodistal aspect) representing 60 days of healing. (b) A large portion of the woven bone has been replaced with bone marrow. (c) Note the presence of a large number of adipocytes residing in a tissue that still contains woven bone.

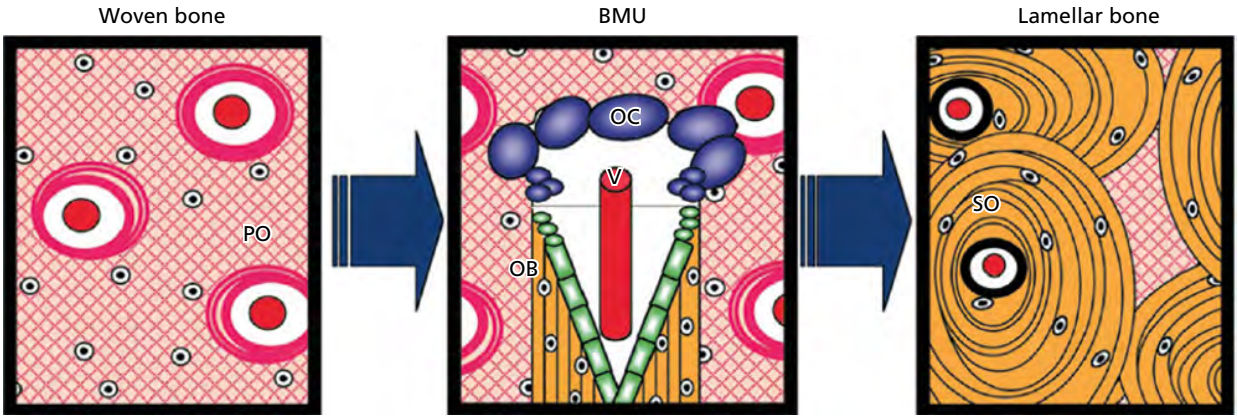

Fig. 3-20 Woven bone is replaced by lamellar bone. Woven bone with primary osteons (PO) is substituted by lamellar bone in a process that involves the presence of bone multicellular units (BMU). The BMU contains osteoclasts (OC), as well as vascular structures (V) and osteoblasts (OB). Thus, the osteoblasts in the BMU produce bone tissue in a concentric fashion around the vessel, and lamellar bone with secondary osteons (SO) is formed.

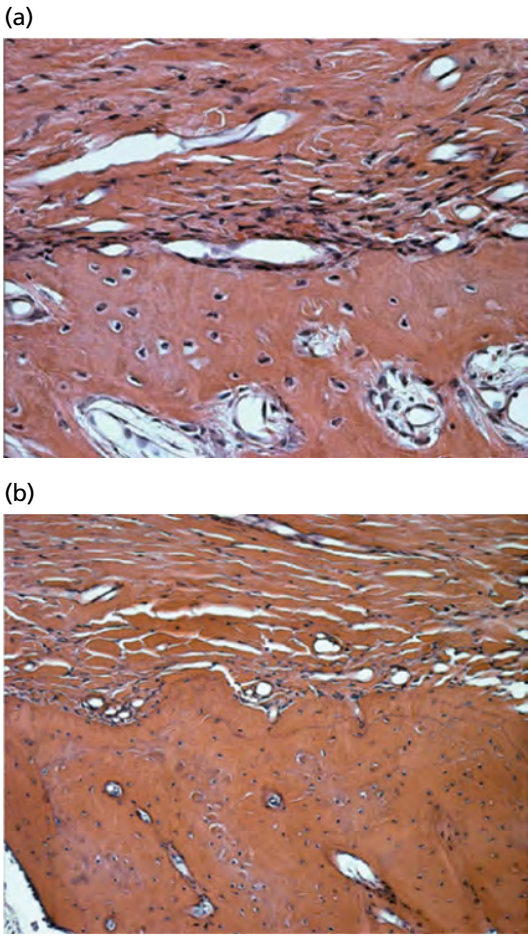

Fig. 3-21 Histologic sections (mesiodistal aspect) describing the hard tissue that has formed at the entrance of a healing extraction socket and the process of corticalization. (a) Woven bone with primary osteons occupies the socket entrance after 60 days of healing. (b) After 180 days, the woven bone has mainly been replaced with lamellar bone.

Since there is no stress from forces elicited during mastication and other occlusal contacts, there is no demand on the mineralized bone in the areas previously occupied by the tooth. Thus, in this model the socket apical of the hard tissue cap will remodel mainly into marrow.

Extra-alveolar processes

In an experiment using the dog model (Araújo & Lindhe 2005), alterations in the profile of the edentulous ridge that occurred following tooth extraction were carefully examined. In this study the third and fourth mandibular premolars were hemisected. Buccal and lingual full-thickness flaps were raised; the distal roots were carefully removed. The flaps were replaced and sutured to cover the fresh extraction socket. Biopsy specimens, including an individual extraction socket and adjacent roots, were obtained after 1, 2, 4, and 8 weeks of healing. The blocks were sectioned in the *buccolingual* plane.

- *1 week after tooth extraction* (Fig. 3-22). At this interval the socket is occupied by a coagulum. Furthermore, a large number of osteoclasts can be seen on the outside as well as on the inside of the buccal and lingual bone walls. The presence of osteoclasts on the inner surface of the socket walls indicates that the bundle bone is being resorbed.
- *2 weeks after tooth extraction* (Fig. 3-23). Newly formed immature bone (woven bone) resides in the apical and lateral parts of the socket, while more central and marginal portions are occupied by a provisional connective tissue. In the marginal and outer portions of the socket walls, numerous osteoclasts can be seen. In several parts of the socket walls the bundle bone has been replaced with woven bone.
- *4 weeks after tooth extraction* (Fig. 3-24). The entire socket is occupied with woven bone at this stage of healing. Large numbers of osteoclasts are present in the outer and marginal portions of the hard tissue walls. Osteoclasts also line the trabeculae of woven bone present in the central and lateral aspects of the socket. In other words, the newly formed woven bone is being replaced with a more mature type of bone.
- *8 weeks after tooth extraction* (Fig. 3-25). A layer of cortical bone covers the entrance to the extraction site. Corticalization has occurred. The woven bone that was present in the socket at the 4-week

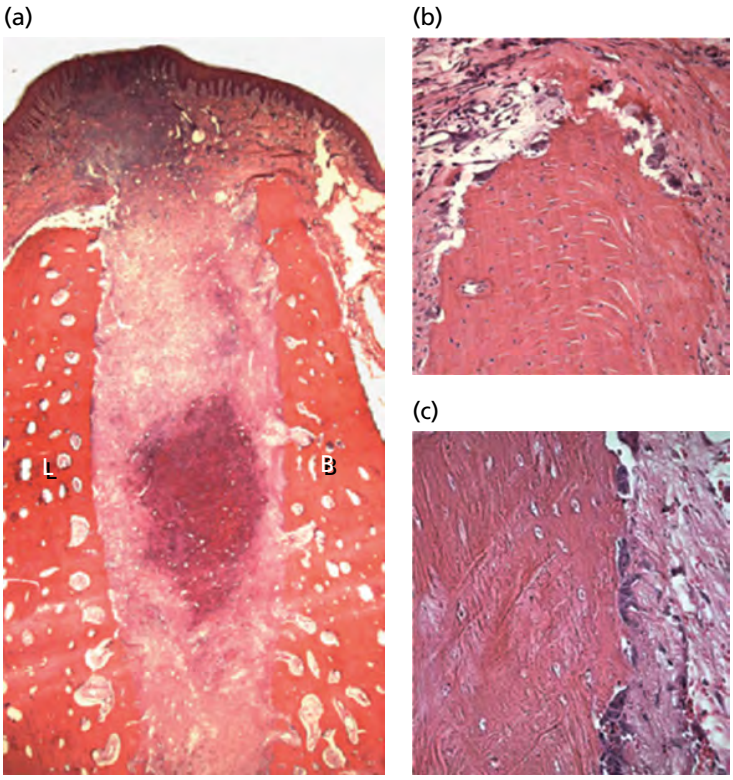

Fig. 3-22 (a) Histologic section (buccolingual aspect) of the socket after 1 week of healing. Note the presence of a large number of osteoclasts on the crestal portion (b) and inner portion (c) of the buccal wall. B, buccal bone; L, lingual bone.

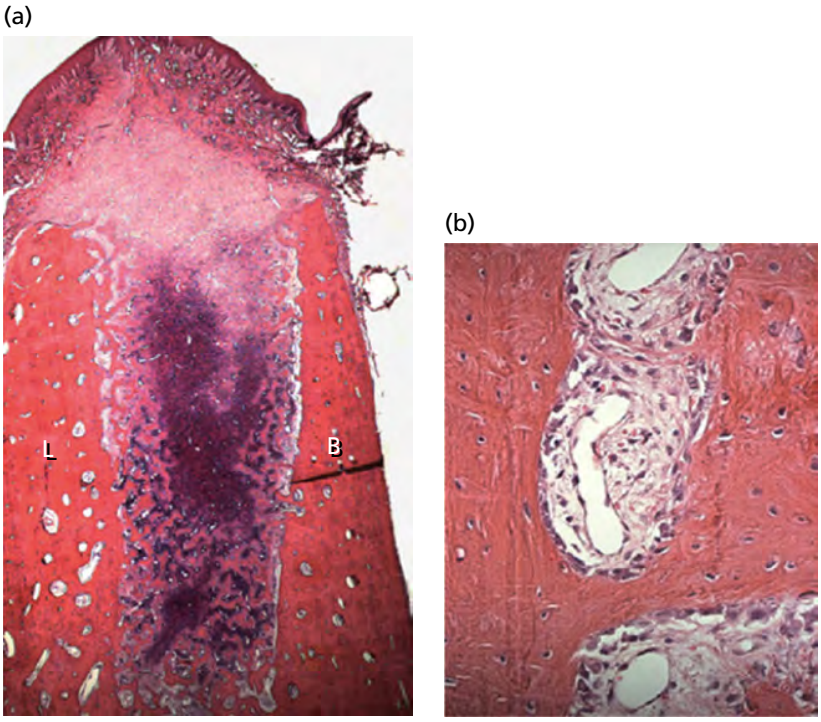

Fig. 3-23 (a) Histologic section (buccolingual aspect) of the socket after 2 weeks of healing. (b) Note that the bundle bone in the lingual aspect of the socket is being replaced with woven bone. B, buccal bone; L, lingual bone.

interval is replaced with bone marrow and some trabeculae of lamellar bone in the 8-week specimens. On the outside and on the top of the buccal and lingual bone wall there are signs of ongoing hard tissue resorption. The crest of the buccal bone wall is located apical of its lingual counterpart.

The relative change in the location of the crest of the buccal and lingual bone walls that took place during the 8 weeks of healing is illustrated in Fig. 3-26. While the level of the margin of the lingual wall remained reasonably unchanged, the margin of the buccal wall shifted several millimeters in an apical direction. The reason why more bone loss occurred in the buccal than in the lingual wall during socket healing in this animal model is not completely understood.

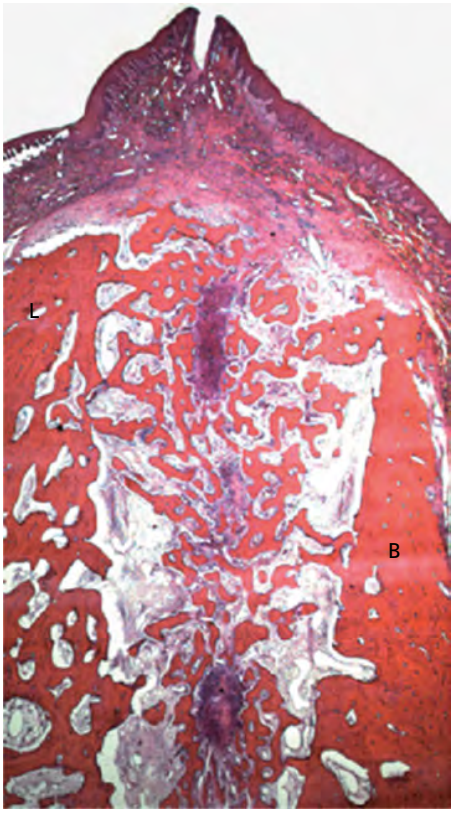

Fig. 3-24 Histologic section (buccolingual aspect) of the socket after 4 weeks of healing. The extraction socket is filled with woven bone. On the top of the buccal wall, the old bone in the crest region is being resorbed and replaced with either connective tissue or woven bone. B, buccal bone; L, lingual bone.

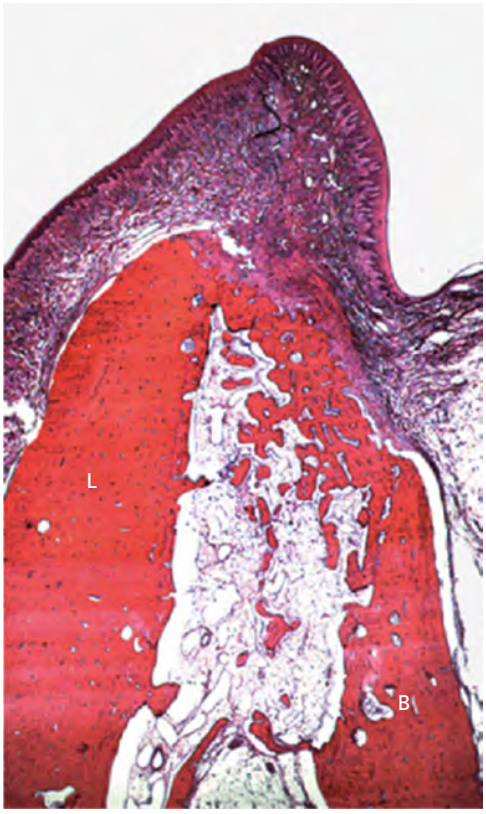

Fig. 3-25 Histologic section (buccolingual aspect) of the socket after 8 weeks of healing. The entrance of the socket is sealed with a cap of newly formed mineralized bone. Note that the crest of the buccal wall is located apical of the crest of the lingual wall. B, buccal bone; L, lingual bone.

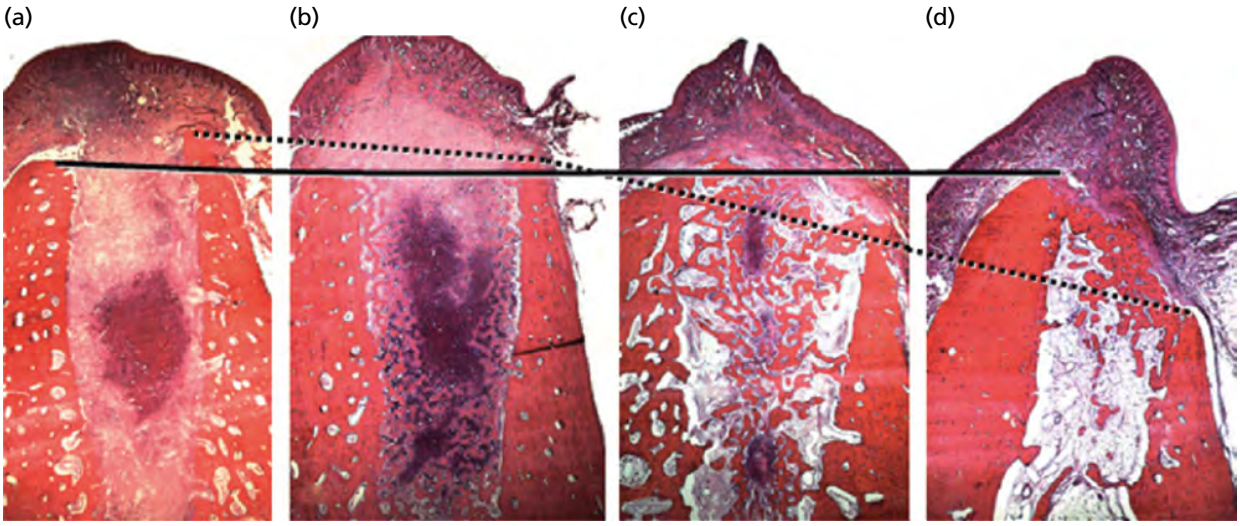

Fig. 3-26 Histologic sections (buccolingual aspects) showing the profile of the edentulous region in the dog after (a) 1, (b) 2, (c) 4, and (d) 8 weeks of healing following tooth extraction. While the marginal level of the lingual wall was maintained during the process of healing (solid line), the crest of the buccal wall was displaced >2 mm in the apical direction (dotted line).

Prior to tooth extraction, the marginal 1–2 mm of the crest of the thin buccal bone wall was occupied by bundle bone. Only a minor fraction of the crest of the wider lingual wall contained bundle bone. Bundle bone, as stated above, is a tooth-dependent tissue and will gradually disappear after tooth extraction. Thus, because there is relatively more bundle bone in the crest region of the buccal than of the lingual wall, hard tissue loss may become most pronounced in the buccal wall.

Topography of the edentulous ridge: summary

As described previously in this chapter, the processes of modeling and remodeling that occur following tooth extraction (loss) result in resorption of the various components of the previous alveolar process. The amount of tissue loss that occurs in these processes varies considerably from subject to subject and from site to site in the same individual (Figs. 3-27, 3-28).

As a rule, the resorption of the buccal bone wall is more pronounced than the resorption of the lingual/palatal wall and hence the center of the ridge will move in a lingual/palatal direction. In the extreme case, the entire alveolar process may be lost following tooth removal and then only the basal bone of the mandible and the maxilla may remain to constitute the ridge.

The outer (cortical) walls of the remaining portion of the alveolar ridge (basal bone and residues of the alveolar process) are comprised of lamellar bone. The cortical plates of the ridge often enclose the cancellous bone that harbors trabeculae of lamellar bone and marrow (Fig. 3-29). The bone marrow contains numerous vascular structures as well as adipocytes and pluripotent mesenchymal cells.

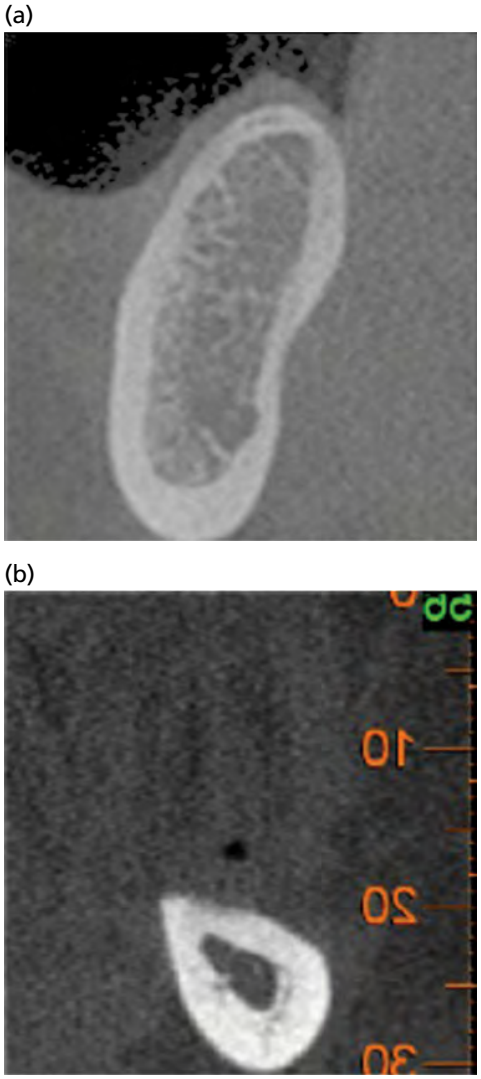

Fig. 3-28 Cone-beam computed tomograms illustrating edentulous regions of the first molar region of the mandible. (a) Remaining bone of the ridge is voluminous, is lined by dense cortical bone, and harbors large amounts of trabecular bone. (b) In this edentulous site, the entire alveolar process is lost and only the tissue of the corpus mandibulae remains.

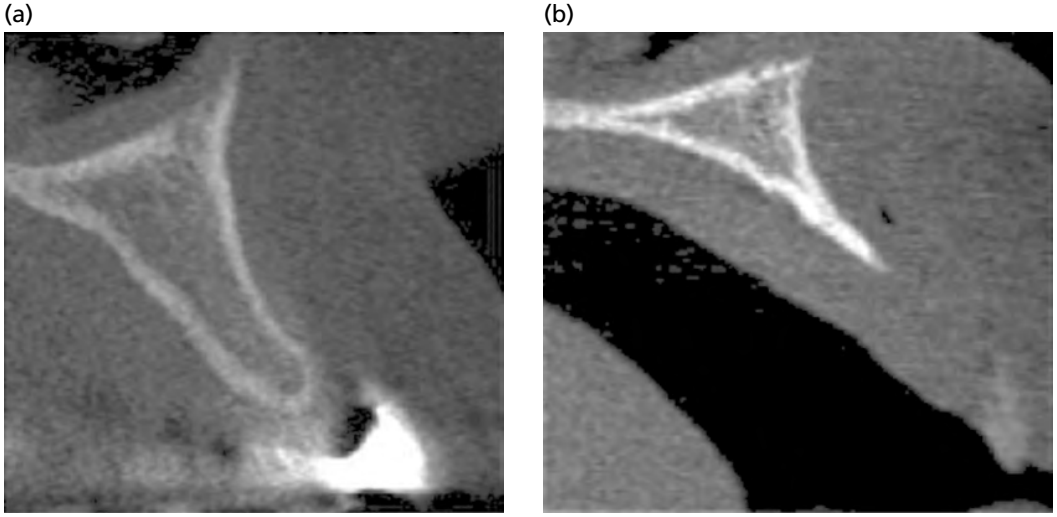

Fig. 3-27 Cone-beam computed tomograms that illustrate edentulous incisor sites of the maxilla with (a) large amounts of remaining hard tissue (cortical bone as well as trabecular bone) and (b) minute remnants of ridge tissue (only cortical bone).

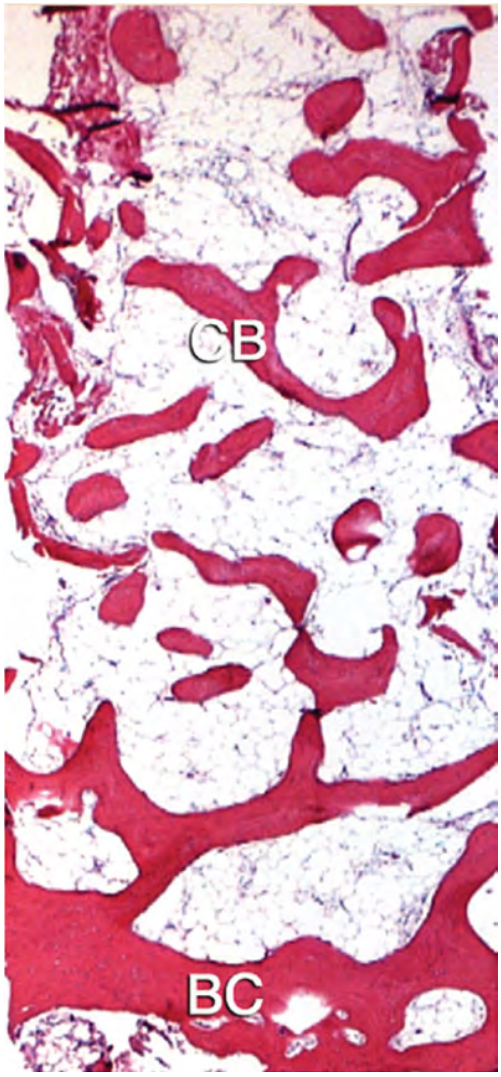

Fig. 3-29 Histologic section representing an edentulous maxilla. The biopsy was obtained >6 months postextraction. The marginal portion of the tissue (the bone crest [BC]) is comprised of dense lamellar bone, while more central portions harbor the cancellous bone (CB).

Depending on factors such as the type of jaw (maxilla or mandible), location (anterior, posterior) in the jaw, depth of the buccal and lingual vestibule, and amount of hard tissue resorption, the edentulous ridge may be lined with either masticatory, keratinized mucosa, or lining, non-keratinized mucosa.

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Chapter 4

The Mucosa at Teeth and Implants

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Gingiva

Dimensions of the supracrestal attachment

A term traditionally used to describe the dimensions of the soft tissues that face the teeth was the *biologic width of the soft tissue attachment*. In a consensus report from the World Workshop on Periodontology (Jepsen *et al*. 2018), this term was replaced with the *supracrestal attachment*.

The development of the *biologic width/supracrestal attachment concept* was based on studies and analyses by, among others, Gottlieb (1921), Orban and Köhler (1924), and Sicher (1959), who documented that the soft tissue attached to the teeth was comprised of two parts, one of fibrous tissue and one of epithelium. In a publication by Gargiulo *et al*. (1961) called "Dimensions and relations of the dentogingival junction in humans", sections from autopsy block specimens that exhibited different degrees of "passive tooth eruption" (i.e. periodontal tissue breakdown) were examined. Histometric assessments were made to describe the length of the sulcus (not part of the attachment), the epithelial attachment (today called the junctional epithelium), and the connective tissue attachment (Fig. 4-1). It was observed that the length of the connective tissue attachment varied within narrow limits (1.06–1.08 mm), while the length of the attached epithelium was about 1.4 mm at sites with normal periodontium, 0.8 mm at sites with moderate, and 0.7 mm at sites with advanced periodontal tissue breakdown. In other words, (1) the dimension of the attachment varied between about 2.5 mm in the normal case and 1.8 mm in the advanced disease case, and (2) the most variable part of the attachment was the length of the epithelial attachment (junctional epithelium).

Dimensions of the buccal tissue

The morphologic characteristics of the gingiva are related to the dimension of the alveolar process, the form (anatomy) of the teeth, events that occur during tooth eruption, and the eventual inclination and position of the fully erupted teeth (Wheeler 1961; O'Connor & Biggs 1964; Weisgold 1977). Oschenbein and Ross (1969) and Becker *et al*. (1997) proposed (1) that the anatomy of the gingiva is related to the contour of the osseous crest and (2) that two basic types of gingival architecture may exist, namely the "*pronounced scalloped*" and the "*flat*" phenotype.

Subjects who belong to the "*pronounced scalloped*" phenotype have long and slender teeth with tapered crown form, delicate cervical convexity, and minute

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

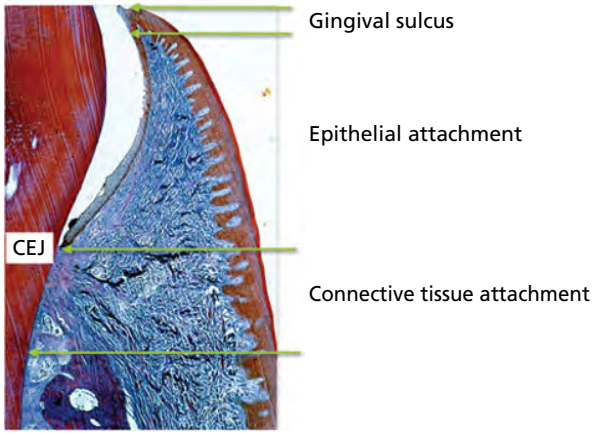


Fig. 4-1 Histological section describing the dimensions of the various components of the soft tissue attachment at the buccal surface of a tooth with healthy periodontium. The combined length of the junctional epithelium (epithelial attachment) and the connective tissue attachment is considered to represent the "supracrestal attachment/biologic width" of the soft tissue. Note the gingival sulcus is *not* part of the attachment. CEJ, cementoenamel junction.

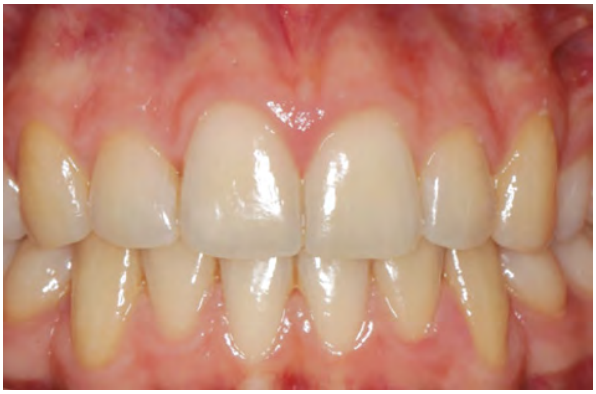


Fig. 4-2 A subject who belongs to the "pronounced scalloped" gingival phenotype. The crowns of the teeth are comparatively long and slender. The papillae are comparatively long, the gingival margin is thin, and the zone of attached gingiva is short.

interdental contact areas that are located close to the incisal edge (Fig. 4-2). The maxillary front teeth of such individuals are surrounded by a thin free gingiva, the buccal margin of which is located at or apical of the cementoenamel junction. The zone of gingiva is narrow, and the outline of the gingival margin is highly scalloped (Olsson *et al*. 1993). On the other hand, subjects who belong to the "*flat*" gingival phenotype have incisors with squared crown form with pronounced cervical convexity (Fig. 4-3). The gingiva of such individuals is wider and more voluminous, the contact areas between the teeth are large and more apically located, and the interdental papillae are short. It was reported that subjects with a pronounced scalloped gingiva often exhibited more advanced soft tissue recession in the anterior maxilla than subjects with a flat gingiva (Olsson & Lindhe 1991).

Kan *et al*. (2003) measured the dimension of the gingiva – as determined by bone sounding – at the buccomesial and buccodistal aspects of maxillary anterior teeth. Bone sounding determines the distance between the soft tissue margin and the crest of the bone and, hence, provides an estimate that is about 1 mm greater than that obtained in a regular probing pocket depth measurement. The authors reported that the thickness of the gingiva varied between subjects of different gingival phenotypes. Thus, the height of the gingiva at the buccal-approximal surfaces in subjects who belonged to the flat phenotype was, on average, 4.5 mm, while in subjects belonging to the pronounced scalloped phenotype the corresponding dimension (3.8 mm) was significantly smaller.

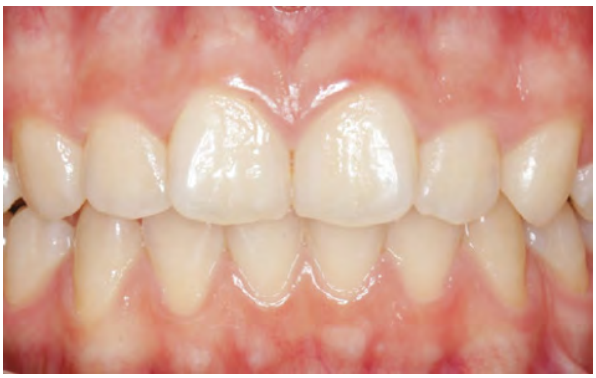


Fig. 4-3 A subject who belongs to the "flat" gingival phenotype. The crowns of the teeth are comparatively short but wide. The papillae are comparatively short but voluminous and the zone of attached gingiva is wide.

Pontoriero and Carnevale (2001) evaluated the reformation of the gingival unit at the buccal aspect of teeth exposed to crown lengthening procedures using a denudation technique. At the 1-year follow-up examination after surgery, the regain of soft tissue – measured from the level of the denuded osseous crest – was greater in patients with a thick (flat) phenotype than in those with a thin (pronounced scalloped) phenotype (3.1 mm versus 2.5 mm). No assessment was made of the bone level change that had occurred between the baseline and the follow-up examination. It must, however, be anticipated that some bone resorption had taken place during healing and that the height of the new connective tissue attachment had been re-established coronal to the level of the resected osseous crest.

The dimensions of the buccal gingiva may also be affected by the buccolingual position of the tooth within the alveolar process. A change of the tooth position in the buccal direction results in reduced dimensions of the buccal gingiva, while an increase is observed following a lingual tooth movement (Coatoam *et al*. 1981; Andlin-Sobocki & Brodin 1993). In fact, Müller and Könönen (2005) demonstrated in a study of the variability of the thickness of the buccal gingiva of young adults that most of the variation in gingival thickness was due to the tooth position and that the contribution of subject variability (i.e. flat and pronounced scalloped phenotypes) was minimal.

Dimensions of the interdental papilla

The interdental papilla in a normal, healthy dentition has one buccal and one lingual/palatal component that are joined in the col region (see Chapter 1). Experiments performed in the 1960s (Kohl & Zander 1961; Matherson & Zander 1963) revealed that the shape of the papilla in the col region was not determined by the outline of the bone crest, but by the shape of the contact relationship that existed between adjacent teeth.

Tarnow *et al*. (1992) studied whether the distance between the contact point (area) between teeth and the crest of the corresponding interproximal bone could influence the degree of papilla fill that occurred at the site. Presence or absence of a papilla was determined visually in periodontally healthy subjects. If there was no space visible apical of the contact point, the papilla was considered complete. If a "black space" was visible at the site, the papilla was considered incomplete. The distance between the facial level of the contact point and the bone crest (Fig. 4-4) was measured by sounding. The measurement thus included not only the epithelium and connective tissue of the papilla, but in addition the entire supra-alveolar connective tissue in the interproximal area (Fig. 4-5). The authors reported that the papilla was complete when the distance from the contact point to the crest of the bone was ≤5 mm. When this distance was 6 mm, papilla fill occurred in about 50% of cases and when ≥7 mm, it was incomplete in about 75% of cases. Considering that the supracrestal connective tissue attachment is about 1 mm high, these data indicate that the papilla height may be limited to about 4 mm in most cases. Interestingly, papillae of similar height (3.2–4.3 mm) were found to reform following surgical denudation procedures (van der Velden 1982; Pontoriero & Carnevale 2001), but to a greater height in patients with a thick (flat) phenotype than in those with a thin (pronounced scalloped) phenotype.

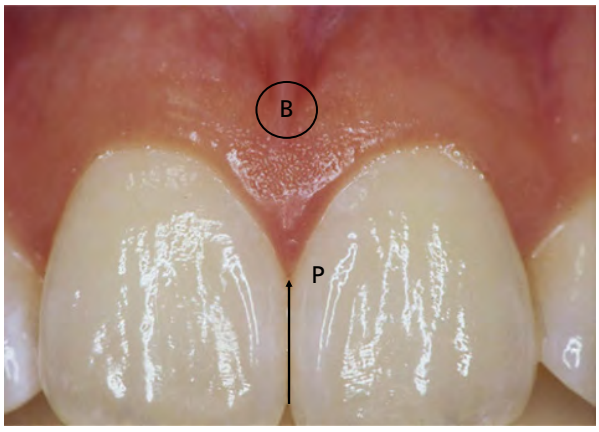


Fig. 4-4 Tarnow *et al*. (1992) measured the distance between the contact point (P) between the crowns of the teeth and the bone crest (B) using sounding (transgingival probing).

Fig. 4-5 Mesiodistal section of the interproximal area between the two central incisors. Arrows indicate the location of the cementoenamel junction. Dotted line indicates the outline of the marginal bone crest. The distance between the contact point (P) between the crowns of the teeth and the bone crest (B) indicates the height of the papilla.

Summary:

- *Flat gingival (periodontal)* phenotype: the buccal marginal gingiva is comparatively thick, the papillae are often short, the bone of the buccal cortical wall is thick, and the vertical distance between the interdental bone crest and the buccal bone is short (about 2 mm).
- *Pronounced scalloped gingival (periodontal)* phenotype: the buccal marginal gingiva is delicate and may often be located apical of the cementoenamel junction (receded), the papillae are high and slender, the buccal bone wall is often thin, and the vertical distance between the interdental bone crest and the buccal bone is long (>4 mm).

Peri-implant mucosa

The soft tissue that surrounds dental implants is termed *peri-implant mucosa*. Features of the peri-implant mucosa are established during the process of wound healing that occurs subsequent to the closure of mucoperiosteal flaps following implant installation (one-stage procedure) or following abutment connection (two-stage procedure) surgery. Healing of the mucosa results in the establishment of a soft tissue attachment (transmucosal attachment) to the implant. This attachment serves as a seal that prevents products from the oral cavity reaching the bone tissue, and thus ensures osseointegration and the rigid fixation of the implant.

The peri-implant mucosa and the gingiva have several clinical and histologic characteristics in common. Some important differences, however, also exist between the gingiva and the peri-implant mucosa.

Dimensions of the supracrestal attachment

The structure of the mucosa that surrounds implants made of titanium has been examined in humans and several animal models. In a study in the dog, Berglundh *et al*. (1991) compared some anatomic features of the gingiva at teeth and the mucosa at implants. Details of the research model used in this study are briefly outlined here, as this model was used in subsequent experiments that will be described in this chapter.

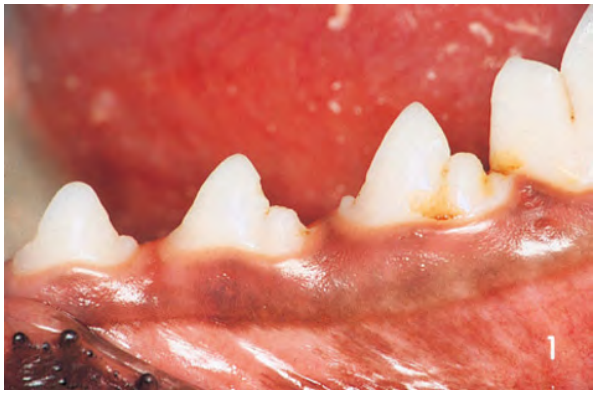
The mandibular premolars on one side of the mandible were extracted, leaving the corresponding teeth in the contralateral jaw quadrant. After 3 months of healing following tooth extraction, implants were installed (Fig. 4-6) and submerged. Another 3 months later, abutment connection was performed and the animals were placed in a plaque-control program. Four months later biopsies of tooth and implant sites were harvested.

The clinically healthy gingiva and peri-implant mucosa had a pink color and a firm consistency (Fig. 4-7). On radiographs obtained from the tooth sites, it was observed that the alveolar bone crest was located about 1 mm apical of a line connecting the cementoenamel junction of neighboring teeth (Fig. 4-8). In the implant sites the bone crest was located close to the junction between the abutment and the implant (Fig. 4-9).

Histologic examination revealed that the two soft tissue units, the gingiva and the peri-implant mucosa, had several features in common. The oral epithelium of the gingiva was well keratinized and continuous with the thin junctional epithelium that faced the enamel and that ended at the cementoenamel junction (Fig. 4-10). The supra-alveolar connective tissue was about 1 mm high and the periodontal ligament about 0.2–0.3 mm wide. The principal fibers extended from the root cementum in a fan-shaped pattern into the soft and hard tissues of the marginal periodontium (Fig. 4-11).

The outer surface of the peri-implant mucosa was also covered by a keratinized oral epithelium, which in the marginal border connected with a thin barrier epithelium (similar to the junctional epithelium at the teeth) that faced the abutment part of the implant (Fig. 4-12). The barrier epithelium was a few cell layers thick (Fig. 4-13) and terminated about 2 mm apical of the soft tissue margin (Fig. 4-12) and 1–1.5 mm from the bone crest. The connective tissue in the

(a)



(b)

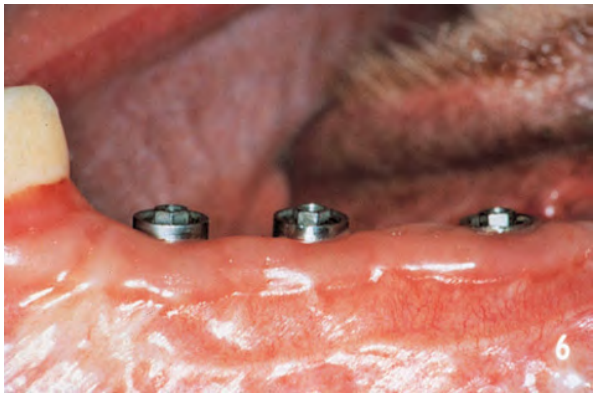


Fig. 4-7 At the end of the study, the gingiva (a) and the peri-implant mucosa (b) were clinically healthy.

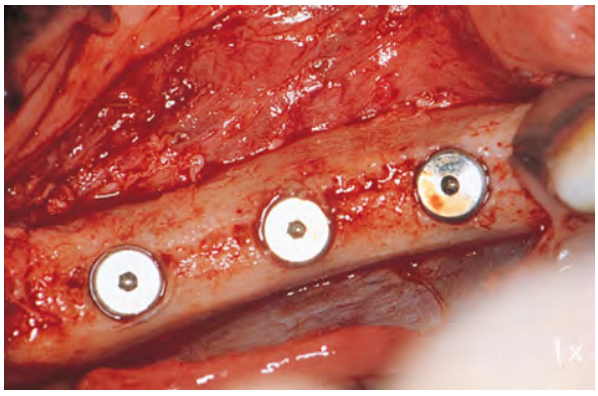


Fig. 4-6 Three titanium implants (Brånemark System®) were installed. (Source: Berglundh *et al*. 1991. Reproduced with permission from John Wiley & Sons.)

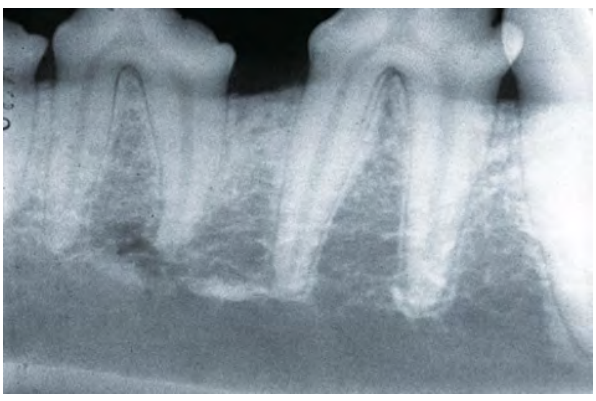


Fig. 4-8 Radiograph of the premolars in the left side of the mandible.

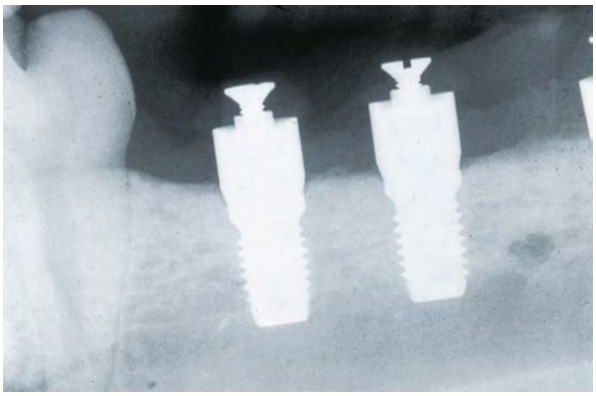


Fig. 4-9 Radiograph of the implants in the right side of the mandible.

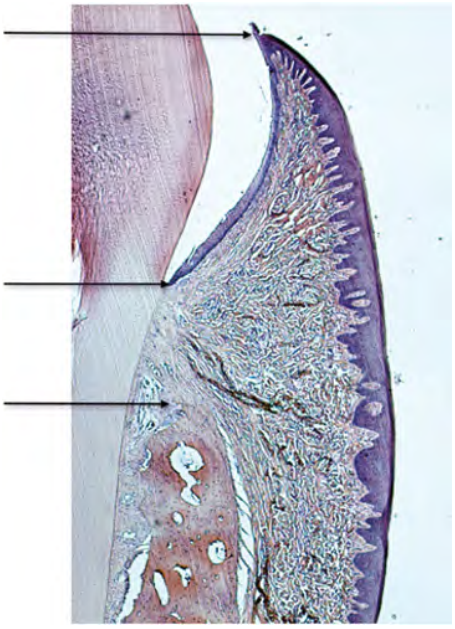


Fig. 4-10 Microphotograph of a cross-section of the buccal and coronal part of the periodontium of a mandibular premolar. Note the position of the soft tissue margin (top arrow), the apical cells of the junctional epithelium (center arrow), and the crest of the alveolar bone (bottom arrow). The junctional epithelium is about 2 mm long and the supracrestal connective tissue portion about 1 mm high.

compartment above the bone appeared to be in direct contact with the surface of the implant (Figs. 4-12, 4-13). The collagen fibers in this connective tissue originated from the periosteum of the bone crest and extended towards the margin of the soft tissue in directions parallel to the surface of the abutment.

The observation that the barrier epithelium of the healthy mucosa consistently ended at a certain distance (1–1.5 mm) from the bone is important. During healing, fibroblasts of the connective tissue of the mucosa apparently formed a biologic attachment to the titanium surface of the abutment portion of the implant. This attachment zone was evidently not recognized as a wound and was therefore not covered with an epithelial lining.

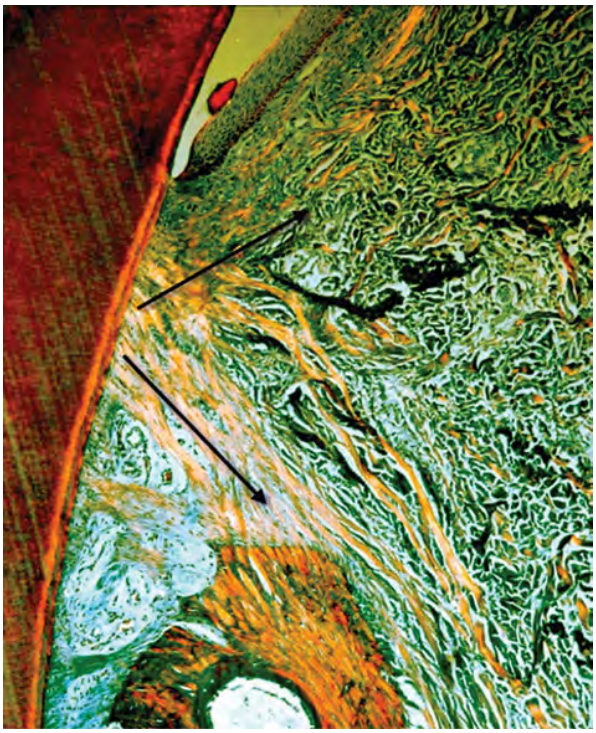


Fig. 4-11 Higher magnification of the supracrestal connective tissue portion seen in Fig. 4-10. Note the direction of the principal fibers.

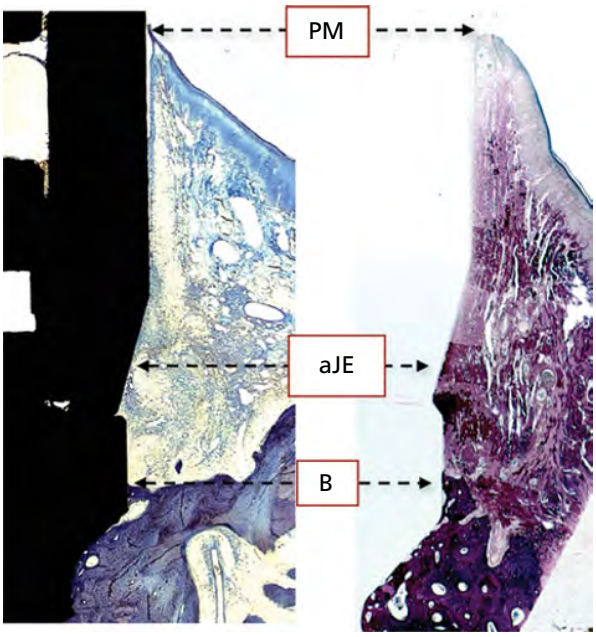


Fig. 4-12 Microphotographs of buccolingual sections of the peri-implant mucosa. Note the position of the soft tissue margin (PM; top arrow), the apical cells of the junctional epithelium (aJE; center arrow), and the crest of the marginal bone (B; bottom arrow). The junctional epithelium is about 2 mm long and the implant–connective tissue interface about 1.5 mm high.

In further preclinical *in vivo* experiments (Abrahamsson *et al*. 1996, 2002), it was observed that a similar mucosal attachment formed when different types of implant systems were used. In addition, the formation of the attachment appeared to be

independent of whether the implants were initially submerged or not.

Studies by Abrahamsson *et al*. (1998) and Welander *et al*. (2008) demonstrated that the material used in the abutment part of the implant was of decisive importance for the location of the connective tissue portion of the transmucosal attachment. Abutments made of aluminum-based sintered ceramic (Al_2O_3) and zirconium dioxide (ZrO_2) allowed for the establishment of a mucosal attachment similar to that which occurred at titanium abutments. Abutments made of a gold alloy or dental porcelain, however, provided conditions for inferior mucosal healing. When such materials were used, the connective tissue attachment failed to develop at the abutment level. Instead, the connective tissue attachment occurred in a more apical location. Thus, during healing following the abutment connection surgery, some resorption of the marginal peri-implant bone took place to expose the titanium portion of the implant to which the connective tissue attachment eventually formed. The histological analysis made by Welander *et al*. (2008) further revealed that the connective tissue interface at gold (Au/Pt)-alloy abutments contained lower amounts of collagen and fibroblasts and larger fractions of leukocytes than that at abutments made of titanium and zirconium dioxide (ZrO_2) (Figs. 4-14, 4-15).

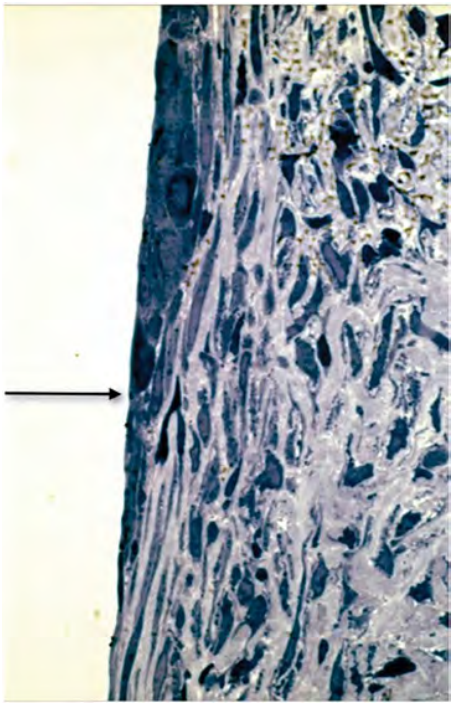


Fig. 4-13 Higher magnification of the apical portion of the junctional epithelium (arrow) in Fig. 4-12.

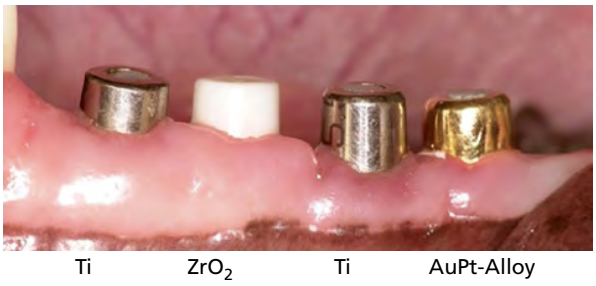


Fig. 4-14 Implants with abutments made of titanium (Ti), zirconium dioxide (ZrO_2) and gold (Au-Pt) alloy. (Source: Welander *et al*. 2008. Reproduced with permission from John Wiley & Sons.)

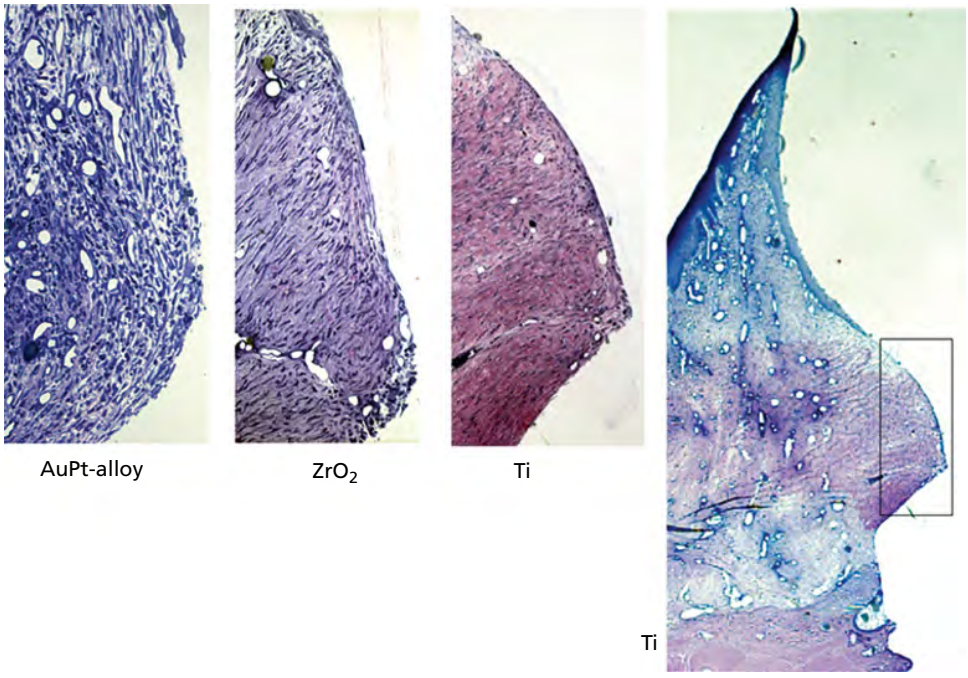


Fig. 4-15 Microphotographs illustrating bucco-lingual sections of the peri-implant mucosa adjacent abutments made of titanium (Ti), zirconium dioxide (ZrO_2) and gold (Au-Pt) alloy. (Source: Welander *et al*. 2008. Reproduced with permission from John Wiley & Sons.)

The location and dimensions of the transmucosal attachment were examined in a preclinical study by Berglundh and Lindhe (1996). Implants were installed and submerged. After 3 months of healing, abutment connection was performed. On the left side of the mandible, the volume of the ridge mucosa was maintained, while on the right side the vertical dimension of the mucosa was reduced to 2 mm or less (Fig. 4-16) before the flaps were replaced and sutured. In biopsy specimens obtained after another 6 months, it was observed that the transmucosal attachment at all implants included a barrier epithelium component that was about 2 mm long and a zone of connective tissue that was about 1.3–1.8 mm high.

Further examination disclosed that at sites with a thin mucosa, wound healing had consistently included marginal bone resorption to establish space for a mucosa that eventually could harbor both the epithelial and the connective tissue components of the transmucosal attachment (Figs. 4-17).

Thus, the dimensions of the epithelial and connective tissue components of the transmucosal attachment at implants are established during wound healing following implant surgery. As is the case for bone healing after implant placement (see Chapter 5), the wound healing in the mucosa around implants is a delicate process that requires several weeks of tissue remodeling.

In a preclinical *in vivo* experiment, Berglundh *et al*. (2007) described the morphogenesis of the peri-implant mucosa. A non-submerged implant installation technique was used and the mucosal tissues were secured to the marginal portion of the implants. A plaque-control program was initiated. Biopsies were harvested at various intervals to provide healing periods extending from day 0 (2 hours) to 12 weeks.

Large numbers of neutrophils infiltrated and degraded the coagulum that occupied the compartment between the mucosa and the implant during the initial phase of healing. The first signs of epithelial proliferation were observed after 1–2 weeks of healing and a mature barrier epithelium was seen after 6–8 weeks (Fig. 4-18). The collagen fibers

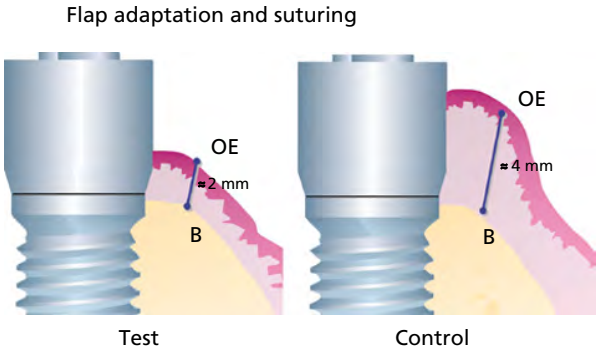


Fig. 4-16 The mucosa at the test site was reduced to about 2 mm. (Source: Berglundh & Lindhe 1996. Reproduced with permission from John Wiley & Sons.)

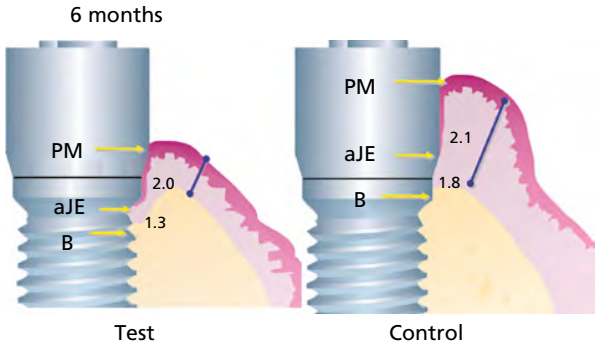


Fig. 4-17 The peri-implant mucosa at both control and test sites contained a 2-mm long barrier epithelium and a zone of connective tissue that was about 1.3–1.8 mm high. Bone resorption occurred in order to accommodate the soft tissue attachment at sites with a thin mucosa. (Source: Berglundh & Lindhe 1996. Reproduced with permission from John Wiley & Sons.)

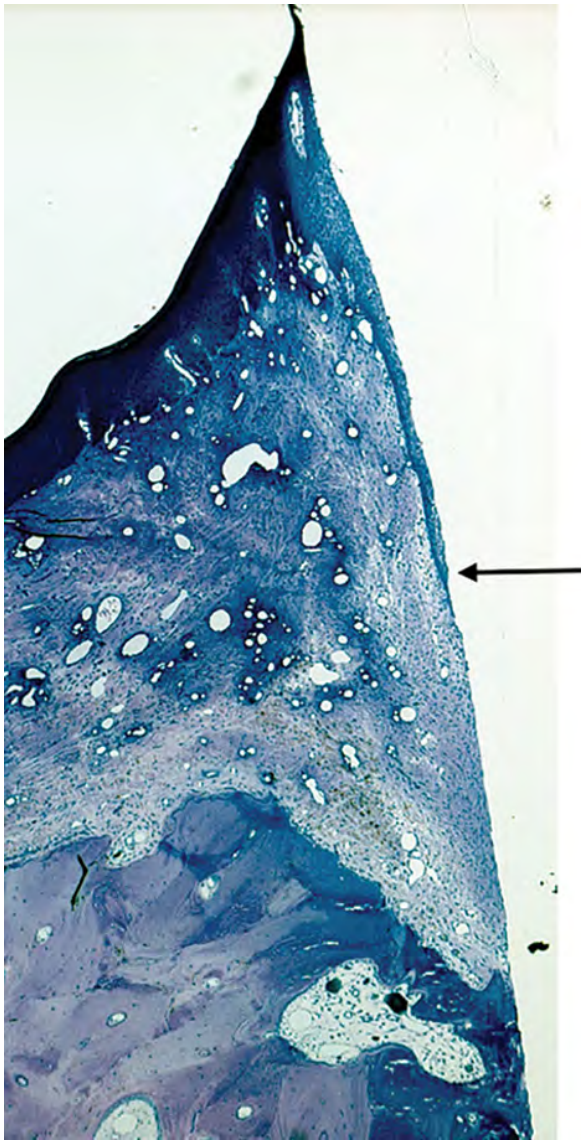


Fig. 4-18 Microphotograph illustrating a buccolingual section of the peri-implant mucosa after 6 weeks of healing. Arrow indicates apical cells of the junctional epithelium. (Source: Berglundh *et al*. 2007. Reproduced with permission from John Wiley & Sons.)

of the mucosa were organized after 4–6 weeks of healing (Fig 4-19).

Tomasi *et al*. (2013, 2016) used a novel human biopsy model to study the early healing of peri-implant mucosa. Biopsies of peri-implant soft tissues were retrieved in 21 patients after 2, 4, 6, 8, and 12 weeks of healing. The histological analysis revealed that dimensional and qualitative changes in the mucosa over time were consistent with those reported in previous preclinical *in vivo* studies. Further analysis disclosed that densities of inflammatory cells and vascular structures in the peri-implant mucosa decreased over time and that the formation of the junctional epithelium was completed at 8 weeks of healing (Fig. 4-20).

Summary: The junctional and barrier epithelia are about 2 mm long and the zones of supra-alveolar connective tissue are between 1 and 1.5 mm high. Both epithelia are attached via hemidesmosomes to the tooth/implant surface (Gould *et al*. 1984). The main attachment fibers (the principal fibers) invest in the root cementum of the tooth, but at the implant site the equivalent fibers run in a direction parallel to the implant and fail to attach to the metal body. The soft tissue attachment to implants is properly established first after several weeks of healing.

Structure and composition

The connective tissue in the supra-alveolar compartments at teeth and implants was examined by Berglundh *et al*. (1991). The main difference between the mesenchymal tissue at a tooth and at an implant site was the occurrence of cementum on the root of the tooth. From this cementum (Fig. 4-11), coarse dentogingival and dentoalveolar collagen fiber bundles projected in lateral, coronal, and apical directions. At the implant site, the collagen fiber bundles were orientated in an entirely different manner. Thus, the fibers invested in the periosteum at the bone crest and projected in directions parallel to the implant surface (Figs. 4-19, 4-20).

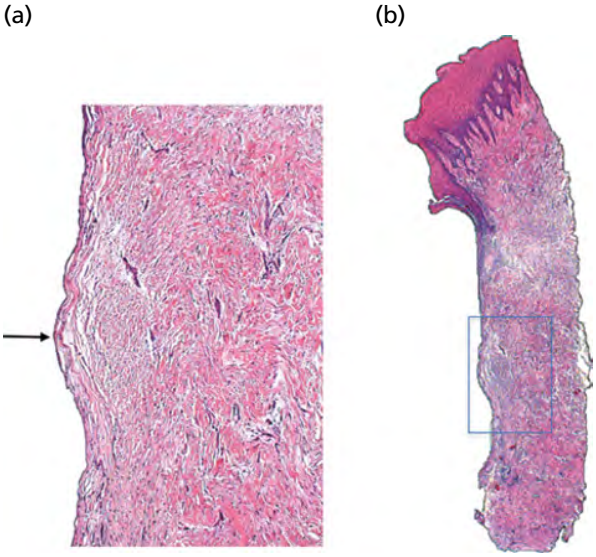


Fig. 4-20 Microphotograph illustrating a section of a human peri-implant mucosa after 8 weeks of healing (a). Higher magnification (b). Arrow indicates apical cells of the junctional epithelium. Note the direction of collagen fibers, which is parallel to the surface of the abutment device. (Source: Tomasi *et al*. 2013. Reproduced with permission from John Wiley & Sons.)

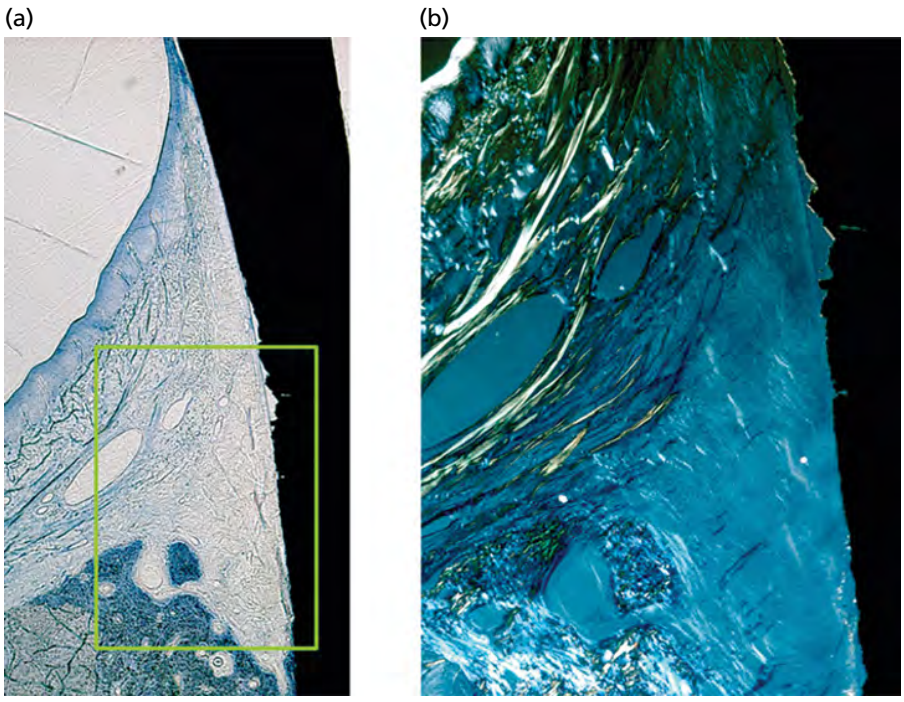


Fig. 4-19 Microphotograph illustrating a buccolingual ground section of the peri-implant tissues after 6 weeks of healing (a). Higher magnification (b) demonstrating collagen fibers running from the periosteum of the bone crest and extending in directions parallel to the surface of the implant. (Source: Berglundh *et al*. 2007. Reproduced with permission from John Wiley & Sons.)

The connective tissue in the supracrestal area at implants contained more collagen fibers, but fewer fibroblasts and vascular structures than the corresponding tissue at teeth. Moon *et al*. (1999), in a preclinical *in vivo* study, reported that the attachment tissue close to the implant (Fig. 4-21) contained few blood vessels and a large number of fibroblasts that were orientated with their long axes parallel to the implant surface (Fig. 4-22). In more lateral compartments, there were fewer fibroblasts, but more collagen fibers and more vascular structures. It was concluded that the connective tissue attachment between the titanium surface and the connective tissue is established and maintained by fibroblasts.

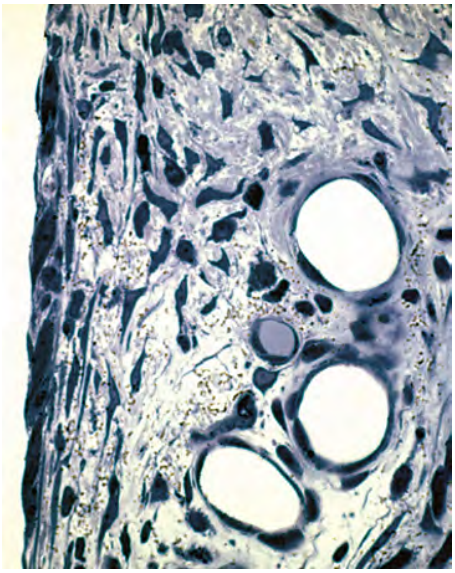


Fig. 4-21 Microphotograph of the implant–connective tissue interface of the peri-implant mucosa. A large number of fibroblasts reside in the tissue next to the implant.

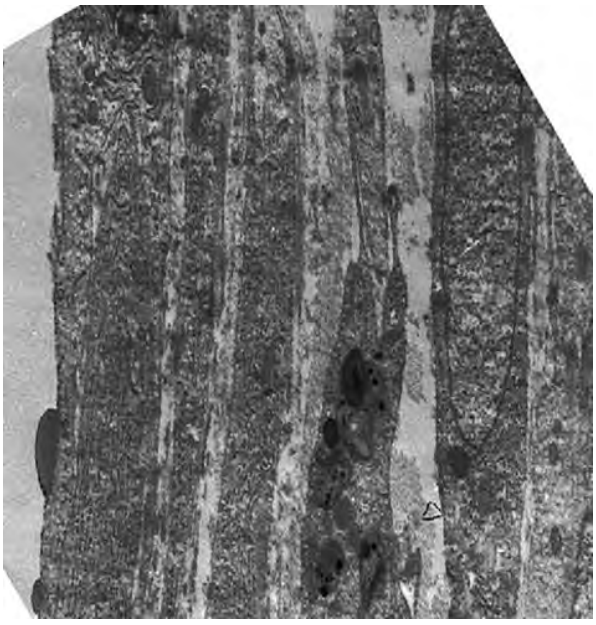


Fig. 4-22 Electron micrograph of the implant–connective tissue interface. Elongated fibroblasts are interposed between thin collagen fibrils (magnification ×24 000).

Vascular supply

The vascular supply to the gingiva comes from two different sources (Fig. 4-23). The first source is represented by the large *supraperiosteal blood vessels* that put forth branches to form (1) the capillaries of the connective tissue papillae under the oral epithelium and (2) the vascular plexus lateral to the junctional epithelium. The second source is the *vascular plexus of the periodontal ligament*, from which branches run in a coronal direction and terminate in the supra-alveolar portion of the free gingiva. Thus, the blood supply to the zone of supra-alveolar connective tissue attachment in the periodontium is derived from two apparently independent sources (see Chapter 1).

Berglundh *et al*. (1994) observed that the vascular system of the peri-implant mucosa (Fig. 4-24) originated *solely* from the large *supraperiosteal blood vessels* on the outside of the alveolar ridge. These vessels gave off branches to the supra-alveolar mucosa and formed (1) the capillaries beneath the oral epithelium and (2) the vascular plexus located immediately lateral to the barrier epithelium. The connective tissue part of the transmucosal attachment to titanium implants contained only a few vessels, all of which could be identified as terminal branches of the *supraperiosteal blood vessels*.

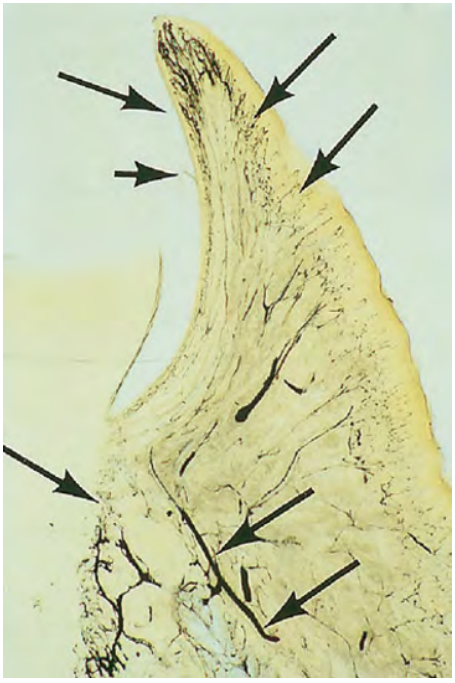


Fig. 4-23 Buccolingual cleared section of the marginal portion of a tooth. The vessels were filled with carbon (arrows). Note the presence of supraperiosteal vessels on the outside of the alveolar bone, the presence of a plexus of vessels within the periodontal ligament, as well as vascular structures in the very marginal portion of the gingiva.

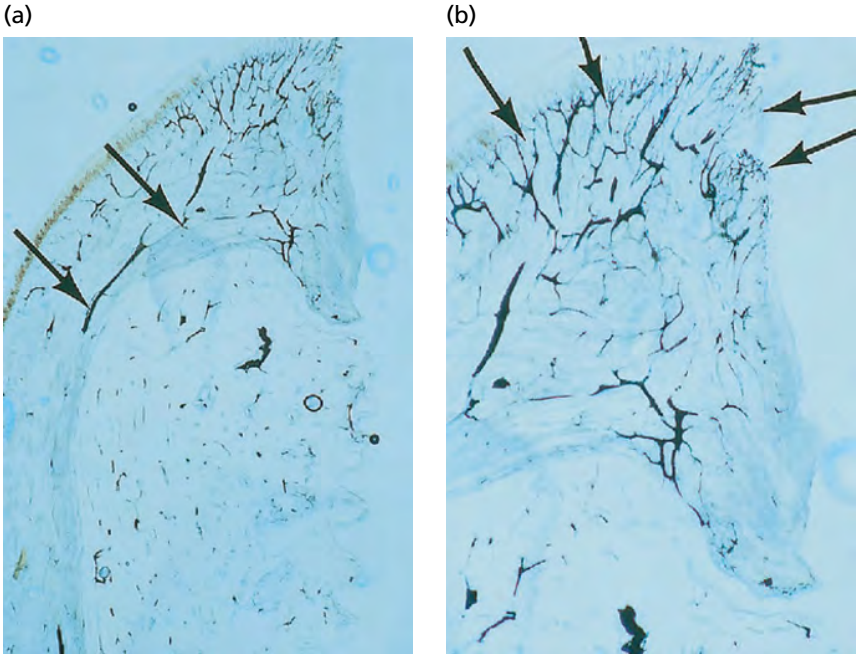


Fig. 4-24 (a) Buccolingual cleared section of the marginal portion of peri-implant tissues (the implant was positioned to the right). Note the presence of a supraperiosteal vessel on the outside of the alveolar bone (arrows), but also that there is no vasculature that corresponds to the periodontal ligament plexus. (b) Higher magnification (of a) of the peri-implant soft tissue and the bone implant interface. Note the presence of a vascular plexus lateral to the junctional epithelium (arrows), but the absence of vessels in the more apical portions of the soft tissue facing the implant and the bone.

Summary: The gingiva and the peri-implant mucosa share some characteristics, but differ in the composition of the connective tissue, the alignment of the collagen fiber bundles, and the distribution of vascular structures.

Probing gingiva and peri-implant mucosa

It was assumed for many years that the tip of the probe in a pocket depth measurement identified the most apical cells of the junctional (pocket) epithelium or the marginal level of the connective tissue attachment. This assumption was based on findings by, for example, Waerhaug (1952), who reported that the "epithelial attachment" (e.g. Gottlieb 1921; Orban & Köhler 1924) offered no resistance to probing. Waerhaug (1952) inserted thin blades of steel or acrylic into the gingival pocket of various teeth of young subjects without signs of periodontal pathology. He concluded that the insertion of the blades could be performed without resulting in bleeding and that the device consistently reached the cementoenamel junction (Fig. 4-25).

Subsequent studies observed, however, that the tip of a periodontal probe in a pocket depth measurement seldom identified the base of the dentogingival epithelium. Thus, in the absence of an inflammatory lesion, the probe frequently failed to reach the apical part of the junctional epithelium (e.g. Armitage *et al*. 1977). If an inflammatory lesion was present in the gingival connective tissue, however, the probe penetrated beyond the epithelium to reach the apicolateral border of the infiltrate.

Lang *et al*. (1994) in a preclinical *in vivo* study prepared the implant sites in such a way that at probing some were healthy, a few exhibited signs of mucositis, and some exhibited peri-implantitis. Probes with different geometry were inserted into the pockets using a standardized probing procedure and a force of 0.2 N. The probe locations were studied in histologic ground sections. The mean "histologic" probing depth at healthy and peri-implant mucositis sites was about 1.8 mm, while at sites with peri-implantitis the corresponding values were about 3.8 mm. Lang *et al*. (1994) further stated that at healthy and mucositis sites, the probe tip identified "the connective tissue adhesion level" (i.e. the base of the barrier epithelium), while at peri-implantitis sites, the probe exceeded the base of the ulcerated pocket epithelium by a mean distance of 0.5 mm. At such peri-implantitis sites, the probe reached the base of the inflammatory cell infiltrate.

Schou *et al*. (2002) compared probing measurements at implants and teeth in another preclinical *in vivo* study. Ground sections were produced from tooth and implant sites that were (1) clinically healthy, (2) slightly inflamed (mucositis/gingivitis), and (3) severely inflamed (peri-implantitis/periodontitis) and in which probes had been inserted. An electronic probe (Peri-Probe®) with a tip diameter 0.5 mm and a standardized probing force of 0.3–0.4 N was used. It was demonstrated that the probe tip was located at a similar distance from the bone in healthy tooth sites and implant sites. On the other hand, at implants exhibiting mucositis and peri-implantitis, the probe tip was consistently identified at a more apical position than at corresponding tooth sites (gingivitis and periodontitis).

Abrahamsson and Soldini (2006) in a preclinical *in vivo* study evaluated the location of the probe tip in healthy periodontal and peri-implant tissues. They reported that probing with a force of 0.2 N resulted in a probe penetration that was similar at implants and teeth. Furthermore, the tip of the probe was often at or close to the apical cells of the junctional/barrier epithelium. The distance between the

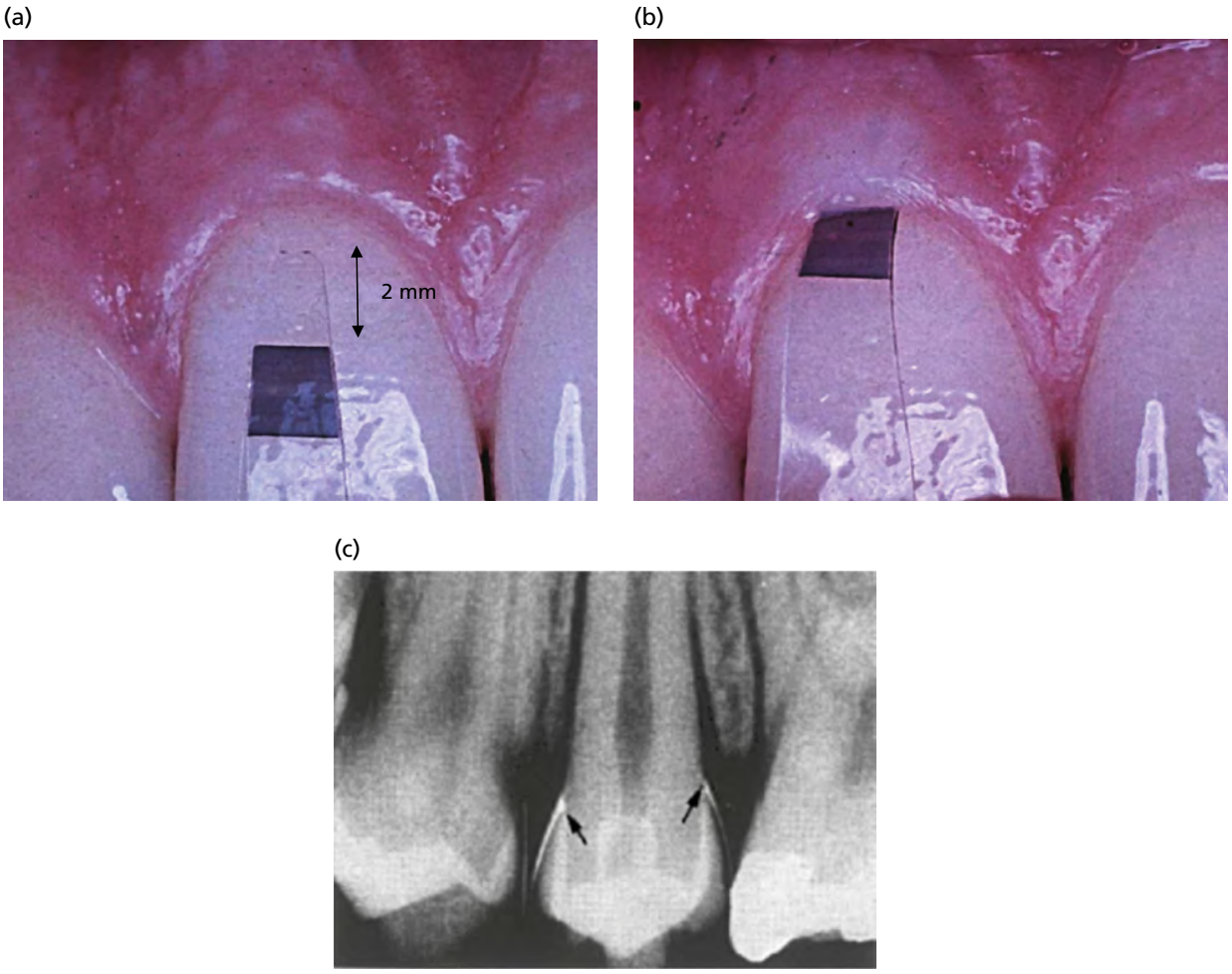


Fig. 4-25 Acrylic strip with a blue zone located 2 mm from the strip margin (a) prior to and (b) after its insertion into a buccal "pocket". With a light force the strip could be inserted 2 mm into the "pocket". (c) Thin blades of steel were inserted into pockets at approximal sites of teeth with healthy periodontal tissue. On radiographs, Waerhaug (1952) could observe that the blades consistently reached the cementoenamel junction.

tip of the probe and the bone crest was about 1 mm at both teeth and implants (Figs. 4-26, 4-27). Similar observations were reported from clinical studies in which different implant systems were used (Buser *et al*. 1990; Quirynen *et al*. 1991; Mombelli *et al*. 1997). In these studies, the distance between the probe tip and the bone was assessed in radiographs and varied between 0.75 and 1.4 mm when a probing force of 0.25–0.45 N was used.

By comparing the findings from the studies reported above, it becomes apparent that probing depth and probing attachment level measurements are meaningful at implant sites.

Dimensions of the buccal soft tissue at implants

Chang *et al*. (1999) compared the dimensions of the periodontal and peri-implant soft tissues of subjects who had been treated with an implant-supported single-tooth restoration in the esthetic zone of the maxilla and who had a non-restored natural tooth in the contralateral position (Fig. 4-28). In comparison to the natural tooth, the implant-supported crown was bordered by a thicker buccal mucosa (2.0 mm versus 1.1 mm), as assessed at a level corresponding to the bottom of the probeable pocket and had a greater probing pocket depth (2.9 mm versus 2.5 mm) (Fig. 4-29). It was further observed that the soft tissue margin at the implant was more apically located (about 1 mm) than the gingival margin at the contralateral tooth.

Kan *et al*. (2003) studied the dimensions of the peri-implant mucosa at single implants that had been placed in the anterior maxilla for about 3 years. Bone sounding measurements performed at the buccal aspect of the implants showed that the height of the mucosa was 3–4 mm in the majority of the cases. Less than 3 mm of mucosa height was found at only 9% of the implants. It was suggested that implants in this category (1) were found in subjects who belonged to a *thin periodontal phenotype*, (2) had been placed too labially, and/or (3) had the emergence of an over-contoured facial prosthetic. A peri-implant soft tissue dimension of >4 mm was usually associated with a *thick periodontal phenotype*.

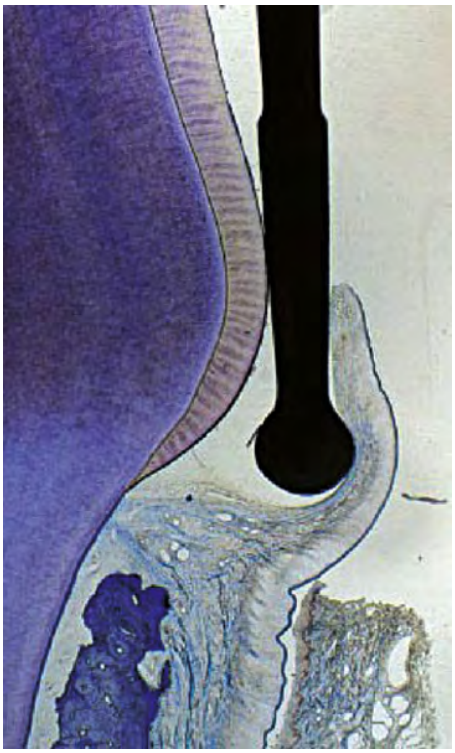


Fig. 4-26 Buccolingual ground section from a tooth site illustrating the probe tip position in relation to the bone crest. (Source: Abrahamsson & Soldini 2006. Reproduced with permission from John Wiley & Sons.).

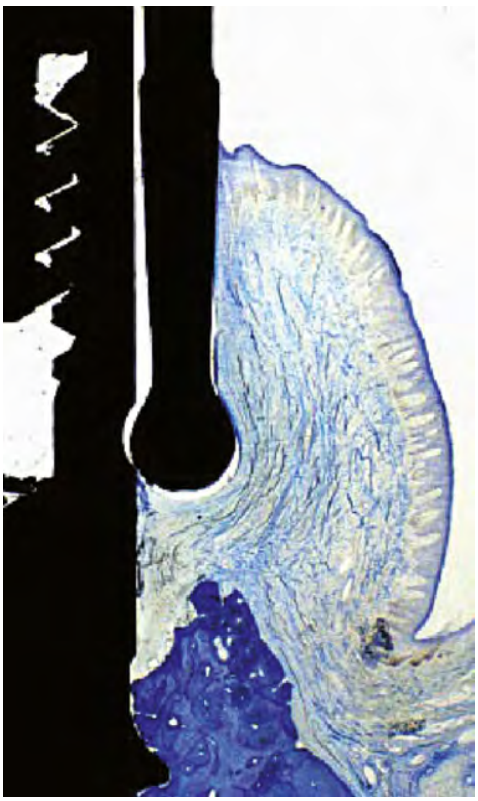


Fig. 4-27 Buccolingual ground section from an implant site illustrating the probe tip position in relation to the bone crest. (Source: Abrahamsson & Soldini 2006. Reproduced with permission from John Wiley & Sons.)

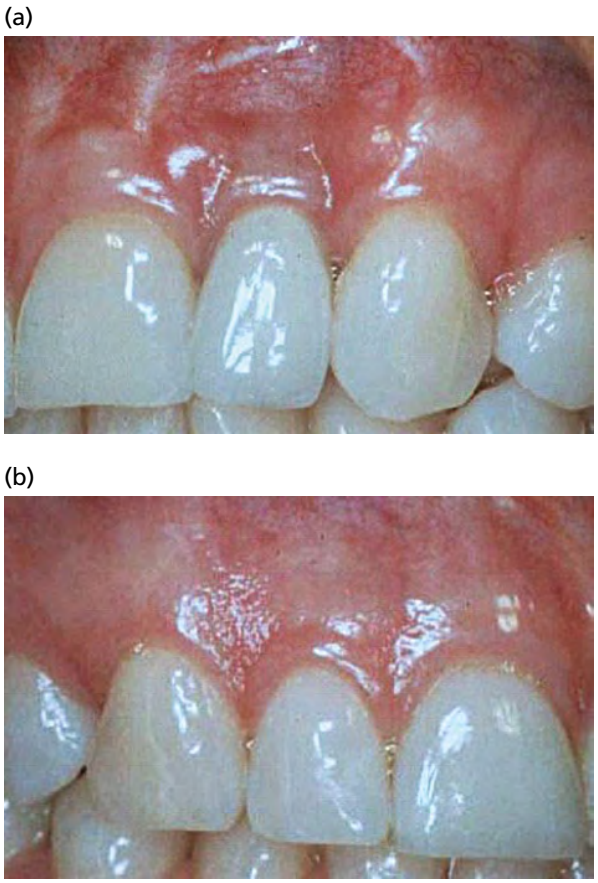


Fig. 4-28 (a) An implant-supported single-tooth replacement in position 12 and (b) the natural tooth in the contralateral position. (Source: Chang *et al*. 1999. Reproduced with permission from John Wiley & Sons.)

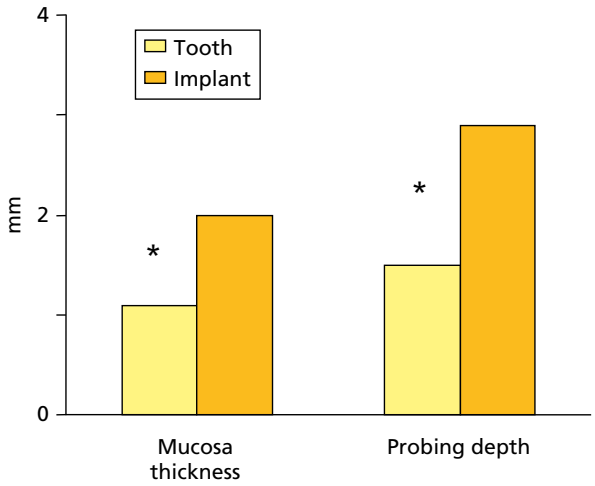


Fig. 4-29 Comparison of mucosa thickness and probing depth at the facial aspect of single-implant restorations and the natural tooth in the contralateral position. (Source: Modified from Chang *et al*. 1999. Reproduced with permission from John Wiley & Sons.)

Dimensions of the papilla between teeth and implants

Schropp *et al*. (2003) demonstrated that following single-tooth extraction the height of the papilla at the adjacent teeth was reduced by about 1 mm. Concomitant with this reduction (recession) of the papilla height, the pocket depth was reduced and some loss of clinical attachment occurred.

Following single-tooth extraction and subsequent implant installation, the height of the papilla in the tooth implant site will be dependent on the attachment level of the tooth. Choquet *et al*. (2001) studied the papilla level adjacent to single-tooth dental implants. The distance between the apical extension of the contact point between the crowns and the bone crest, as well as the distance between the soft tissue level and the bone crest, was measured on radiographs. The examinations were made 6–75 months after the insertion of the crown restoration. The authors observed that the papilla height consistently was about 4 mm and, depending on the location of the contact point between adjacent crown papilla, fill was either complete or incomplete (Fig. 4-30). The closer the contact point was to the incisal edge of the crowns (restorations), the less complete was the papilla fill.

Chang *et al*. (1999) studied the dimensions of the papillae at implant-supported single-tooth restorations in the anterior region of the maxilla and at non-restored contralateral natural teeth. They found that the papilla height at the implant-supported crown was significantly shorter and showed less fill of the embrasure space than the papilla at the natural tooth (Fig. 4-31). It is evident that the anatomy of the adjacent natural teeth (e.g. the diameter of the root, the proximal outline/curvature of the cementoenamel junction/connective tissue attachment level) has a profound influence on the dimension of the papilla lateral to an implant.

Kan *et al*. (2003) assessed the dimensions of the peri-implant mucosa lateral to single implants placed in the anterior maxilla and the adjacent teeth using bone sounding measurements. The bone sounding measurements were performed at the proximal aspects of the implants and at the teeth. The authors reported that the thickness of the mucosa at the mesial/distal surfaces of the implant sites was on average 6 mm, while the corresponding dimension at the adjacent tooth sites was about 4 mm. It was further observed that the dimensions of the peri-implant mucosa of subjects who belonged to the *thick periodontal phenotype* were significantly greater than those of subjects with a *thin phenotype*.

The level of the connective tissue attachment on the adjacent tooth surface and the position of the contact point between the crowns are obviously key factors that determine whether or not a complete papilla fill will be obtained at the single-tooth implant-supported restoration (Fig. 4-32). Although there are indications that the dimensions of the approximal soft tissue may vary between individuals having thin and thick periodontal phenotypes, the height of the papilla at single-implant restorations seems to have a biologic limit of about 4 mm (compare this with the dimension of the interdental papilla). Hence, to achieve a complete papilla fill of the embrasure space, a correct location of the contact area between the

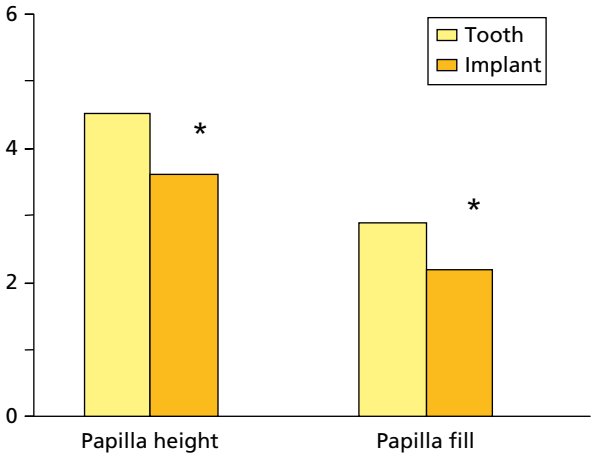


Fig. 4-31 Comparison of papilla height and papilla fill adjacent to single-implant restorations and the natural tooth in the contralateral position. (Source: Modified from Chang *et al*. 1999. Reproduced with permission from John Wiley & Sons.)

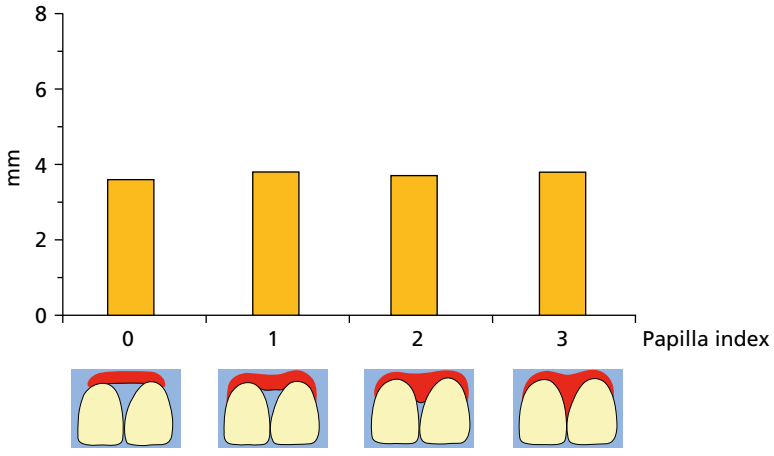


Fig. 4-30 Soft tissue height adjacent to single-tooth dental implants in relation to the degree of papilla fill. (Source: Modified from Choquet *et al*. 2001. Reproduced with permission from John Wiley & Sons.)

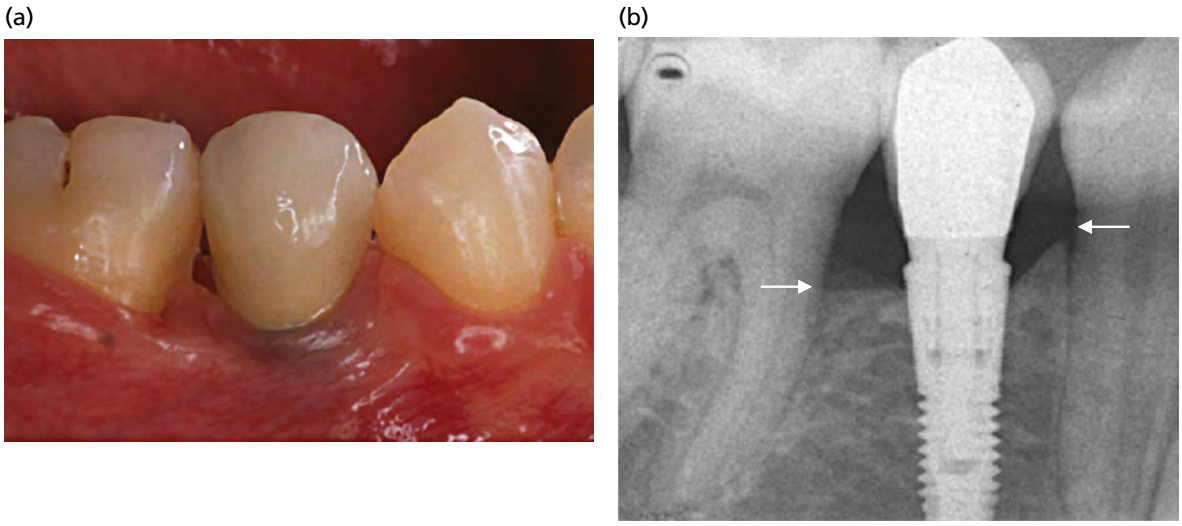


Fig. 4-32 Single implant in a mandibular premolar region. (a) Papilla fill between the implant and the first premolar is optimal, while the papilla fill between the implant and the molar is compromised and a black space is visible. (b) Radiograph from the same site showing the position of the cementoenamel junction (on the premolar) and the marginal bone level (on the molar) (arrows).

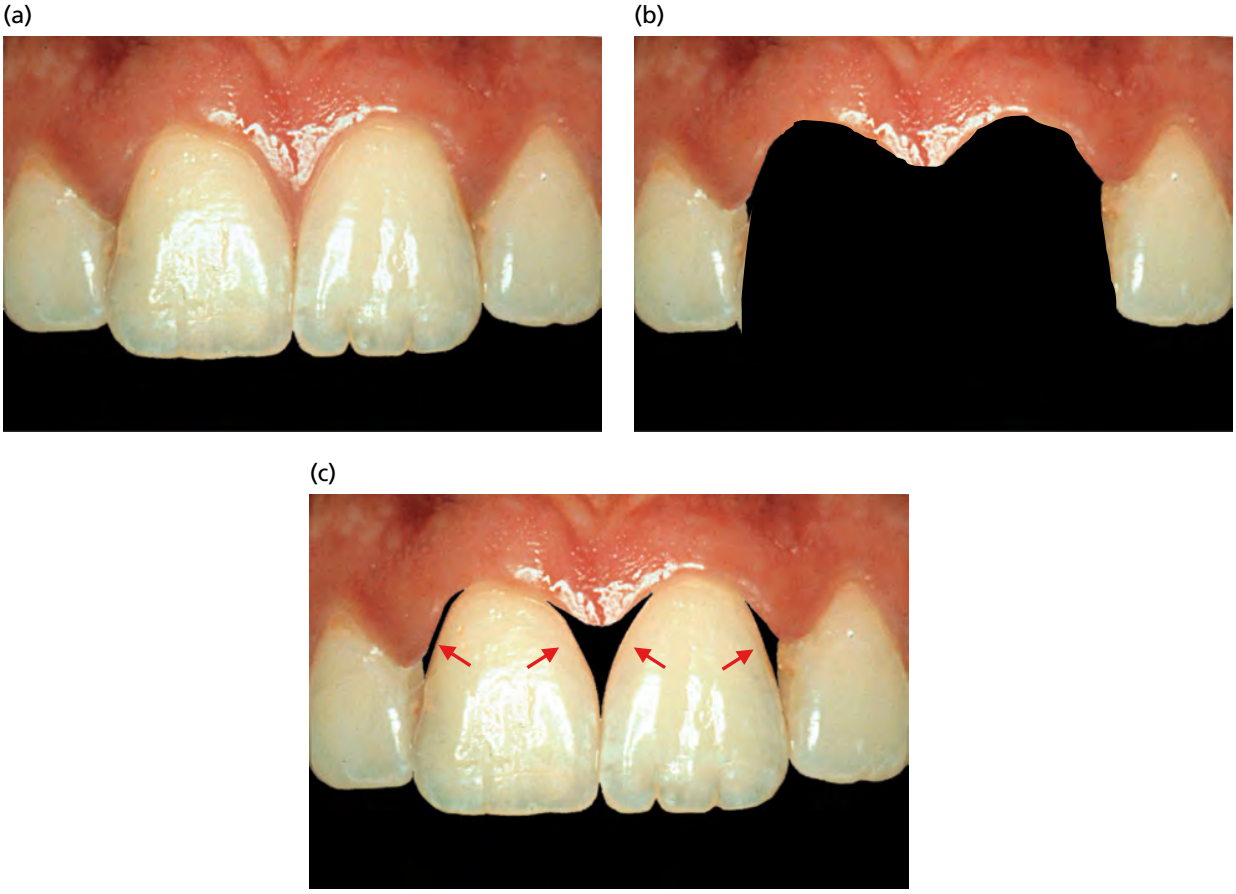


Fig. 4-33 See text for details. Arrows indicate the position of the soft tissue borders prior to the removal of the incisors.

implant crown and the tooth crown is mandatory. In this respect it must also be recognized that the papilla fill at single-tooth implant restorations is unrelated to whether the implant is inserted according to a one- or two-stage protocol and whether a crown restoration is inserted immediately following surgery or delayed until the soft tissues have healed (Jemt 1999; Ryser *et al*. 2005).

Dimensions of the "papilla" between adjacent implants

When two neighboring teeth are extracted, the papilla at the site will be lost (Fig. 4-33). Hence, at replacement of the extracted teeth with implant-supported restorations, the topography of the bone crest and the thickness of the supracrestal soft tissue

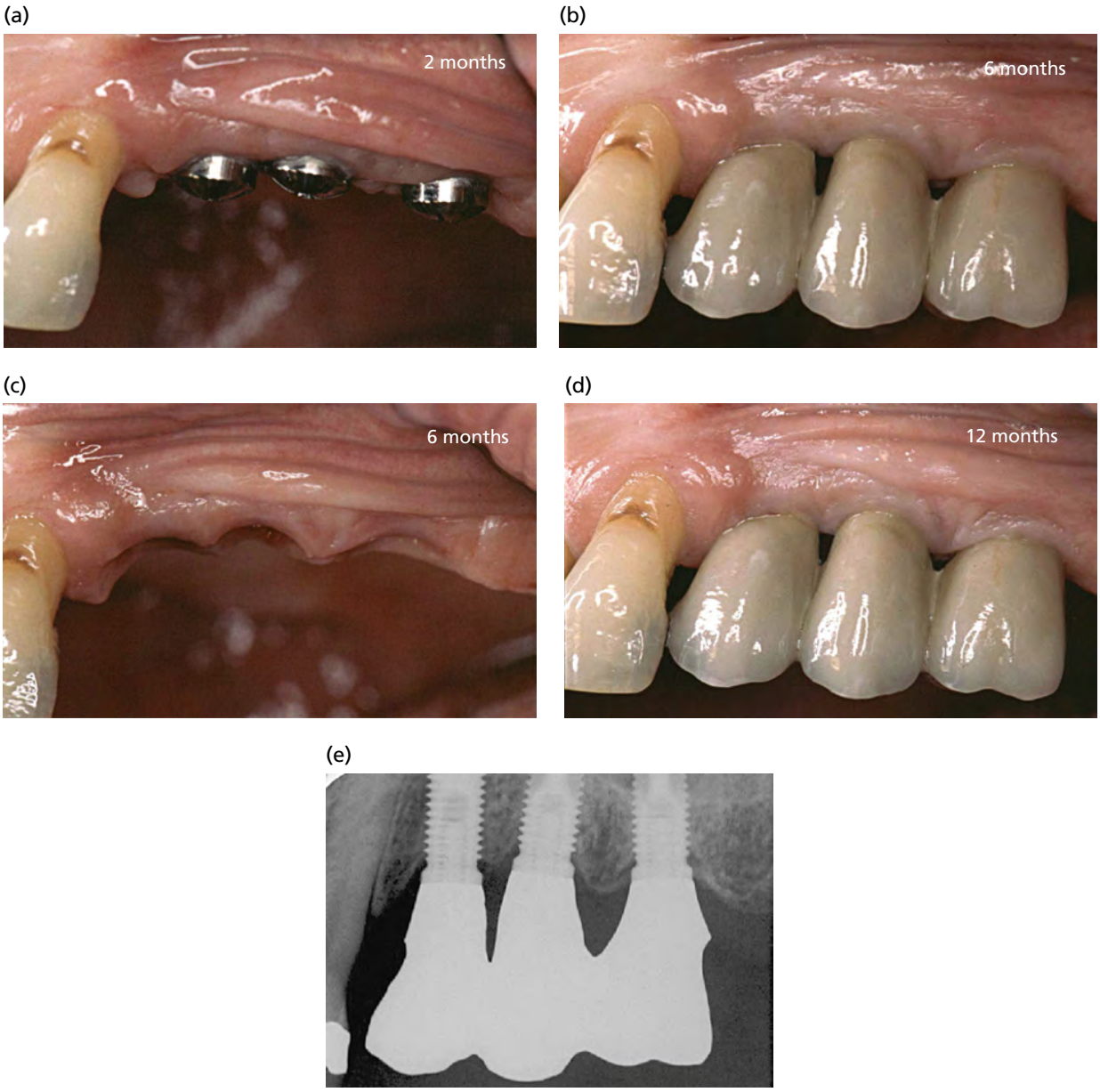


Fig. 4-34 See text for details.

portion are the factors that determine the position of the soft tissue margin in the interimplant area ("implant papilla"). Tarnow *et al*. (2003) assessed the height above the bone crest of the interimplant soft tissue ("implant papilla") by transmucosal probing. It was found that the mean height of the "papillae" was 3.4 mm, with 90% of the measurements in the range of 2–4 mm.

The dimension of the soft tissues between adjacent implants seems to be independent of the implant design. Lee *et al*. (2006) examined the soft tissue height between implants of two different systems, as well as the potential influence of the horizontal distance between implants. The height of the interimplant "papilla", that is the height of soft tissue coronal to the bone crest measured on radiographs, was about 3.1 mm for both implant systems. No difference was found regarding the "papilla" height for either of the implant systems at sites with a horizontal distance between the implants of <3 mm and those with a distance of 3 mm or greater. Gastaldo *et al*. (2004) evaluated the presence or absence of "papilla" between two adjacent implants. They found that complete "papilla" fill occurred only at sites where the distance from the bone crest to the contact point between the crown restorations was <4 mm. Thus, these observations show that the soft tissue between two implants will have a maximum height of 3–4 mm, and that the distance from the contact point between the crown restorations to the bone crest determines whether a complete papilla fill will occur or not (Fig. 4-34).

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Chapter 5

Osseointegration

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Introduction

The fully healed site of the edentulous ridge (see Chapter 3) is most often covered by a masticatory mucosa that is about 2–3 mm thick. The masticatory mucosa is covered by a keratinized oral epithelium and includes a connective tissue rich in fibroblasts and collagen fibers that are firmly attached to the bone via the periosteum. The outer walls of the edentulous ridge, the cortical plates, are comprised of lamellar bone and enclose the cancellous bone that contains trabeculae of lamellar bone that are embedded in bone marrow. The bone marrow contains numerous vascular structures as well as adipocytes and pluripotent progenitor cells.

Different implant systems have been used to replace missing teeth, including subperiosteal implants, endosseous implants with fibrous encapsulation, and endosseous implants with direct bone contact (*osseointegrated*).

One definition of *osseointegration* (a term originally proposed by Brånemark *et al*. [1969]) was provided by Albrektsson *et al*. (1981) who suggested that this was "a direct functional and structural connection between living bone and the surface of a load carrying implant". Another definition was provided by Zarb and Albrektsson (1991) who proposed that *osseointegration* was "a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading". Schroeder *et al*. (1976, 1981, 1995) used the term *"functional ankylosis"* to describe the rigid fixation of the implant to the jaw bone, and stated that "new bone is laid down directly upon the implant surface, provided that the rules for atraumatic implant placement are followed and the implant exhibits primary stability".

Thus, in order to acquire proper conditions for osseointegration (or functional ankylosis), the implant must exhibit proper initial fixation (primary stability) following installation in the recipient site. This initial or primary stability is the result of the contact relationship or friction that is established between mineralized bone (often the cortical bone) at the recipient site and the implant device.

Implant installation

Tissue injury

Basic rule: The less traumatic the surgical procedure and the smaller the tissue injury (the damage) in the recipient site during implant installation, the more expeditious is the process through which new bone is formed and laid down on the implant surface.

The various steps used at implant installation, such as (1) *incision* of the mucosa, often but not always followed by (2) the elevation of *mucosal flaps* and the

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

separation of the periosteum from the cortical plates, (3) the preparation of the *canal* in the cortical and spongy (cancellous) bone of the recipient site, and (4) the insertion of the implant device into this canal, bring to bear a series of mechanical insults and injury to both the mucosa and the bone tissue. The host responds to this injury with an inflammatory reaction, the main objective of which is to eliminate the damaged portions of the tissues and prepare the site for regeneration or repair. To the above-described injury to the hard tissues must be added the effect of the so-called "press fit", that is when the inserted implant is slightly wider than the canal prepared in the host bone. In such situations, (1) the mineralized bone tissue around the implant is compressed and exhibits a series of microfractures, (2) the blood vessels, particularly in the cortical portion, of the canal will collapse, (3) the nutrition to the bone in this portion is compromised, and (4) the affected tissues most often become non-vital.

The injury to the soft and hard tissues of the recipient site, however, also initiates the process of wound healing that ultimately ensures that (1) the implant becomes "ankylotic" with the bone, that is osseointegrated, and (2) a delicate mucosal attachment (see Chapter 4) is established and a soft tissue seal forms that protects the bone tissue from substances in the oral cavity.

Wound healing

The healing of the severed bone following implant installation is a complex process that apparently involves different events in different compartments of the surgical site.

In the *cortical bone compartment*, the non-vital mineralized tissue must first be removed (resorbed) before new bone can form. In the *spongy (cancellous) compartment* of the recipient site, on the other hand, the surgically inflicted damage (preparation of the canal and the installation of the implant) results mainly in soft tissue (marrow) injury that initially involves localized bleeding and clot (coagulum) formation. The coagulum is gradually resorbed and becomes replaced with granulation tissue. This is associated with an in-growth of blood vessels, leukocytes, and mesenchymal cells from the walls of the prepared canal. As a result of the continuous migration of mesenchymal cells from the surrounding marrow, the granulation tissue, in turn, is replaced with provisional soft connective tissue (provisional matrix) and eventually with osteoid. In the osteoid, deposition of hydroxyapatite crystals will occur in the collagen network around the newly formed vascular structures. Hereby, immature woven bone is formed (for detail see Chapter 3) and sequentially osseointegration occurs.

Cutting and non-cutting implants

Although today, various implant materials such as titanium alloys and zirconia are available on the market, this chapter only discusses screw-shaped implants made of c.p. titanium. The design of the metal device and the installation protocol followed may influence the speed of the process that leads to osseointegration.

"*Non-cutting*" implants (Fig. 5-1) require meticulous handling of the recipient site, including the preparation of a standardized track (thread) on the inside of the hard tissue canal. This track (thread) is prepared (precutting) using a thread-tap that is fitted with cutting edges (Fig. 5-2).

"Non-cutting" implants are usually designed as a cylinder with a rounded "apical" base. Pilot and twist drills of gradually increasing dimensions are used to prepare the hard tissue canal of the recipient site to a final diameter corresponding to the diameter of the implant body. On the surface of the cylinder,

Fig. 5-1 Ground section of a "non-cutting" implant and surrounding tissues obtained from a biopsy performed 24 hours after implant installation.

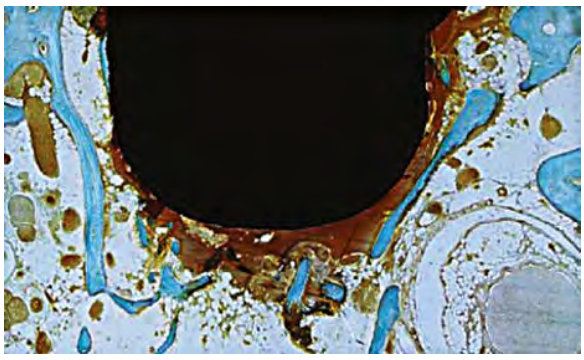

Fig. 5-2 Detail from the apical region of the implant described in Fig. 5-1. Note the presence of a coagulum in the bone marrow.

the implant is designed with a helix-shaped pitch, which results in an increase of the total diameter of the implant. The implant and the cavity prepared in the hard tissues of the recipient site become congruent. When the implant is installed, the pitch on the device will capture and follow the helix-shaped track on the wall of the hard tissue canal and thereby guide the implant with a minimum of force into the preprepared position (Fig. 5-1).

Proper initial fixation (stability) of the implant was obtained by the large contact area that was achieved between the metal screw and the bone wall in the cortical compartment of the recipient site (Fig. 5-1). During site preparation and placement of the implant, bone trabeculae in the spongy compartment of the site were obviously dislocated into the bone marrow. Blood vessels in the marrow compartment were severed, bleeding was provoked, and a coagulum had formed (Fig. 5-2).

After 16 weeks of healing (Fig. 5-3) the marginal portions of the "non-cutting" implant are surrounded by dense lamellar bone that is in direct contact with the rough surface of the metal device. Also, in the apical portion of the implant, a thin coat of mature bone can be seen to contact the implant surface and to separate the titanium screw from the bone marrow.

Cutting or self-tapping implants are designed with cutting edges placed in the "apical" portion of the screw-shaped device. The threads of the screw are prepared during manufacturing by cutting a continuous groove into the body of the titanium cylinder. When a self-tapping implant is to be placed, the recipient site is first prepared with pilot and twist drills to establish a hard tissue canal that may have a final diameter of slightly less than that of the twist drill. During insertion, the cutting edges in the "apical" portion of the implant create a narrow track in the walls of the canal and thereby establish the final implant dimension. When the implant has reached its insertion depth, contact has been established between the outer portions of the threads and the mineralized bone in the cortical compartment (initial or primary fixation is thereby secured) and with the severed bone marrow tissue in the spongy (cancellous) bone compartment.

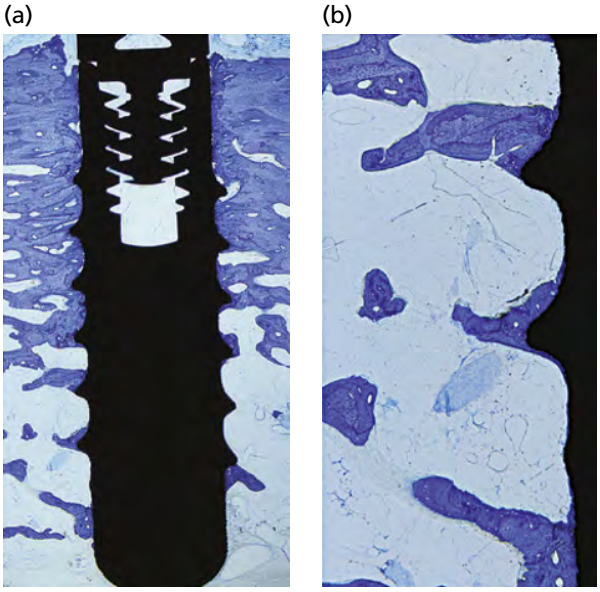

Fig. 5-3 (a) Ground section showing a "non-cutting" implant and surrounding bone after 16 weeks of healing. In the cortical portion of the recipient site, the bone density is high. (b) Detail of (a). In more apical areas, a thin coat of bone is present on the implant surface. Note also the presence of trabeculae of lamellar bone that extend from the implant into the bone marrow.

Figure 5-4 illustrates a recipient site with a self-tapping implant possessing a rough surface

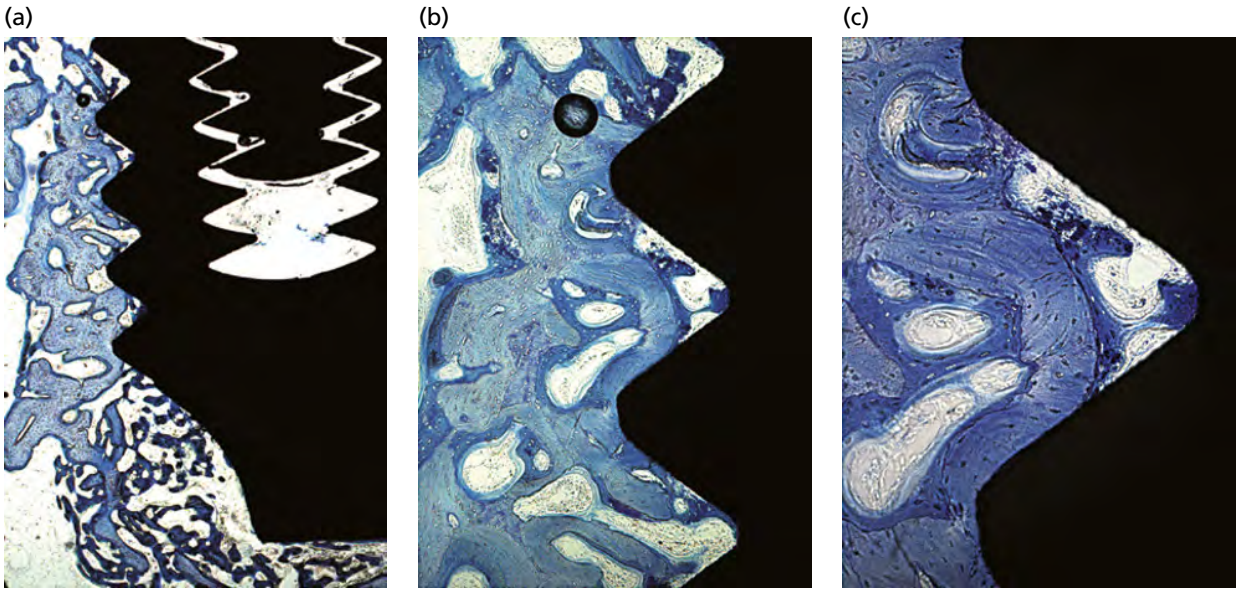

Fig. 5-4 (a) Ground section of a self-tapping implant site from a biopsy sampled after 2 weeks of healing. In the apical area, large amounts of woven bone have formed. (b) Detail of (a). In the threaded region, newly formed bone can be seen to reach contact with the implant surface. (c) Higher magnification of (b). Newly formed bone extends from the old bone and reaches the titanium surface in the invagination between two consecutive "threads".

modification. The biopsy was harvested 2 weeks after installation surgery. The outer portion of the thread is in contact with the "old" bone, while new bone formation is the dominant feature in the invaginations between the threads and in areas lateral to the "apical" portions of the implant. Thus, discrete areas of newly formed bone can be seen also in direct contact with the implant surface. In sections representing 6 weeks of healing (Fig. 5-5), it was observed that a continuous layer of newly formed bone covers most of the rough implant surface. This newly formed bone is also in contact with the old, mature bone that is present in the periphery of the recipient site. After 16 months of healing (Fig. 5-6), the bone tissue in

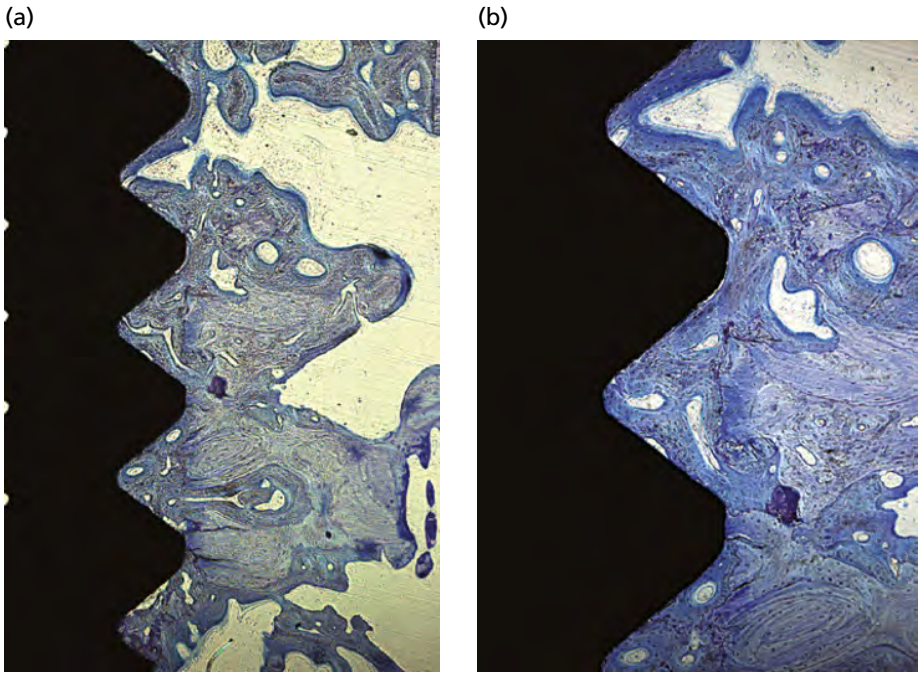

Fig. 5-5 Ground section of an implant site with a self-tapping implant from a biopsy specimen obtained after 6 weeks of healing. (a) In the marginal area, a continuous layer of bone covers most of the implant surface. (b) Higher magnification. Note the zone of newly formed (darker stained) bone that is in direct contact with the implant surface.

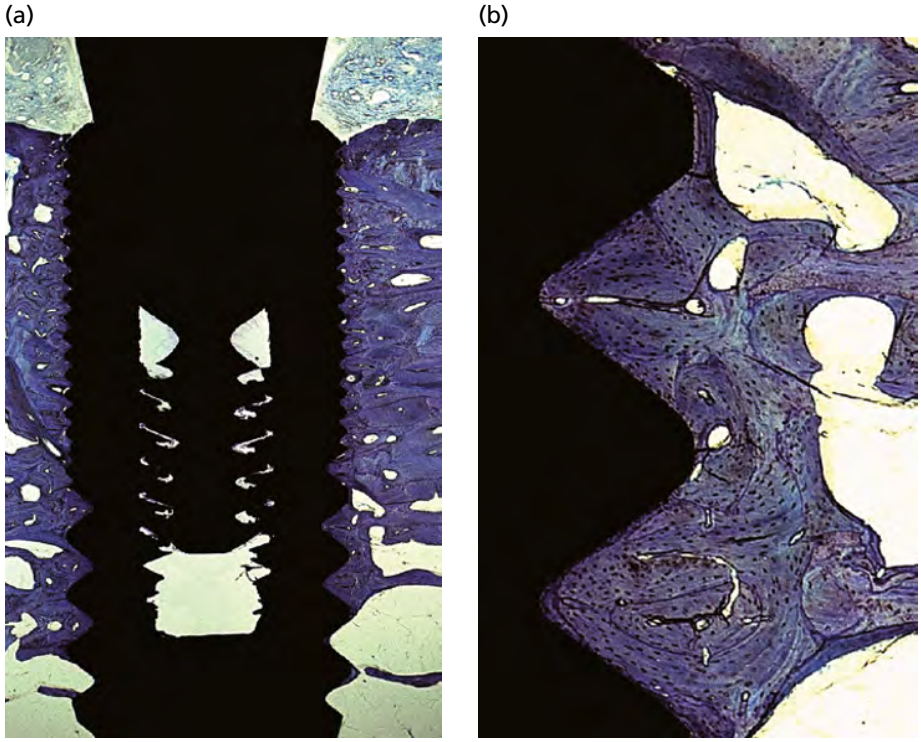

Fig. 5-6 Ground section of a self-tapping implant representing 16 months of healing. (a) The implant is surrounded by dense lamellar bone. (b) Higher magnification of (a) demonstrating a very high percentage of bone-to-implant contact.

the zone of osseointegration has remodeled and the entire hard tissue bed for the implant is comprised of lamellar bone including both concentric and interstitial lamellae.

Process of osseointegration

De novo bone formation in the severed alveolar ridge following implant placement was studied in experiments in various experimental animal models. As an example, Berglundh *et al*. (2003) and Abrahamsson *et al*. (2004) described various steps involved in bone formation and osseointegration to implants placed in the mandible of dogs.

The device: Custom-made implants made of c.p. titanium and in the shape of a solid screw and configured with a rough surface topography were utilized (Fig. 5-7). In the implant device, the distance between two consecutive profiles of the pitch (i.e. the threads in a vertical cross-section) was 1.25 mm. A 0.4-mm deep U-shaped circumferential trough had been prepared within the thread region during manufacturing (Fig. 5-8). The tip of the pitch was left untouched. Following the installation of the non-cutting device (Fig. 5-9), the pitch was engaged in the hard tissue walls prepared by the cutting/tapping device. This provided initial or primary fixation of the device. The void between the pitch and the body of the implant established a geometrically well-defined wound chamber (Fig. 5-10). Biopsies were performed to provide healing periods extending from 2 hours following implant insertion to 12 weeks of healing. The biopsy specimens were prepared for ground sectioning as well as for decalcified sections.

Fig. 5-7 Device used in the dog experiment. The implant is a modification of a solid screw. The distance between two consecutive threads is 1.25 mm. The depth of the trough is 0.4 mm.

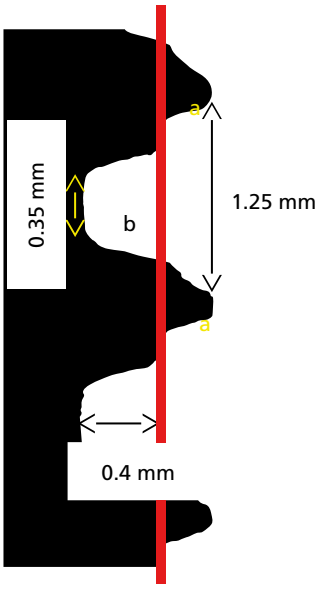

Fig. 5-8 The dimensions of the "wound chamber" in the implant device.

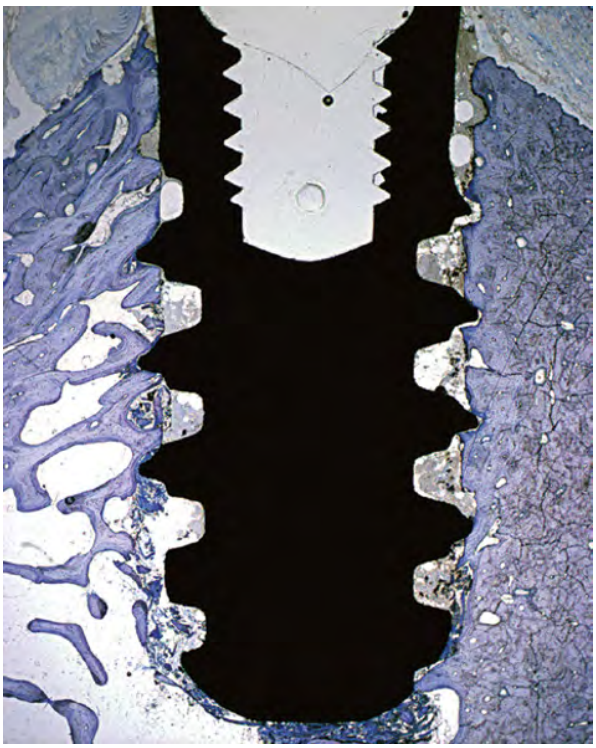

Fig. 5-9 Ground section showing the implant and adjacent tissues immediately after implant installation. The pitch region is engaged in the hard tissue wall. The void between two consecutive pitch profiles includes the wound chamber.

The wound chamber: Figure 5.10 illustrates two wound chambers in a cross-section (ground section) of an implant with surrounding soft and hard tissues from a biopsy specimen sampled 2 hours after installation of the metal device. The peripheral portions of the pitch were in contact with the invaginations of the track prepared by the tap in the cortical bone. The wound chambers (Fig. 5-11a) were occupied with a blood clot in which erythrocytes, neutrophils, and

monocytes/macrophages were trapped in a network of fibrin (Fig. 5-11b). The leukocytes were apparently engaged in the wound cleansing process.

Fibroplasia: Figure 5-12a illustrates a device with surrounding tissues after 4 days of healing. The coagulum had in part been replaced with granulation tissue that contained numerous mesenchymal cells, extracellular matrix components, and newly formed vascular structures (angiogenesis) (Fig. 5-12b). A *provisional connective tissue (matrix)* had been established.

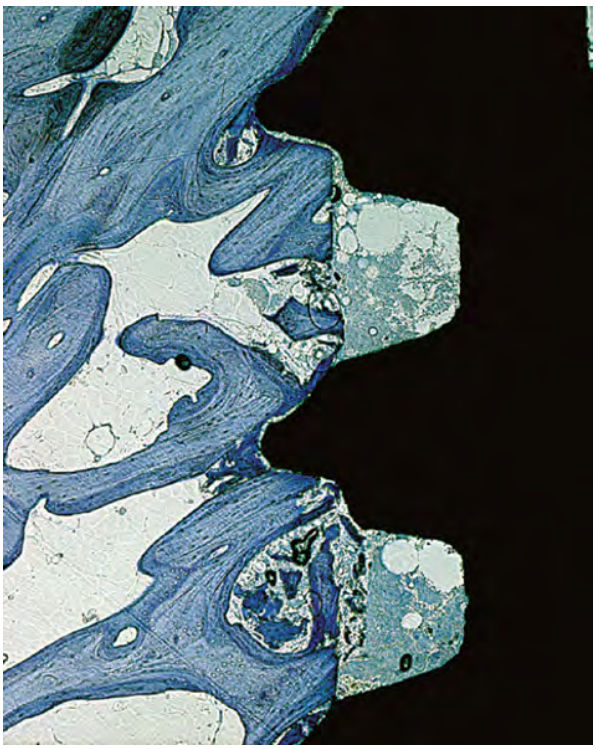

Fig. 5-10 Detail of Fig. 5-9. The wound chamber was filled with blood and a coagulum has formed.

Bone modeling: After 1 week of healing, the provisional connective tissue in the wound chambers was rich in vascular structures and contained numerous mesenchymal cells (Fig 5-13a). The number of remaining inflammatory cells was small. In several compartments of the chamber, a cell-rich immature bone (woven bone) was seen in the provisional soft connective tissue that surrounded the blood vessels. Woven bone formation occurred in the center of the chamber as well as in discrete locations that apparently were in direct contact with the surface of the titanium device (Fig. 5-13b). This was considered to represent the very first phase of osseointegration; contact between the implant surface and newly formed woven bone.

After 2 weeks of healing, woven bone formation appeared to be pronounced in all compartments, apical as well as lateral, surrounding the implant (Fig. 5-14a). Large areas of woven bone were found in the bone marrow regions "apical" of the implant. In the wound chamber, portions of the newly formed woven bone apparently extended from the old bone into the provisional connective tissue (Fig. 5-14b) and had in many regions reached the surface of the titanium device. At this interval, most of the implant surface was occupied by newly formed bone and a more comprehensive and mature osseointegration had been established (Fig. 5-14c). In the pitch regions, there were signs of ongoing new bone formation (Fig. 5-14d). Thus, areas of the recipient site located lateral to the device, that were in direct contact with the host bone immediately following installation

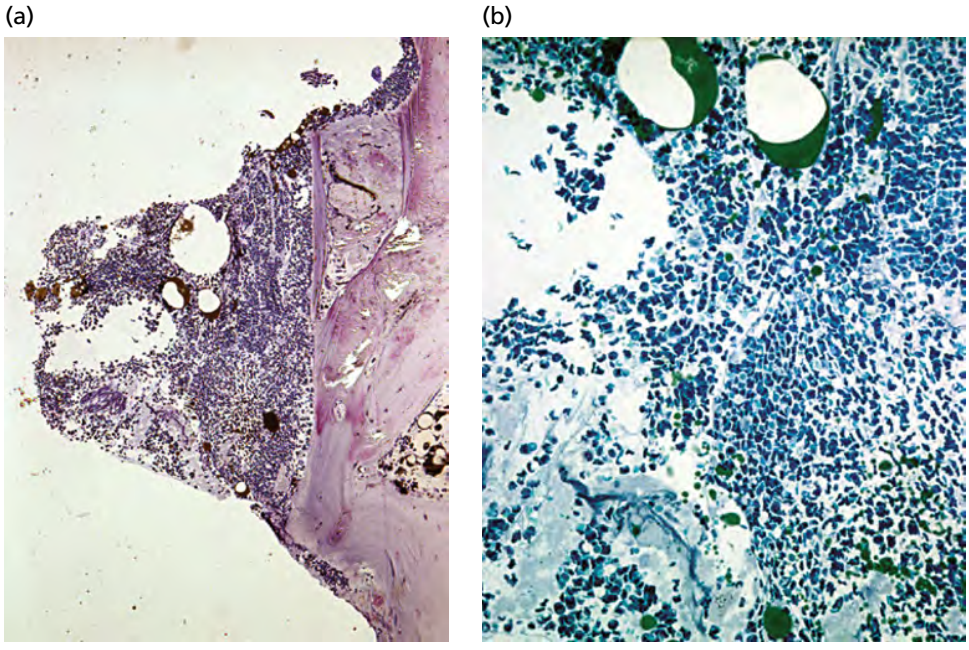

Fig. 5-11 Wound chamber 2 hours after implant installation. Decalcified section. (a) The wound chamber is filled with blood. (b) Erythrocytes, neutrophils, and macrophages are trapped in a fibrin network.

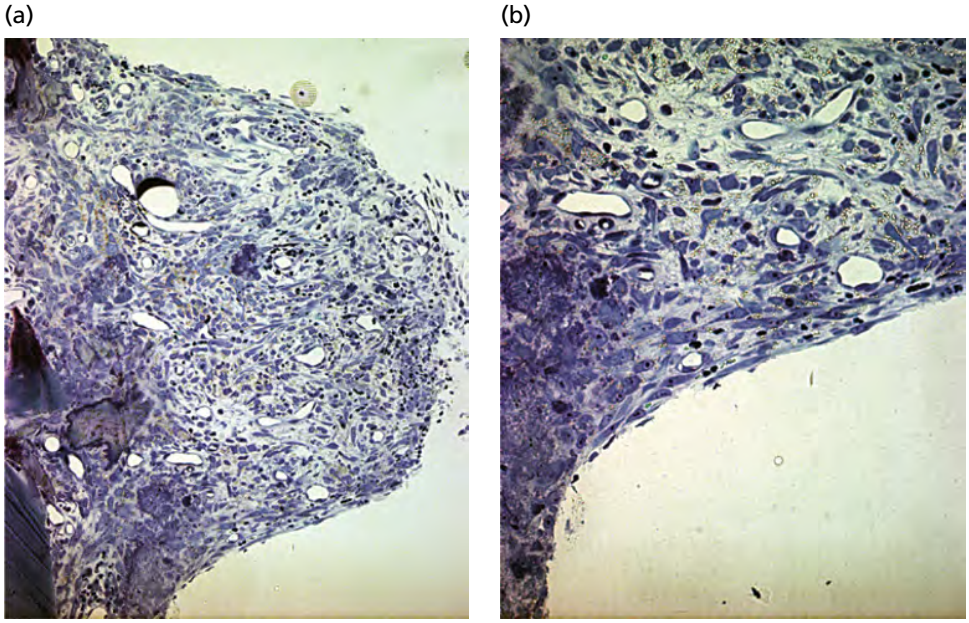

Fig. 5-12 Wound chamber after 4 days of healing. Decalcified section. (a) Most portions of the wound chamber are occupied by granulation tissue (fibroplasia). (b) In some areas of the chamber, provisional connective tissue (matrix) is present. This tissue includes large numbers of mesenchymal cells.

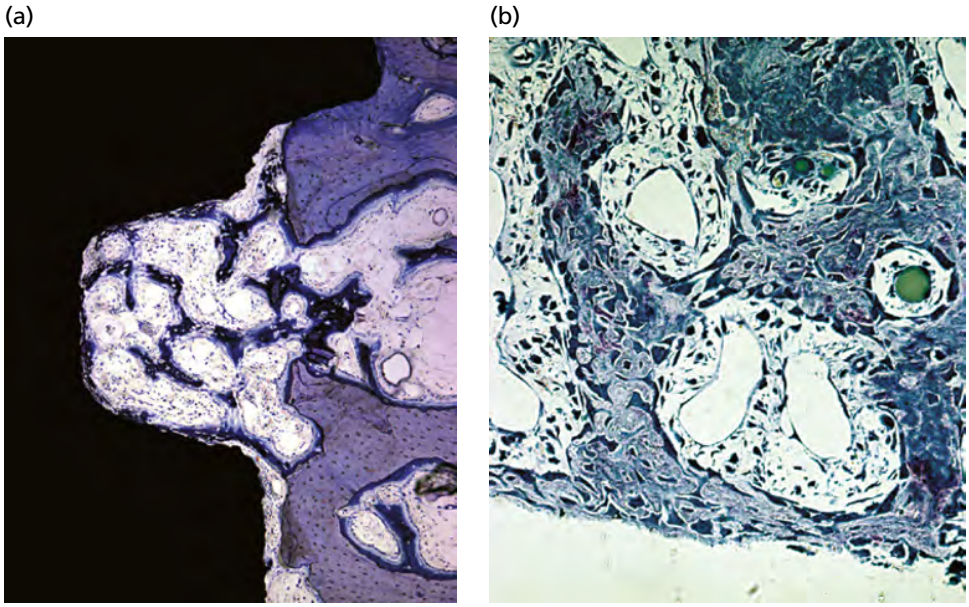

Fig. 5-13 (a) Ground section representing 1 week of healing. Note the presence of newly formed woven bone in the wound chamber. (b) Decalcified section. The woven bone is in direct contact with the implant surface.

surgery and provided initial fixation for the implant, had undergone resorption and were also involved in new bone formation after 2 weeks of healing.

At 4 weeks (Fig. 5-15a), the newly formed mineralized bone extended from the cut bone surface into the chamber and a continuous layer of cell-rich, woven bone covered most of the titanium wall of the chamber. The central portion of the chamber was filled with a primary spongiosa (Fig. 5-15b), rich in vascular structures and a multitude of mesenchymal cells.

Remodeling: After 6–12 weeks of healing, most of the wound chambers were filled with mineralized bone (Fig. 5-16). Bone tissue, including primary and secondary osteons, could be seen in the newly formed tissue and in the mineralized bone that made contact with the implant surface. Bone marrow that contained blood vessels, adipocytes, and mesenchymal cells was observed to surround the trabeculae of mineralized bone.

Summary: The wound chambers were first occupied with a coagulum. With the in-growth of vessels and migration of leukocytes and mesenchymal cells, the coagulum was replaced with granulation tissue. The migration of mesenchymal cells continued and the granulation tissue was replaced with a provisional matrix, rich in vessels, mesenchymal cells, and

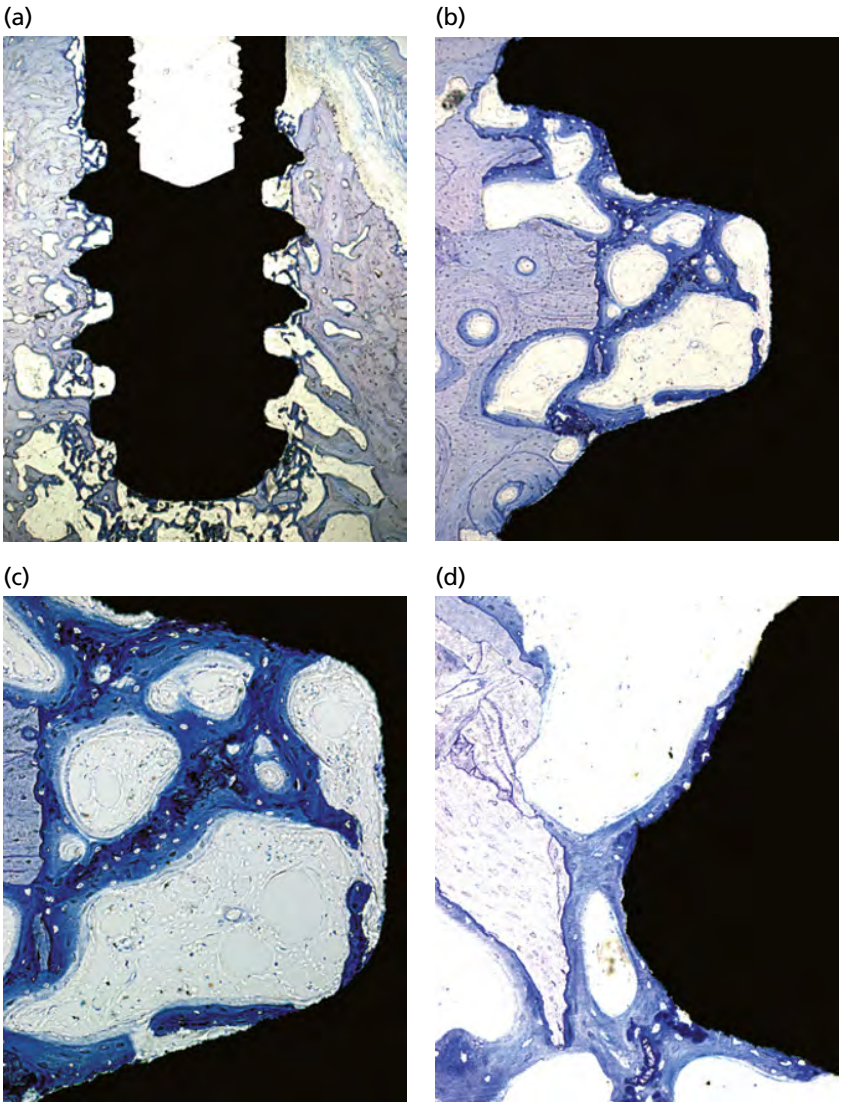

Fig. 5-14 Ground sections showing, in various magnifications, the tissues in the wound chamber after 2 weeks of healing. (a) Darker stained woven bone is observed in the apical area of the metal device. (b–d) Most portions of the implant surface are coated with new bone.

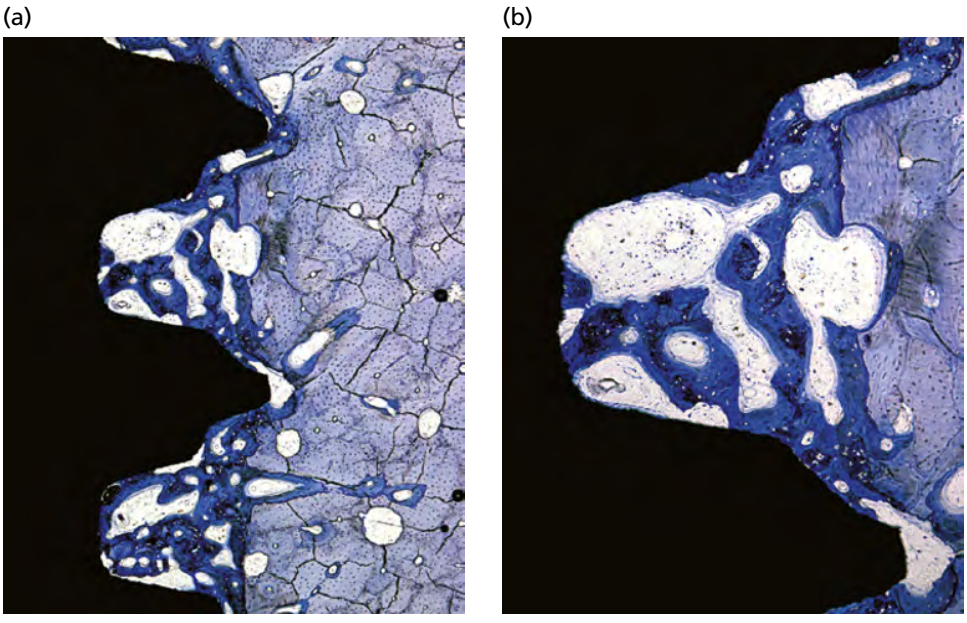

Fig. 5-15 Ground section representing 4 weeks of healing. (a) Newly formed bone (dark blue) extends from the "old" bone into the wound chamber. (b) Appositional growth. Note the presence of primary osteons.

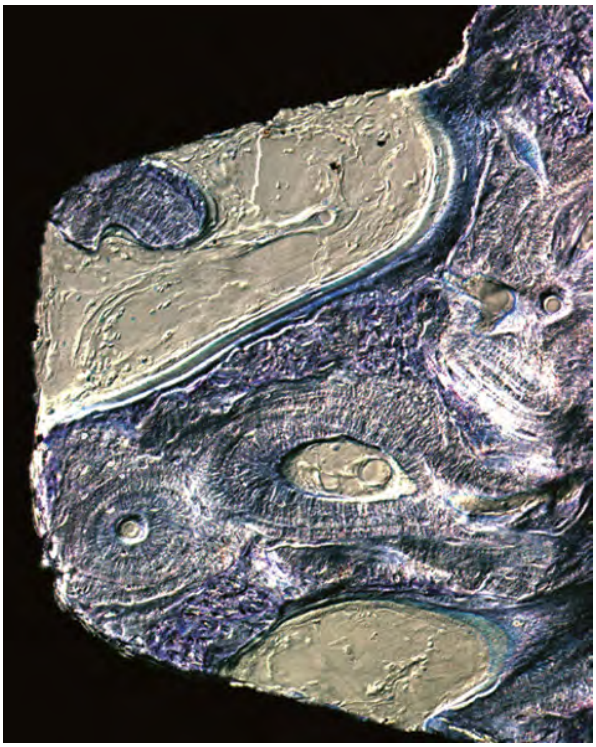

Fig. 5-16 Ground section representing 12 weeks of healing. The woven bone is being replaced with lamellar bone and marrow. Note the formation of secondary osteons. Phase contrast light microscopy.

fibers. The process of *fibroplasia* and angiogenesis had started. Formations of newly formed bone could be recognized already during the first week of healing; the newly formed woven bone projected from the lateral wall of the cut bony bed (appositional bone formation; distance osteogenesis) (Davies 1998), but *de novo* formation of new bone could also be seen on the implant surface, that is at a distance from the parent bone (contact osteogenesis) (Davies 1998). During subsequent weeks, the trabeculae of woven bone were replaced with mature bone, that is lamellar bone and marrow (bone remodeling).

Morphogenesis of osseointegration

A series of publications have described the process of osseointegration of titanium implants placed in human volunteers (Bosshardt *et al*. 2011; Donos *et al*. 2011; Ivanovski *et al*. 2011; Lang *et al*. 2011). In these studies, solid screw devices with a moderately rough surface were placed in the retromolar region of the mandible and submerged healing conditions were established. Biopsies including the implant with surrounding tissues were retrieved with the use of a trephine drill after 1, 2, 4, and 6 weeks. The examination of the samples included histologic and morphometric measurements and particular attention was paid to tissue elements that were in direct contact with or close to the implant surface (the tissue–implant interface), for example old bone, osteoid, newly formed bone, and non-mineralized mesenchymal soft tissue. In addition, at all examination intervals bone debris and solid bone particles were present in the wound lateral to the implant. Such constituents were obviously remnants of the drilling procedure used to prepare the hard tissue canal into which the implant was subsequently introduced.

Overall pattern of implant integration

Figure 5-17 describes the changes in the morphometric measurements in the tissue–implant interface region during the course of the study. After 1 week of healing, about 40% of the interface region was made up of soft tissue (granulation tissue, provisional connective tissue) and an additional 50% of bone debris and old bone. After 2 weeks, the amount of newly formed bone was still small, but the amount of soft tissue was markedly reduced. In the interval between 2 and 4 weeks, new bone formation was apparently pronounced in the interface zone. Thus, in this interval, newly formed bone increased from about 10% to about 30%, while the amount of hard tissue debris was markedly reduced. Also, in the period between 4 and 6 weeks, new bone formation was pronounced (from 30% to about 60%) and the diminution of old bone and bone debris markedly decreased. In other words, in humans the process of osseointegration appears to be most active in the interval between 2 and 6 weeks.

Summary: During the 6 weeks of healing that was monitored in this particular study in humans, it was observed that while the amount of old bone, bone debris,

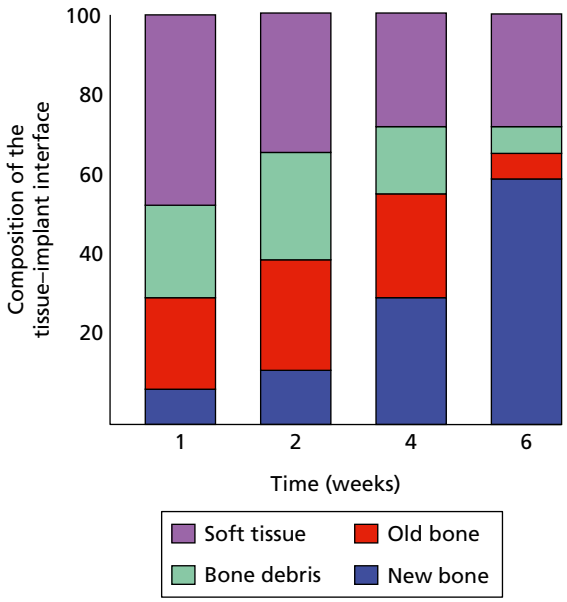

Fig. 5-17 The percentages of new bone, old bone, bone debris, and soft tissue in the "tissue–implant interface" after 1, 2, 4, and 6 weeks of healing. Note that the percentage of old bone, soft tissue, and bone debris that was present in the zone next to the implant surface decreased over time and that the amount of newly formed bone increased. There are reasons to suggest that (1) the contact between old bone and the implant established the initial "mechanical" stability of the titanium device, while (2) the newly formed bone subsequently achieved osseointegration.

and soft tissue that initially occurred in close proximity to the implant gradually decreased, the amount of newly formed bone increased (Fig. 5-17). This pattern of healing that eventually resulted in osseointegration is in close agreement with the results obtained from the animal experiments reported earlier in this chapter.

Biopsy sample observations

Early wound

An implant with surrounding tissues sampled in the early phase after the surgical installation of the device is shown in Fig. 5-18. Note the presence of old bone, particularly in the cortical (marginal) region of the site. This old compact bone appeared to be in direct contact with the implant and obviously facilitated the initial mechanical stability of the device. Note also that more apical portions of the implant were surrounded by non-mineralized tissue, bone debris, and bone particles.

Healing process

After *1 week of healing*, substantial amounts of old bone occupied the marginal portion of the surgically prepared site. This bone tissue appeared to be in close contact with the implant device (Fig. 5-19). As stated above, this close fit between the remaining old bone and the titanium device was most likely a prerequisite for initial implant stability and of importance in establishing optimal healing conditions in the hard tissue wound. At this early interval, newly formed bone occurred on the surface of old bone tissue (Fig. 5-20), while areas of bone resorption could be identified in adjacent regions of the tissue wound.

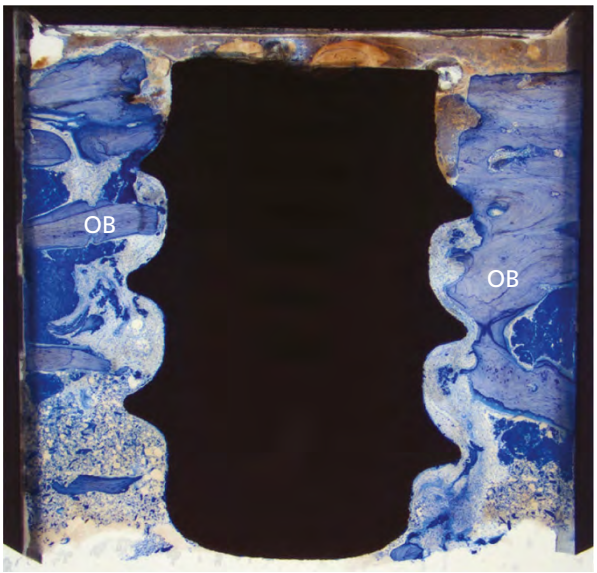

Fig. 5-18 Longitudinal ground section through a biopsy including a solid screw implant device. While compact old bone (OB) is found in contact with the coronal portion of the implant, the apical portion is comprised of less dense tissues and debris.

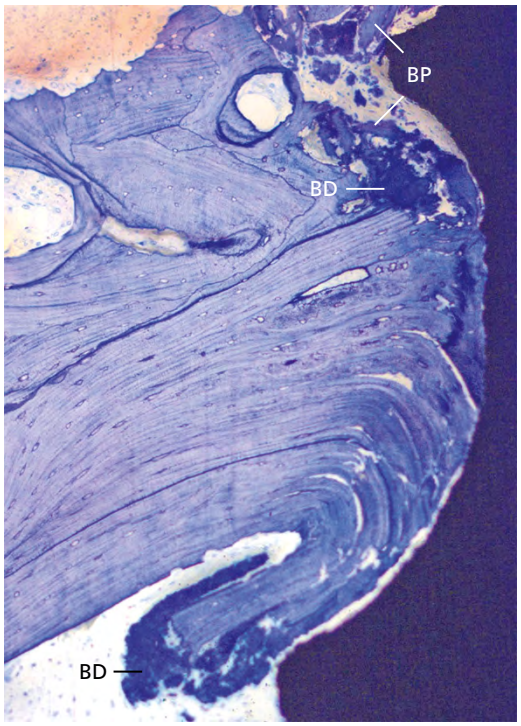

Fig. 5-19 Compact bone in direct contact with the implant surface in the coronal portion after 1 week of healing. Note the presence of bone particles (BP) and bone debris (BD) of varying size close to the implant surface.

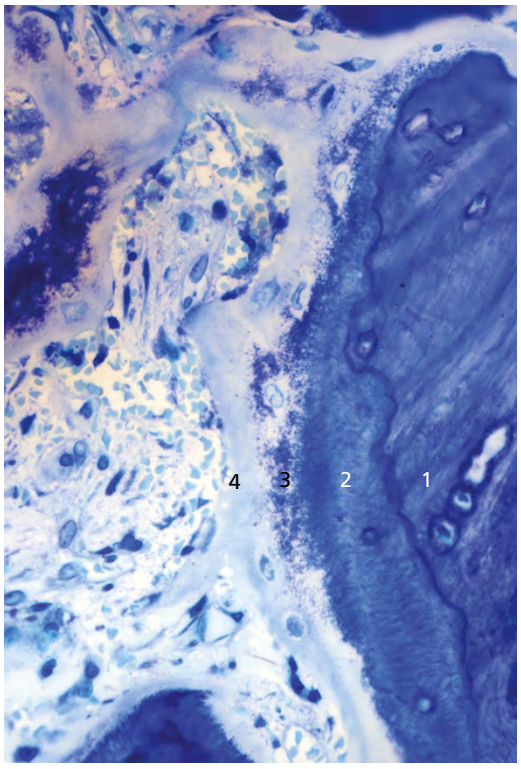

Fig. 5-20 Initial stage of bone apposition onto the surface of old bone occurring at a distance from the implant surface after 1 week of healing. 1, old bone; 2, new mineralized bone matrix; 3, mineralization foci at the mineralization front; 4, osteoid lined by osteoblasts.

In other words, phenomena such as hard tissue apposition and resorption characterized the healing process in this early phase.

Bone debris, bone particles, soft mesenchymal tissue as well as thin layers of osteoid tissue were also frequently found on or close to the implant surface (Figs. 5-21, 5-22).

At the *2-week interval*, remnants of old bone apparently still remained in the marginal portion of the implant site. Areas of hard tissue resorption (Howship´s lacunae; Fig. 5-23) could be found immediately adjacent to as well as at a distance from the implant. In addition, minute areas of newly formed bone occurred on or immediately lateral to the surface of the implant device. This formation of woven bone was the first sign of what may be called osseointegration (Figs. 5-24, 5-25). Furthermore, at this interval, tiny ledges of newly formed woven bone apparently connected old bone to the titanium screw device (Fig. 5-25).

At the *4-week interval*, the healing process features of modeling and remodeling were pronounced. Thus, in some areas close to the implant surface resorptive processes were discernible, while in adjacent areas woven bone had formed (Fig. 5-26).

At the *6-week interval*, large amounts of newly formed woven bone (Fig. 5-27), but also lamellar bone and marrow, were present in close proximity to the implant device. This kind of newly formed hard tissue was apparently part of a more stable "bone–implant contact", in other words osseointegration.

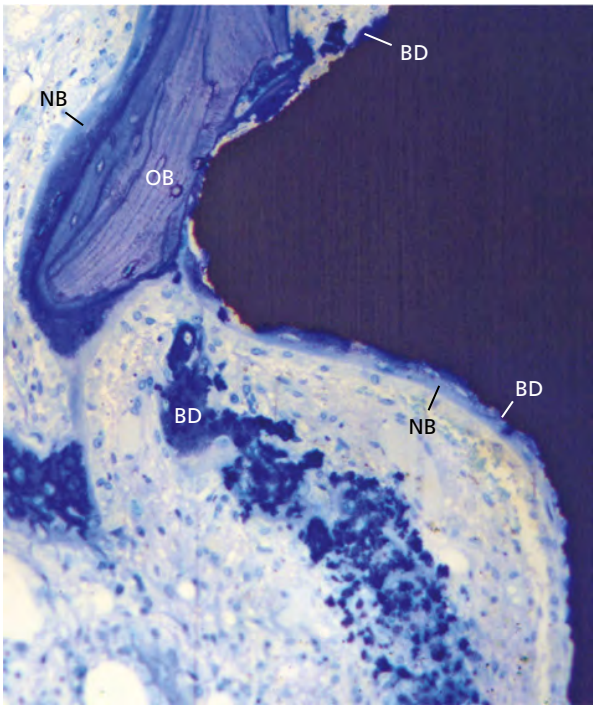

Fig. 5-22 After a healing period of 1 week, old bone (OB) is still in contact with the pitch of the implant thread. Newly formed bone (NB) is present (1) on the ledges of old bone and (2) on the implant surface. Bone debris (BD) is found adhering to the implant surface, but is also embedded in the adjacent mesenchymal soft tissue. The newly formed bone mainly consists of a partly mineralized osteoid lined by osteoblasts.

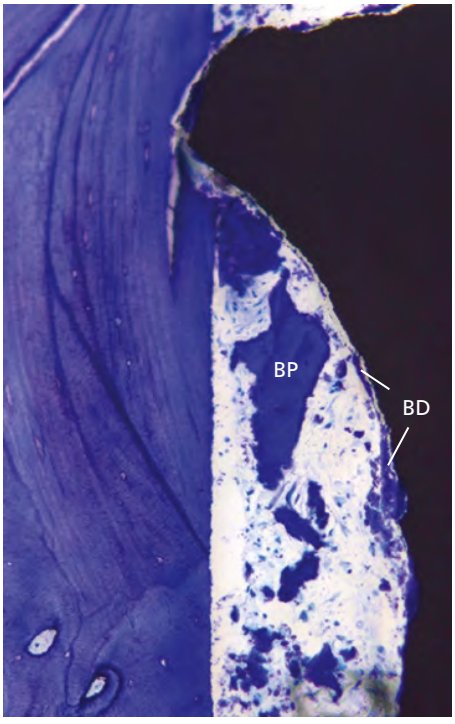

Fig. 5-21 After 1 week of healing, a considerable amount of bone debris (BD) and larger bone particles (BP) are present in the gap between the implant surface and the cut bone bed.

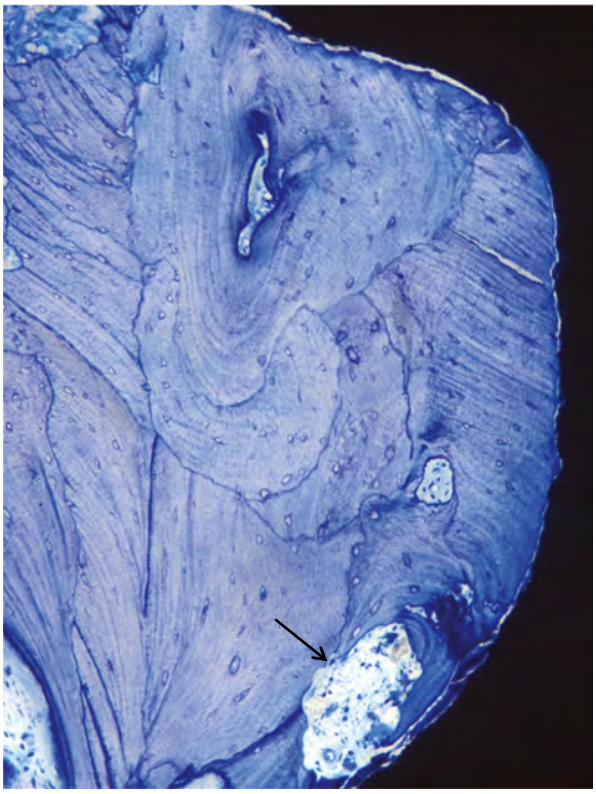

Fig. 5-23 Area of compact old bone in contact with the most coronal portion of the implant after a healing period of 2 weeks. Note the presence of bone resorption at the bottom of the micrograph (arrow).

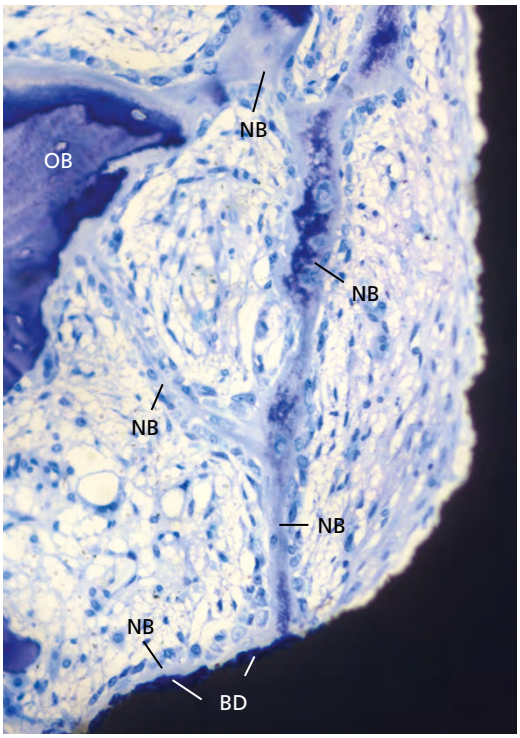

Fig. 5-24 Site characterized by active tissue modeling, in other words woven bone formation. The newly formed trabeculae of woven bone extend from old bone into the provisional connective tissue. OB, old bone; NB, new bone; BD, bone debris.

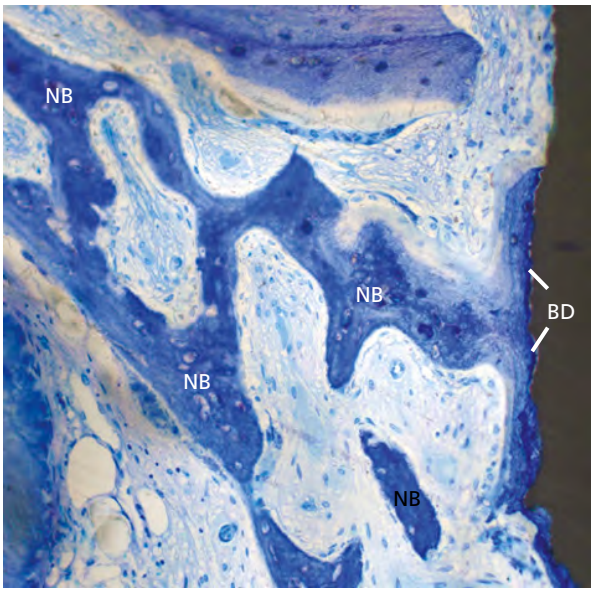

Fig. 5-26 Micrograph showing the implant–tissue interface and the peri-implant tissues of an implant after 4 weeks of healing. The newly formed bone (NB) forms a tiny trabecular network connecting the surface of the old bone with the implant surface. Deposition of new bone on the implant surface was associated with the presence of bone debris (BD).

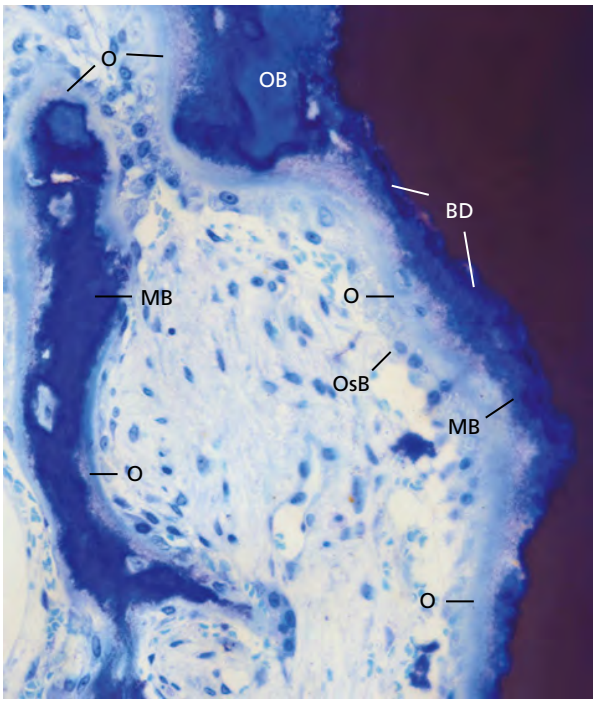

Fig. 5-25 Micrograph showing the implant–tissue interface of an implant site after 2 weeks of healing. The area is filled with a provisional connective tissue matrix and zones of new bone are discernible as well as osteoid tissue on the implant surface. Note the presence of bone debris (BD) on the surface of the implant. Tissue elements, including mineralized matrix of immature bone (MB) as well as osteoid tissue (O) and old bone (OB), are in contact with the implant surface. OsB, osteoblasts between osteoid and connective tissue.

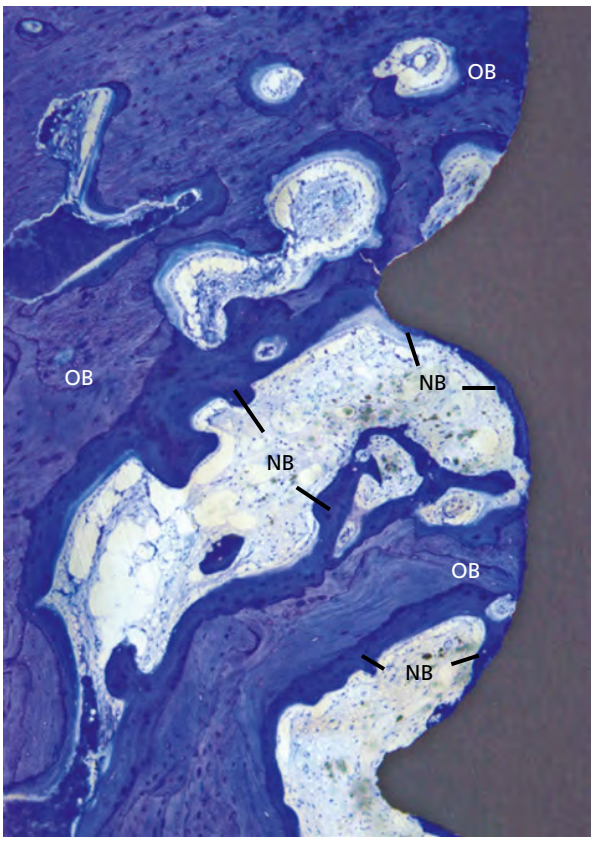

Fig. 5-27 Micrograph showing the implant–tissue interface after 6 weeks of healing. New bone (NB) is found on the surface of old bone (OB) and on the implant surface.

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Part 2: Epidemiology

Chapter 6

Epidemiology of Periodontitis

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Introduction

The term epidemiology is of Hellenic origin; it consists of the preposition "epi", which means "among" or "against", and the noun "demos", which means "people". As denoted by its etymology, epidemiology is defined as "the study of the distribution of disease or a physiological condition in human populations and of the factors that influence this distribution" (Lilienfeld 1978). An older but more inclusive description by Frost (1941) emphasizes that "epidemiology is essentially an inductive science, concerned not merely with describing the distribution of disease, but equally or more with fitting it into a consistent philosophy". Thus, inferences drawn from epidemiologic investigations extend beyond the description of the distribution of diseases in different populations (*descriptive* epidemiology) but also: (1) elucidate their etiology by integrating information derived from other disciplines such as genetics, biochemistry, microbiology, sociology and others to evaluate the consistency of epidemiologic data with hypotheses developed clinically or experimentally (*analytical* epidemiology); and (2) provide the basis for developing and evaluating preventive procedures and public health practices (*interventional* epidemiology).

Based on the above, epidemiologic research in periodontology must: (1) fulfill the task of providing data on the *prevalence* of periodontal diseases in different populations, that is, the frequency of their occurrence, as well as on the *severity* of such conditions (i.e. the amount of pathologic changes); (2) elucidate aspects related to the *determinants* and the *etiology* of these diseases (*risk* and *causative* factors); and (3) provide documentation concerning the effectiveness of preventive and therapeutic measures on a population basis.

Methodological issues

Examination methods: index systems

Examination of the periodontal status of a given individual includes clinical assessments of inflammation in the gingiva, recordings of probing depths and clinical attachment levels, as well as radiographic assessments of the amount of loss of supporting alveolar bone. A variety of index systems for the scoring of

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

these parameters have been developed, some of which were designed exclusively for examination of patients in a dental practice set-up, while others were developed for use in epidemiologic research. The design of the index systems and the definition of the various scores inevitably reflect the knowledge of the etiology and pathogenesis of periodontal diseases at the time these systems were introduced, as well as concepts related to therapeutic approaches and strategies accepted at the time. This section will not provide a complete list of all available scoring systems, but rather give a brief description of a limited number of indices that are either currently used or are likely to be encountered in the recent literature. For a detailed description of earlier scoring systems and a historical perspective of their development, the reader is referred to Ainamo (1989).

Assessment of inflammation of the periodontal tissues

Presence of inflammation in the gingiva is usually recorded by the use of a probe, and often according to the principles of the Gingival Index System outlined by Löe (1967). According to this system, absence of visual signs of inflammation in the gingival unit is scored as 0, while a slight change in color and texture is scored as 1. Visual inflammation and bleeding tendency from the gingival margin right after a periodontal probe is run along the gingival margin is scored as 2, while overt inflammation with tendency for spontaneous bleeding is scored as 3. Plaque deposits are scored in a parallel index (Plaque Index System) on a scale from 0 to 3 (Silness & Löe 1964): the absence of plaque is scored as 0, plaque disclosed after running the periodontal probe along the gingival margin as 1, visible plaque as 2, and abundant plaque as 3. Simplified variants of both the gingival and the plaque indices have been used extensively (Ainamo & Bay 1975), assessing presence/absence of inflammation or plaque, respectively, in a binomial fashion (*dichotomous scoring*). In such systems, bleeding from the gingival margin and visible plaque correspond to a score of 1, while absence of bleeding and no visible plaque correspond to a score of 0.

Bleeding after probing to the base of the probeable pocket (Gingival Sulcus Bleeding Index) has been a common way of establishing the occurrence of subgingival inflammation (i.e. the presence of an inflammatory infiltrate adjacent to the ulcerated pocket epithelium) (Mühlemann & Son 1971). In this dichotomous registration, bleeding emerging within 15 seconds after probing is scored as 1.

Assessment of loss of periodontal tissue support

One of the early indices providing indirect information on the loss of periodontal tissue support was the Periodontal Index (PI) developed in the 1950s by Russell (1956), and was the most widely used index in epidemiologic studies of periodontal disease until the 1980s. Its criteria are applied to each tooth and the scoring is as follows: a tooth with healthy periodontium scores 0, a tooth with gingivitis around only part of the tooth circumference scores 1, a tooth with gingivitis encircling the tooth scores 2, pocket formation scores 6, and loss of function due to excessive tooth mobility scores 8. Due to the nature of the criteria used, the PI is a reversible scoring system, and a tooth or an individual can have the score lowered or reduced to 0 after treatment.

In contrast to the PI system, the Periodontal Disease Index (PDI), developed by Sigurd Ramfjord in 1959 (Ramfjord 1959), is a system designed to assess *destructive* disease; it measures *loss of attachment* instead of *pocket depth* and is, therefore, an irreversible index. The scores, ranging from 0 to 6, denote periodontal health or gingivitis (scores 0–3) and various levels of attachment loss (scores 4–6).

In contemporary epidemiologic studies, loss of periodontal tissue support is assessed by measurements of probing pocket depth (PPD) and probing attachment level (PAL). PPD is defined as the distance from the gingival margin to the apical location of the tip of a periodontal probe that is inserted into the pocket using a moderate probing force. Likewise, PAL or clinical attachment level (CAL) is defined as the distance from the cemento-enamel junction (CEJ) to the location of the probe tip. Probing assessments are usually carried out at several locations along the tooth circumference (buccal, lingual, mesial, and distal). The number of probing assessments per tooth has varied in epidemiologic studies from two to six, while the examination may include either all teeth present (*full-mouth*) or a subset of *index* teeth (*partial-mouth* examination).

Carlos *et al*. (1986) proposed an index system which records loss of periodontal tissue support. The index was denoted the Extent and Severity Index (ESI) and consists of two components (*bivariate* index): (1) the *Extent*, describing the proportion of tooth sites of a subject showing signs of destructive periodontitis; and (2) the *Severity*, describing the amount of probing attachment loss at the diseased sites, expressed as a mean value. An attachment loss threshold of >1 mm was set as the criterion that qualified a tooth site as affected by the disease. The introduction of a threshold value serves a dual purpose: (1) it readily distinguishes the fraction of the dentition affected by disease at levels exceeding the error inherent in the clinical measurement of attachment loss; and (2) it prevents unaffected tooth sites from contributing to the individual subject's mean attachment loss value. In order to limit the number of measurements to be performed, a partial examination comprising the mid-buccal and mesiobuccal aspects of the upper right and lower left quadrants was recommended. It has to be emphasized that the

system was designed to assess the cumulative effect of destructive periodontal disease rather than the presence of the disease itself. The bivariate nature of the index facilitates a rather detailed description of attachment loss patterns: for example, an ESI of (90, 2.5) suggests a generalized but rather mild form of destructive disease, in which 90% of the tooth sites are affected by an average attachment loss of 2.5 mm. In contrast, an ESI of (20, 7.0) describes a severe, localized form of disease.

Radiographic assessment of alveolar bone loss

The potential and the limitations of intraoral radiography to describe loss of supporting periodontal tissues were reviewed in classic publications (Lang & Hill 1977; Benn 1990) and more recent reports (Vandenberghe *et al*. 2010). Radiographs have been commonly employed in older cross-sectional epidemiologic studies to quantify the amount of alveolar bone loss due to periodontitis rather than the presence of the disease itself, and provide valid estimates of the extent and severity of destructive periodontitis affecting interproximal surfaces (Pitiphat *et al*. 2004). Assessments of bone loss in intraoral radiographs are usually performed by evaluating a multitude of qualitative and quantitative features of the visualized interproximal bone, including (1) the presence of an intact lamina dura, (2) the width of the periodontal ligament space, (3) the morphology of the bone crest ("even" or "angular" appearance), and (4) the distance between the CEJ and the most coronal level at which the periodontal ligament space is considered to exhibit normal width. The threshold for bone loss, that is, the CEJ–bone crest distance considered to indicate that bone loss has occurred, varies between 1 and 3 mm in different studies. Radiographic data are usually presented as (1) mean bone loss scores per subject (or group of subjects) and (2) number or percentage of tooth surfaces per subject (or group of subjects) exhibiting bone loss exceeding certain thresholds. In early studies, bone loss was frequently recorded using "ruler" devices, describing the amount of lost or remaining bone as a percentage of the length of the root or the tooth (Schei *et al*. 1959; Lavstedt *et al*. 1975). An increased awareness of the adverse effects of ionizing radiation no longer allows the use of intraoral radiography as a screening tool to survey periodontal conditions in epidemiologic studies.

Assessment of periodontal treatment needs

An index system aimed at assessing the need for periodontal treatment in large population groups was developed, on the initiative of the World Health Organization (WHO), by Ainamo *et al*. (1982). The principles of the Community Periodontal Index for Treatment Needs (CPITN) can be summarized as follows:

1. The dentition is divided into six *sextants* (one anterior and two posterior tooth regions in each dental arch). The treatment need in a sextant is recorded when two or more teeth not intended for extraction are present. If only one tooth remains in the sextant, the tooth is included in the adjoining sextant.
2. Probing assessments are performed either around all teeth in a sextant or around certain index teeth (the latter approach has been recommended for epidemiologic studies). Only the most severe measure in the sextant is chosen to represent the sextant.
3. The periodontal conditions are scored as follows:
   - *Code 0* is given to a sextant with no pockets, calculus, or overhangs of fillings and no bleeding on probing.
   - *Code 1* is given to a sextant with no pockets, calculus, or overhangs of fillings, but in which bleeding occurs after gentle probing in one or several gingival units.
   - *Code 2* is assigned to a sextant if there are no teeth with pockets exceeding 3 mm, but in which dental calculus and plaque-retaining factors are identified subgingivally.
   - *Code 3* is given to a sextant that harbors teeth with 4–5-mm deep pockets.
   - *Code 4* is given to a sextant that harbors teeth with pockets that are 6 mm deep or deeper.
4. The treatment needs (TN) scores range from 0 to 4 and are based on the most severe periodontal condition code in the entire dentition, recorded as above. Thus, TN 0 indicates no need for periodontal therapy in the presence of gingival health (*Code 0*), TN 1 need for improved oral hygiene (*Code 1*); TN 2 need for scaling, removal of overhangs, and improved oral hygiene (*Codes 2 + 3*); and TN 3 more advanced treatment needs (*Code 4*).

Although not designed for epidemiologic purposes, this index system has been extensively used, and CPITN-based studies have often been the sole source of epidemiologic information on periodontal conditions, particularly those from developing countries. A later modification of the index, termed Community Periodontal Index (CPI) (WHO 1997), places more emphasis on the assessment of periodontal conditions rather than the assessment of periodontal treatment needs. A substantial amount of data generated by the use of CPITN/CPI have been accumulated in the WHO Global Oral Data Bank (Miyazaki *et al*. 1992; Pilot & Miyazaki 1994; Petersen & Ogawa 2005, 2018; Petersen *et al*. 2010) and are accessible electronically through servers maintained at the WHO Collaborating Centers at the Niigata University, Japan and the University of Malmö, Sweden.

Periodontitis "case definition" in epidemiologic studies

A fundamental prerequisite for any meaningful comparative assessment of prevalence is a valid and accurate definition of the disease under investigation. Unfortunately, no uniform criteria have been established in periodontal research for this purpose. Epidemiologic studies have employed, in an inconsistent manner, a wide array of symptoms, including gingivitis, PPD, clinical (or probing) attachment level, and radiographically assessed alveolar bone loss. Considerable variation characterizes the threshold values employed for defining periodontal pockets as "deep" or "pathologic", or the CAL and alveolar bone scores required for assuming that loss of periodontal tissue support has, in fact, occurred. In addition, the number of "affected" tooth surfaces required for assigning an individual subject as a "case", that is, as suffering from periodontal disease, has varied. These inconsistencies in the definitions inevitably affect the data describing the distribution of the disease (Papapanou 1996; Kingman & Albandar 2002; Demmer & Papapanou 2010; Catunda *et al*. 2019) and, consequently, the identification of risk factors (Borrell & Papapanou 2005). Any review of the literature charged with the task of comparing disease prevalence or incidence in different populations or at different time periods must first confront the interpretation of the published data and literally "decode" them in order to extract relevant information that is amenable to inter-study comparisons. These problems have been addressed in the literature and three specific aspects have attracted special attention, namely (1) the ability of partial recordings to reflect full-mouth conditions, (2) the use of the CPITN system in studies of periodontal disease, and (3) the definition of a "periodontitis case" in epidemiologic studies.

It is clear that an optimal examination of periodontal conditions should include circumferential probing assessments around all teeth. Nevertheless, the majority of epidemiologic studies have, for practical reasons, employed partial recording methodologies. The rationale for the use of partial examinations has been based on: (1) the fact that the time required for carrying out a partial recoding is significantly decreased, resulting in lower costs and better patient acceptance; and (2) the assumption that the amount of information lost is kept to a minimum (i.e. that the examined segments adequately reflect the periodontal condition of the entire dentition). However, attempts to quantify accurately the amount of information lost through the different partial recording systems made by several investigators (Diamanti-Kipioti *et al*. 1993; Eaton *et al*. 2001; Susin *et al*. 2005; Kingman *et al*. 2008) have revealed that the discrepancy between the findings obtained by means of partial- and full-mouth surveys may be substantial. These studies have typically employed full-mouth data for a series of periodontal parameters and compared them with the values obtained by assessments of a subset of teeth or tooth surfaces. Their results suggest that:

1. Reasonably high correlations between full-mouth and half-mouth clinical attachment loss scores should be expected in adult populations, due to the apparent symmetry of periodontal conditions around the midline.
2. The performance of a partial recording system is directly dependent on the actual prevalence and extent of periodontal disease in the population in question and, consequently, on the age of the subjects examined; the less frequent the disease in the population and the lower the proportion of affected sites affected in each individual, the more difficult it becomes for the partial examination to portray accurately the full-mouth periodontal status.
3. A full-mouth examination provides the best means of accurately assessing the prevalence and severity of periodontal disease in a population.

The use of the CPITN system in epidemiologic studies of periodontal disease was critically evaluated in a number of publications (Schürch *et al*. 1990; Butterworth & Sheiham 1991; Baelum *et al*. 1993a, b; Baelum & Papapanou 1996; Benigeri *et al*. 2000). At the time the system was designed, the conversion from periodontal health to periodontitis was thought to follow a continuum of conditions of increasing severity, ranging from health to gingivitis, calculus deposition, formation of deep pockets, and destructive, progressive disease. Consequently, treatment approaches were primarily focused on probing depths to determine the choice between non-surgical and more complex, surgical periodontal therapy. As mentioned earlier, the CPITN system was originally intended for population screening in order to determine treatment needs and to facilitate preventive and therapeutic strategies; it was not meant to describe the prevalence, extent, and severity of periodontal disease and several studies have questioned the suitability of the CPITN for such purposes. For example, Butterworth and Sheiham (1991) examined the ability of CPITN to reflect changes in periodontal conditions in patients of a general dental practice before and after periodontal therapy. Despite a substantial improvement in periodontal status, that is, a reduction in gingivitis, calculus scores, and deep pockets, the CPITN scores were only marginally improved. Furthermore, in a rural Kenyan subject sample, Baelum *et al*. (1993b) refuted the validity of the *hierarchical principle* of the CPITN, that is, the assumption that a tooth with calculus is assumed to be also positive for bleeding on probing, or that a tooth with deep pockets is assumed to be positive for both calculus and bleeding. In a companion paper, results from a full-mouth examination were compared with those generated by the use of the 10 index teeth recommended by the WHO for surveys of adults (Baelum *et al*. 1993a). The study revealed that the partial CPITN methodology

seriously underestimated the more severe periodontal conditions both in terms of prevalence and severity, by failing to detect a substantial proportion of subjects with periodontal pockets. Finally, an examination of the relationship between CPITN findings and the prevalence and severity of clinical attachment loss demonstrated that the CPITN scores do not correlate consistently with clinical attachment loss measures, but tend to overestimate prevalence and severity among younger subjects and underestimate such parameters in elderly populations (Baelum *et al*. 1993a). Collectively, the above data call for caution in the interpretation of epidemiologic studies based on the CPITN/CPI systems.

In 1999, an International Workshop for a Classification of Periodontal Diseases and Conditions (Armitage 1999), introduced eight categories of periodontal disease, but defined two principal forms of periodontitis, *chronic* and *aggressive periodontitis*. *Chronic periodontitis* was described as the more "common" form that occurs primarily in adults, and progresses at a relatively slow rate, resulting in an extent and severity of periodontal tissue loss that is largely commensurate with the presence of local etiologic factors. In contrast, *aggressive periodontitis* was defined as a more infrequently occurring form that affects primarily, but not exclusively, young, systemically healthy individuals, progresses rapidly, and results in substantial loss of periodontal tissue support that may be disproportionate to the occurrence of local etiology. Importantly, a primary feature of *aggressive periodontitis* was considered to be *familial aggregation,* that is, a propensity to affect several members of the same family (parents and siblings), indicating that genetic predispositions and common environmental exposures may be important determinants of the disease. However, none of the three primary features of *aggressive periodontitis* (a systemically healthy patient; rapid attachment loss and bone loss; familial aggregation) (Lang *et al*. 1999) can facilitate the differential diagnosis between *chronic* and *aggressive periodontitis* in the setting of an epidemiologic study: the first because it is entirely non-specific; the second because it requires at least two examinations over time to determine how "rapidly" the periodontal destruction has occurred; and the third because it is subject to *reporting bias*, and requires extensive interviewing and verification to ascertain reliably. As a result, very sparse epidemiologic data have been generated to date by strictly adhering to the primary criteria of these principal forms of periodontitis.

Instead, several studies have reported periodontitis prevalence data using the periodontitis case definition introduced by a working group from the Centers for Disease Control (CDC) and the American Academy of Periodontology (AAP) that is based on a combination of probing depth and CAL assessments (Page & Eke 2007; Eke *et al*. 2012). The CDC/AAP case definitions do not distinguish between chronic and aggressive forms of periodontitis, but define: (1) *severe periodontitis* as the presence of at least two interproximal sites with ≥6 mm of clinical attachment loss, not on the same tooth, *and* the presence of at least one interproximal site with a ≥5-mm probing depth; (2) *moderate periodontitis* as the presence of two or more interproximal sites with ≥4 mm of clinical attachment loss occurring at two or more different teeth *or* two or more interproximal sites with a ≥5-mm probing depth, not on the same tooth; and (3) *mild periodontitis* as the presence of two or more interproximal sites with ≥3 mm of clinical attachment loss and two or more interproximal sites with ≥ 4 mm probing depth or one site with probing depth ≥ 5 mm.

An alternative, two-level periodontitis case definition for use in epidemiologic studies was developed by a working group of the 5th European Workshop in Periodontology (Tonetti & Claffey 2005), and consisted of a *sensitive* definition (proximal attachment loss of ≥3 mm in two or more non-adjacent teeth) and a *specific* definition (proximal attachment loss of ≥5 mm in ≥30% of the teeth present). The former definition aimed at capturing incipient forms of the disease, while the latter was meant to reflect periodontitis of substantial extent and severity.

To the best of our knowledge, no epidemiologic studies have been published at the time of authorship of this chapter that have employed the latest classification system of periodontal diseases and conditions that was introduced at the 2017 World Workshop, which is described in detail in Chapter 16. According to this system, patients formerly classified as having either chronic or aggressive periodontitis are now grouped in a single category that is further subdivided on the basis of two-vector system by *Stage* and *Grade* (Papapanou *et al*. 2018; Tonetti *et al*. 2018). *Stage* reflects the severity of the disease (expressed through attachment loss and bone loss), but also factors in *tooth loss* that has occurred as a result of periodontitis. In addition, it reflects the anticipated complexity of the treatment that is required to eradicate/reduce the current level of infection and inflammation, and to restore patient masticatory function. *Grade* describes additional biological dimensions of the disease including the observed or inferred progression rate, the risk for further deterioration, the presence of risk factors and co-morbidities, and the risk that the disease or its treatment may adversely affect the particular patient's general health status.

As mentioned above, a concise "case definition" is essential for assessing disease prevalence and incidence and to generate comparable data across populations. Given the lack of universal consensus on the definitions of periodontitis and the continuously evolving epidemiologic approaches, in the following text we have opted to summarize the available data on the prevalence and progression of periodontal disease according to the age range of the examined cohorts. We thus first present findings from epidemiologic studies in adults, including studies exclusively targeting elderly populations, followed by corresponding findings derived from children, adolescents, and young adults.

Prevalence of periodontitis

Periodontitis in adults

To acquire some historical perspective and appreciate how the concepts of both the descriptive and the analytical epidemiology of periodontitis have evolved over the years, some older epidemiologic investigations are worth mentioning.

Starting with a study performed during the 1950s in India, Marshall-Day *et al*. (1955) used assessments of alveolar bone height to distinguish gingivitis and destructive periodontal disease in 1187 dentate subjects. The authors reported: (1) a decrease in the percentage of subjects with "gingival disease without any bone involvement" with increasing age concomitant with an increase in the percentage of subjects with "chronic, destructive periodontal disease"; and (2) a 100% occurrence of destructive periodontitis after the age of 40 years. Findings from other epidemiologic studies from the same period verified a high prevalence of destructive periodontal disease in the adult population in general, and a clear increase in disease prevalence with age. In the 1960s, Scherp (1964) reviewed the available literature on the epidemiology of periodontal disease and concluded that: (1) periodontal disease appears to be a major, global public health problem affecting the majority of the adult population after the age of 35–40 years; (2) the disease starts as gingivitis in youth, which, if left untreated, leads to progressive destructive periodontitis; and (3) >90% of the variance of the periodontal disease severity in the population can be explained by age and oral hygiene. These notions, based on established concepts of the pathogenesis of periodontal disease of that time, dominated the periodontal literature until the late 1970s.

Studies performed during the 1980s provided a more thorough description of the site-specific features of periodontal disease and the high variation in periodontal conditions between and within different populations. Contrary to previous custom, the prevalence issue was no longer addressed through assigning individuals simply to a "periodontitis-affected" or a "disease-free" group, based on presence or absence of attachment or alveolar bone loss. Instead, studies began to unravel details concerning the *extent* to which the dentition was affected by destructive disease (i.e. the percentage of tooth sites involved) and the *severity* of the defects (expressed as the magnitude of the tissue support lost due to the disease). The traditional description of pocket depth and attachment loss scores in terms of *subject mean values* was soon complemented by *frequency distributions*, revealing percentages of tooth sites exhibiting probing depth or attachment level of varying severity. Such an additional analysis appeared necessary after it became clear that mean values offer a crude description of periodontal conditions and fail to reflect the variability in the severity of periodontal disease within and between individuals. In an article presenting different methods of evaluating periodontal disease data in epidemiologic research, Okamoto *et al*. (1988) proposed the use of *percentile plots* in the graphic illustration of attachment loss data. As exemplified by Fig. 6-1, such plots make it possible to illustrate simultaneously both the proportion of subjects exhibiting attachment loss of different levels and the severity of the loss within the subjects. Similar plots may be produced for other parameters, such as gingivitis, probing depths, and gingival recession, and may provide a comprehensive description of both the prevalence and the severity of periodontal disease in a given sample.

In the mid-1980s, a group of Danish investigators (Baelum *et al*. 1986) described cross-sectional findings for dental plaque, calculus, gingivitis, loss of attachment, periodontal pockets, and tooth loss in a sample of adult Tanzanians aged 30–69 years. Despite the fact that the subjects examined exhibited large amounts of plaque and calculus, pockets deeper than 3 mm and attachment loss of >6 mm occurred at <10% of the tooth surfaces. Edentulism was virtually non-existent, and a very small percentage of subjects had experienced major tooth loss. Of particular interest was the analysis of the distribution of sites within

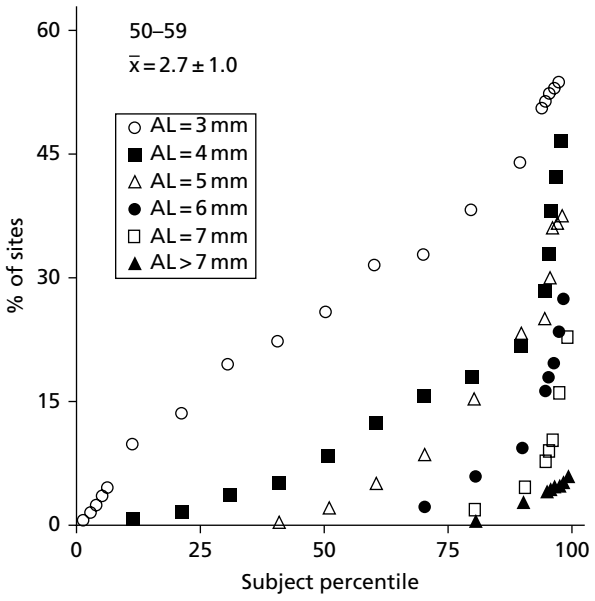


Fig. 6-1 Attachment loss in a group of Japanese subjects aged 50–59 years. The mean value of attachment level and the standard deviation are shown in the top of the figure. The x-axis represents the subject percentile and the y-axis represents the percentage of sites in the subjects showing attachment loss of 3, 4, 5, 6, 7, and >7 mm (represented by 8). Subjects with no or only minor signs of attachment loss are reported to the left and subjects with increasing amounts of periodontal destruction are reported to the right of the graph. For example, the median subject (50th percentile), exhibited 5-mm attachment loss at 2%, 4-mm loss at 8%, and 3-mm loss at 25% of its sites. (Source: Okamoto *et al*. 1988. Reproduced with permission from John Wiley & Sons.)

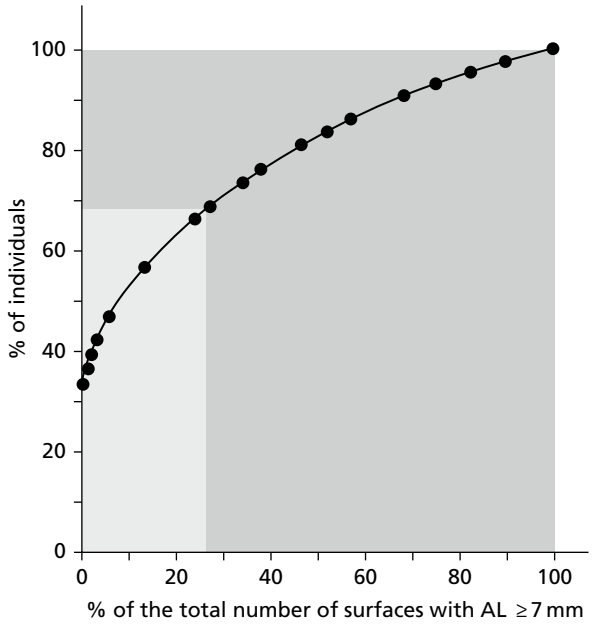


Fig. 6-2 Cumulative distribution of individuals aged ≥50 years according to the cumulated proportion of surfaces with attachment loss (AL) of ≥7 mm. All individuals are arranged according to increasing number of surfaces with AL of ≥7 mm present in each individual. Thus, individuals with few such surfaces are represented on the left side of the diagram and those with many such surfaces on the right side. It is seen that 31% (69–100%) of the individuals account for 75% (25–100%) of the total number of surfaces with AL of ≥7 mm present (shaded area). (Source: Baelum *et al*. 1986. Reproduced with permission from John Wiley & Sons.)

subjects (Fig. 6-2). This analysis revealed that 75% of the tooth sites with attachment loss of >6 mm were found in 31% of the subjects, indicating that a subset of the sample was responsible for the majority of the observed periodontal breakdown. In other words, advanced periodontal disease was not evenly distributed in the population and not readily correlated to supragingival plaque levels; instead, the majority of the subjects examined exhibited negligible periodontal problems, while a limited group was affected by advanced disease.

In a study of similar design performed in Kenya, the same investigators analyzed data from 1131 subjects aged 15–65 years and confirmed their earlier observations (Baelum *et al*. 1988). Poor oral hygiene in the sample was reflected by high plaque, calculus, and gingivitis scores. However, pockets ≥4 mm deep were found in <20% of the surfaces and the proportion of sites per individual with deep pockets and advanced loss of attachment revealed a pronounced skewed distribution. The authors suggested that "destructive periodontal disease should not be perceived as an inevitable consequence of gingivitis which ultimately leads to considerable tooth loss" and called for a more specific characterization of the features of periodontal breakdown in those individuals who seem particularly susceptible.

At approximately the same time, Löe *et al*. (1986) published data from a longitudinal study that showed distinct patterns for the *progression* of untreated periodontitis. In a population never exposed to any preventive or therapeutic intervention related to oral diseases in Sri Lanka, a cohort of 480 14–31-year-old male tea-plantation laborers was recruited in 1970 and underwent subsequent follow-up examinations. A total of 161 individuals among those originally enrolled were re-examined in 1985, essentially generating data on the natural history of periodontal disease between the ages of 14 and 46 years. Despite poor plaque control and virtually ubiquitous gingival inflammation in the entire sample, three distinct patterns of progression of periodontitis were observed over the follow-up period, based on interproximal longitudinal attachment loss and tooth mortality rates: one group, comprising approximately 8% of the total, exhibited rapid progression of periodontal disease (RP); another group (approximately 11%) exhibited no progression (NP) of periodontal disease beyond gingivitis; and a third group between these two extremes (approximately 81%) exhibited moderate progression (MP). The mean loss of attachment in the RP group was 9 mm and 13 mm at the age of 35 and 45 years, respectively, as opposed to 1 mm and 1.5 mm in the NP group, and 4 mm and 7 mm in the MP group. As a result, the annual rate of longitudinal attachment loss in the RP group varied between 0.1 and 1.0 mm, in the MP group between 0.05 and 0.5 mm, and in the NP group between 0.05 and 0.09 mm. Thus, this study clearly demonstrated huge variability in progression of periodontitis in a seemingly homogeneous population, and suggested that variables other than age, plaque, and gingival inflammatory status are important determinants of periodontal deterioration over time.

The common theme that emerged in the above studies, that is, that a relative limited proportion of the population suffers from severe periodontitis, has been corroborated by more recent studies from various parts of the world, a number of which are summarized in Table 6-1. Although what constitutes "severe periodontitis" is far from identical across reports in the literature, a review that consolidated data from 72 epidemiologic studies originating from 37 countries that collectively included data from approximately 300 000 participants estimated this fraction to range between 10 and 12%, to vary considerably between regions and countries, and to show a steep increase between the third and fourth decade in life (Kassebaum *et al*. 2014). The increased rates of tooth loss of periodontally affected teeth occurring after this age appears to account for the subsequent decline in prevalence. It is worth pointing out that studies employing full-mouth examination protocols generally generate higher prevalence estimates, underscoring the decisive impact of the examination methodology employed (Kingman & Albandar 2002;

Table 6-1 Selected population-representative studies of periodontitis prevalence published after 2000. (Sources: NHANES, National Health and Nutrition Examinations Surveys; CDC/AAP, Centers for Disease Control/American Academy of Periodontology.)

Authors/country	Sample/methodology	Findings
Baelum *et al*. (1988a) Kenya	A stratified random sample of 1131 subjects, 15–65 years; full-mouth assessments of tooth mobility, plaque, calculus, BoP, PD, and AL	Plaque in 75–95% and calculus in 10–85% of all surfaces PD ≥4 mm in <20% of sites AL of ≥1 mm in 10–85% of sites Percentage of sites/subject with PD or AL of ≥4 mm or ≥7 mm conspicuously skewed
Brown *et al*. (1990) USA	A sample of 15 132 subjects, stratified by geographic region, representing 100 million employed adults aged 18–64 years; probing assessments at mesial and buccal sites in one upper and one lower quadrant; mesial assessments performed from the buccal aspect of the teeth; assessments of gingivitis, PD, AL, and gingival recession	44% of all subjects had gingivitis at an average of 2.7 sites/subject and at <6% of all sites assessed Pockets 4–6 mm were observed in 13.4% of subjects at an average of 0.6 sites/person and at 1.3% of all sites assessed; corresponding figures for pockets ≥7 mm were 0.6%, 0.01, and 0.03% AL ≥3 mm was prevalent in 44% of subjects (increasing with age from 16% to 80%) affecting an average of 3.4 sites/subject; corresponding figures for AL ≥5 mm were 13% (2–35%) and 0.7 sites/subject
Salonen *et al*. (1991) Sweden	A random sample of 732 subjects, 20–80+ years, representing 0.8% of the population of a southern geographic region; full-mouth radiographic examination; alveolar bone level expressed as a percentage of the root length (B : R ratio); B : R of ≥80% represents intact periodontal bone support	Age group of 20–29 years: 38% of subjects had no sites with a B : R of <80% and 8% of subjects had ≥5 sites below this threshold Corresponding figures for the age group 50–59 years: 5% and 75%; after the age of 40, women displayed more favorable B : R ratios than men
Hugoson *et al*. (1998a) Sweden	Three random samples of 600, 597, and 584 subjects aged 20–70 years, examined in 1973, 1983, and 1993, respectively; full-mouth clinical and radiographic examination; based on clinical and radiographic findings, the subjects were classified according to severity of periodontal disease in five groups, where group 1 (G1) included subjects with close to faultless periodontal tissues and group 5 (G5) subjects with severe disease	Edentulism decreased over the 20-year period from 11% to 8% to 5%; percentage distribution of the subjects in the five groups in 1973, 1983, and 1993 respectively was: G1 8%, 23%, 22%; G2 41%, 22%, 38%; G3 47%, 41%, 27%; G4 2%, 11%, 10%; G5 1%, 2%, 3%; the increase in the prevalence of subjects with severe disease was apparently due to the increased number of dentate subjects at the older ages
Schürch & Lang (2004) Switzerland	A total of 1318 subjects, randomly selected based on community rosters in seven regions, aged 20–89 years; probing assessments of PD and AL for all teeth present; assessments of plaque and gingivitis for index teeth	7.1% of subjects were edentulous; mean number of teeth present in dentate subjects was 21.6 Mean values of PD reached a plateau of 3 mm by the age of 49 years AL increased dramatically after the age of 50 years and paralleled a marked loss of teeth
Susin *et al*. (2004a) Brazil	A sample of 853 dentate individuals, selected by multistage probability sampling, aged 30–103 years; full-mouth examination of AL at six sites/tooth	Moderate AL (≥5 mm) and advanced AL (≥7 mm) occurred in 70% and 52% of the subjects, affecting an average of 36% and 16% of their teeth, respectively; in comparison to 30-39-year-olds, 40-49-year-olds had 3× increased risk for moderate and 7.4× increased risk for advanced AL; corresponding figures for ≥ 50-year-olds were 5.9× and 25.4×, respectively
Dye *et al*. (2007) USA	NHANES 1999–2004 study, nationally representative sample comprising 10 312 individuals in four age cohorts (35–49, 50–64, 65–74, and 75+ years; partial-mouth examination in two randomly selected quadrants (one maxillary and one mandibular) at the mesiofacial and mid-facial sites of all fully erupted teeth excluding third molars	Prevalence of AL ≥3 mm in the four age cohorts was 36.1%, 53.4%, 67.2%, and 75.5%, respectively Corresponding figures for PD ≥4 mm were 11.9%, 13.2%, 11.3%, and 12.1%, respectively
Wang *et al*. (2007) China	A sample of 1590 dentate subjects with ≥14 teeth present, aged >25 years, from four geographic regions, equally farmers and urban professionals; partial-mouth examination at six sites in each of six index teeth	Average of 40% of sites bled on probing in the rural group as compared with 35% in the urban group Prevalence of AL ≥4 mm was approximately 10% in ages 25–34 years, increasing to 31%, 53%, and 70% in ages 35–44, 45–59, and >60 years, respectively, in the rural group; corresponding figures were 18%, 38%, and 57% in the urban group

Table 6-1 (*Continued*)

Authors/country	Sample/methodology	Findings
Holtfreter *et al*. (2010) Germany	The fourth German Dental Health Survey examined a total of 1965 individuals aged 35–44 years (adult sample) and 65–74 years (senior sample); partial-mouth examination of PD and AL at three sites in each of 12 index teeth	AL ≥3 mm was prevalent in 95% of the adults and 99.2% of the seniors (68.7% and 91.4% of teeth affected, respectively) PD ≥4 mm was prevalent in 70.9% and 87.4% of the adult and senior cohorts, respectively
Eke *et al*. (2018) USA	NHANES 2009–2014 study, nationally representative sample comprising 10 683 individuals in three age cohorts (30–44, 45–64, 65+ years); full-mouth examination at six sites per tooth at all fully erupted teeth excluding third molars	Prevalence of AL ≥3 mm in the three age cohorts was 81.3%, 92.1%, 96.5% Prevalence of AL ≥5 mm was 22.7%, 43.1%, 55.1%, respectively Corresponding figures for PD ≥4 mm were 33.3%, 39.9%, and 40.6%, and for PD ≥ 6 mm 6.4%, 10.1%, and 9.4%, respectively Prevalence of severe periodontitis, according to the CDC/AAP definition (Page & Eke 2007) was 4.1% in ages 30–44 years, 10.4% in ages 45–64 years, and 9.0% in ages 65+ years; corresponding figures for total periodontitis (mild + moderate + severe) were 29.5%, 46.0%, and 59.8%, respectively.
Sun *et al*. (2018) China	A multistage stratified sample comprising 4410 individuals in ages 35–44 years from 31 provinces in mainland of China; full-mouth examination at six sites per tooth at all fully erupted teeth excluding third molar	Prevalence of PD 4–5 mm was 45.8%, and PD ≥ 6 mm 6.9% Prevalence of CAL 4–5 mm was 25.5%, CAL 6–8 mm 6.4%, and CAL ≥9 mm 1.3%

AL, attachment level; BoP, bleeding on probing; CDC/AAP, Centers for Disease Control/American Academy of Periodontology; CEJ, cemento-enamel junction; NHANES, National Health and Nutrition Examinations Surveys; PD, probing depth.

Natto *et al*. 2018). A recent study (Billings *et al*. 2018) compared two large, population-based representative samples, one from the National Health and Nutrition Examination Survey for years 2009–2014 (NHANES) in the USA (Dye *et al*. 2014; Dye *et al*. 2019), and another from the Study of Health in Pomerania, Germany (SHIP-Trend) for years 2008–2012 (Völzke *et al*. 2011), to examine the effect of age in the distribution of periodontitis in the general population, and to define age-dependent thresholds for severe periodontitis. The data showed that the mean clinical attachment loss increased linearly with age in both samples and was higher in SHIP-Trend than NHANES across the age spectrum. Although mean pocket depth was relatively constant across age groups in both populations, the upper quintiles of mean clinical attachment loss were consistently lower in NHANES than in SHIP-Trend, underscoring substantial differences in the overall severity of attachment loss between the two population samples.

Table 6-2 summarizes a number of prevalence studies of periodontal disease in elderly subjects. It is evident that attachment loss of moderate magnitude was more frequent and widespread in these cohorts; however, severe disease was again found to affect relatively limited proportions of the samples and usually only a few teeth per person. It must be realized, however, that (1) edentulism increases with age, and (2) "surviving" teeth in elderly individuals are likely those less affected by periodontitis. As discussed later, tooth loss results in an underestimation of the "true" extent and severity of periodontitis in elderly individuals.

Periodontitis in children and adolescents

The form of periodontal disease that affects the *primary* dentition, the condition formerly termed *prepubertal periodontitis*, has been reported to appear in both a generalized and a localized form (Page *et al*. 1983). Information about this disease has mainly been provided by clinical case reports and no data on the prevalence and the distribution of the disease in the general population are available. However, a small number of studies involving samples of children have provided limited data on the frequency with which deciduous teeth may be affected by attachment loss. The criteria used in these studies are by no means uniform, hence the prevalence data vary significantly. In an early study, Jamison (1963) examined the "prevalence of destructive periodontal disease" (indicated by PDI scores >3) in a sample of 159 children in Michigan, USA and reported prevalences of 27% for 5–7-year-old children, 25% for 8–10-year olds, and 21% for 11–14-year olds. Shlossman *et al*. (1986) used an attachment level value of ≥2 mm as a cut-off point and reported prevalences of 7.7% in 5–9-year olds and 6.1% in 10–14-year olds in a sample of native Americans on the Gila River Indian Reservation. Sweeney *et al*. (1987) examined radiographs obtained from 2264 children, aged 5–11 years, who were referred to a University Clinic in Philadelphia, USA for routine dental treatment, and reported that distinct radiographic bone loss was evident at one or more primary molars in 19 children (0.8%), 16 of whom were black, two were Caucasian, and one was Asian.

Table 6-2 Selected prevalence studies of periodontitis in elderly subjects. (Sources: NHANES, National Health and Nutrition Examinations Surveys; CDC/AAP, Centers for Disease Control/American Academy of Periodontology.)

Authors/country	Sample /methodology	Findings
Baelum *et al*. (1988b) China	544 persons, in ages 60+ years, from two urban and one rural area of the Beijing area; assessments of plaque, calculus, gingivitis, loss of attachment, pocket depth, and tooth mobility	0–29% edentulous; mean number of teeth 6.9–23.9, depending on age and sex ≈50% of all surfaces with plaque and calculus 50% of all sites with AL of ≥4 mm <15% with PD ≥4 mm Conspicuously skewed percentage of sites/persons with AL of ≥7 mm and PD ≥4 mm
Beck *et al*. (1990) USA	690 community dwelling adults, in ages 65+ years; probing assessments at mesiobuccal and mid-buccal surfaces, all teeth; "advanced disease": ≥4 sites with AL of ≥5 mm and PD ≥4 mm at ≥1 of those sites; calculation of ESI with AL threshold set at ≥2 mm	Mean ESI in Blacks: 78, 4; in Caucasians: 65, 3.1 Advanced disease in 46% of Blacks and 16% of Caucasians
Gilbert & Heft (1992) USA	671 dentate subjects, in ages 65–97 years, attending senior activity centers; probing assessments at mesial and buccal surfaces of one upper and one lower quadrant; questionnaire data; calculation of ESI with AL threshold set at ≥2 mm	Average of 17.0 teeth/subject 50.7% of subjects with most severe mesial PD of 4–6 mm and 3.4% with PD of ≥7 mm 61.6% with most severe AL of 4.6 mm and 24.2% with AL of ≥7 mm ESI increased with age: 84.8, 3.6 (65–69 years); 88.7, 3.8 (75–79 years); 91.2, 3.9 (85+ years)
Locker & Leake, (1993) Canada	907 subjects, in ages 50–75+ years, living independently in four communities; probing assessments at mesiobuccal and mid-buccal aspects of all teeth; mid-palatal and mesiopalatal probing assessments in upper molars; 23% of subjects edentulous; calculation of ESI with AL threshold set at ≥2 mm; "severe disease": >4 sites with AL ≥5 mm and PD ≥4 mm at ≥1 of those sites	59% of subjects with PD of ≥4 mm, 16% with ≥6 mm, and 3% with ≥8 mm 86% of subjects with AL of ≥4 mm, 42% with ≥6 mm, and 16% with ≥8 mm; 20% of the subjects with a mean PAL of ≥4 mm Severe disease in 22% of subjects; mean ESI: 77, 2.44
Douglass *et al*. (1993) USA	1151 community-dwelling elders, 70+ years old; probing assessments at ≥3 sites/tooth, all teeth; 57% of the sample female, predominantly Caucasian (95%); 37.6% edentulous; mean number of teeth present between 21.5 and 17.9, depending on age	85% of subjects with BoP 66% with 4–6- mm deep pockets affecting an average of 5.3 teeth/subject; 21% with pockets of >6 mm affecting an average of 2.2 teeth 39% with AL of 4–6 mm at 6.7 sites/subject and 56% with AL of >6 mm at 2.7 teeth/subject
Bourgeois *et al*. (1999) France	603 non-institutionalized elderly, in ages 65–74 years; stratified sample with respect to gender, place of residence and socioeconomic group; periodontal conditions assessed by CPITN	16.3% were edentulous 31.5% of subjects had pockets ≥4 mm; 2.3% had pockets ≥6 mm
Hirotomi *et al*. (2002) Japan	761 community dwelling individuals either 70 or 80 years old, in the city of Niigata; full-mouth examination at six sites/ tooth at all functioning, fully erupted teeth	7.5% of those 70 years old and 35.8% of those 80 years old were edentulous; the prevalence of PD ≥6 mm was 10.2%, of CAL ≥5 mm 12.9%, and of severe periodontitis, according to the CDC/AAP definitions, 2%
Levy *et al*. (2003) USA	From a sample of 449 community dwelling elders, mean age 85 years, 342 (76%) were dentate and 236 were examined with respect to PD and AL at four sites/tooth in all teeth present	91% of participants had ≥1 site with ≥4 mm AL, 45% ≥1 site with ≥6 mm AL, and 15% ≥1 site with ≥8 mm AL
Mack *et al*. (2004) Germany	1446 randomly selected subjects in ages 60–79 years, participants in the Study of Health in Pomerania (SHIP); half-mouth examination of PD and AL at four sites/ tooth; plaque calculus and BoP were assessed at index teeth	16% of the 60–65-year-olds and 30% of the 75–79-year-olds were edentulous Among the 70–79-year-olds, median BoP was 37.5% in men and 50% in women Prevalence of PD ≥6 mm was 31.8% and 28.5% in men and women, respectively Prevalence of AL ≥5 mm was 71.9% and 66.9% in men and women, respectively
Syrjälä *et al*. (2010) Finland	1460 individuals, ≥65 years old, participants in the nationally representative Health 2000 Survey; full-mouth examination at four sites/tooth at all erupted teeth except third molars	44.3% were edentulous; 31% of dentate participants had no pockets >3 mm; 28% had 1–3 teeth with ≥4mm pockets, 15% had 4–6 and 26% ≥7 affected teeth; 73% showed BoP at ≥1 sextant

Table 6-2 (*Continued*)

Authors/country	Sample /methodology	Findings
Eke *et al*. (2016b) USA	1983 participants, ≥65 years of age, participants in NHANES 2009–2012; full-mouth examination at six sites per tooth at all fully erupted teeth excluding third molars	19% were edentulous; in ages 65-74 years, 59.7% had mild/moderate periodontitis and 11.8% severe periodontitis, according to the CDC/AAP definitions; corresponding prevalence values were 71.4% and 9.6%, respectively, in ages ≥75 years; the prevalence of PD ≥ 6 mm was 11.9% and of CAL ≥ 5 mm 62.3%
Shariff *et al*. (2018) USA	A tri-ethnic cohort of 1130 participants of the Washington-Heights Inwood Community Aging Project (WHICAP) ≥65 years old; full-mouth examination including assessments of bleeding BoP, PD and CAL at six sites/tooth	14.7% were edentulous; moderate/severe periodontitis according to the CDC/AAP definitions affected 77.5% of the sample Pockets ≥6 mm affected 50.2% of the sample and an average of 5.7% of teeth/person; corresponding figures for CAL ≥5 mm were 71.4% and 23.6%, respectively

AL, attachment level; BoP, bleeding on probing; CDC/AAP, Centers for Disease Control/American Academy of Periodontology; CEJ, cemento-enamel junction; CPITN, Community Periodontal Index of Treatment Needs; ESI, Extent and Severity Index; PD, probing depth.

In contrast, relatively uniform criteria have been used in epidemiologic studies of periodontitis in teenagers and young adults, using the diagnostic criteria of the condition that was earlier termed *localized juvenile periodontitis* (LJP), and was characterized by severe destruction affecting incisors and first molars. Typically, a two-stage approach has been adopted in these studies: first, bite-wing radiographs were used to screen for bone loss adjacent to molars and incisors, and then a clinical examination was performed to verify the diagnosis. As shown by the studies included in Table 6-3 as well as in a recent systematic review (Catunda *et al*. 2019), the prevalence of this form of early-onset disease varied in geographically and/or racially different populations. In Caucasians, the disease appears to affect females more frequently than males and the prevalence is low (approximately 0.1%). In other races, and in particular in Blacks, the disease is more prevalent, probably at levels over 1%, and the gender ratio appears to be reversed, since males are affected more frequently than females. Smoking and low socioeconomic status have been confirmed to be associated with destructive forms of periodontitis in teenage populations (Lopez *et al*. 2001; Susin & Albandar 2005; Levin *et al*. 2006).

Epidemiologic studies of periodontal conditions in adolescents have been also carried out using the CPITN system. Miyazaki *et al*. (1991) presented an overview of 103 CPITN surveys of subjects aged 15–19 years from over 60 countries. The most frequent finding in these groups was the presence of calculus, which was much more prevalent in subjects from non-industrialized than industrialized countries. Probing pocket depths of 4–5 mm were present in about two-thirds of the populations examined. However, the occurrence of deep pockets (≥6 mm) was relatively infrequent: score 4 quadrants were reported to occur in only 10 of the examined populations (in four of the nine examined American samples, one of 16 African samples, one of 10 eastern Mediterranean samples, two of 35 European samples, two of 15 South-East Asian samples, and none of 18 western Pacific samples).

The progression pattern of periodontitis in a sample of 167 adolescents in the UK was studied in a 5-year longitudinal study by Clerehugh *et al*. (1990). In this study, 3% of the initially 14-year-olds had attachment loss of ≥1 mm affecting >1% of sites. However, at age 19 years, 77% showed a similar level of attachment loss and 31% of sites were affected. Presence of subgingival calculus at baseline was significantly associated with disease progression. In a study involving a larger sample size in the USA, Brown *et al*. (1996) studied a nationally representative sample comprising 14 013 adolescents with respect to the pattern of progression of the disease entity formerly termed *early-onset periodontitis*, that is, the type of periodontitis that occurs in individuals of a young age. Subjects were diagnosed at baseline as free from periodontitis, or suffering from LJP, *generalized juvenile periodontitis* (GJP), or incidental attachment loss (IAL). Of the individuals diagnosed with LJP at baseline, 62% continued to display localized periodontitis lesions 6 years later, but 35% developed a generalized disease pattern. Among the group initially diagnosed as suffering from IAL, 28% developed LJP or GJP, while 30% were reclassified in the no attachment loss group. Molars and incisors were the teeth most often affected in all three affected groups. Thus, the study indicated that these three forms of periodontitis may progress in a similar fashion, and that certain cases of LJP may develop into a more generalized form.

The possibility that LJP and *prepubertal periodontitis* are associated conditions, that is, that the former is a development of the latter, has also attracted attention. In an early study, Sjödin *et al*. (1989) retrospectively examined radiographs of the primary dentition of 17 subjects with LJP and reported that 16 of these subjects showed a CEJ–bone crest distance of ≥3 mm in at least one tooth site in their deciduous dentition. The same research group (Sjödin & Matsson 1992) examined the CEJ–bone crest distance in radiographs from

Table 6-3 Selected prevalence studies of periodontitis in adolescents and young adults. (Sources: CDC/AAP, Centers for Disease Control/American Academy of Periodontology.)

Authors/country	Sample/methodology	Findings
Saxén (1980) Finland	A random sample of 8096 16-year-olds; radiographic and clinical criteria (bone loss adjacent to first molars without any obvious iatrogenic factors and presence of pathologic pockets)	Prevalence of LJP 0.1% (8 subjects, 5 of whom were females)
Kronauer *et al*. (1986) Switzerland	A representative sample of 7604 16-year-olds; two step examination (radiographic detection of bone lesion on bitewing radiographs, clinical verification of presence of pathologic pockets)	Prevalence of LJP of 0.1%; 1 : 1 gender ratio
Saxby (1987) UK	A sample of 7266 schoolchildren; initial screening by probing assessments around incisors and first molars; LJP cases diagnosed definitively by full-mouth clinical and radiographic examination	Overall prevalence of LJP of 0.1%, 1 : 1 gender ratio; however, prevalence varied in different ethnic groups (0.02% in Caucasians, 0.2% in Asians, and 0.8% in Afro-Caribbeans)
Neely (1992) USA	1038 schoolchildren 10–12 years old, volunteers in a dentifrice trial; three-stage examination including radiographic and clinical assessments; bitewing radiographs screened for possible cases; bone loss measurements of the CEJ–bone crest distance of ≥2 mm used to identify probable cases; LJP diagnosed clinically as PD of ≥3 mm at ≥1 first permanent molars in the absence of local irritants	117 possible and 103 probable cases identified in steps 1 and 2, respectively; of 99 probable cases contacted, 43 were examined clinically; 2 cases of LJP confirmed in stage 3, yielding a prevalence rate of 0.46%
Cogen *et al*. (1992) USA	4757 children, aged <15 years, from the pool of a children's hospital; retrospective radiographic examination of two sets of bitewings; LJP diagnosed in case of arc-shaped alveolar bone loss in molars and/or incisors	Caucasians: LJP prevalence 0.3%, female : male ratio 4 : 1 Blacks: LJP prevalence 1.5%, female : male ratio ≈1 : 1 Among Black LJP cases with available radiographs from earlier examinations, 85.7% showed evidence of bone loss in the mixed dentition and 71.4% in the deciduous dentition
Löe & Brown (1991) USA	National Survey of US children, multistage probability sampling representing 45 million schoolchildren; 40 694 subjects, 14–17 years old examined; probing assessments at mesial and buccal sites, all teeth; LJP: ≥1 first molar and ≥1 incisor or second molar and ≤2 cuspids or premolars with ≥3 mm AL; GJP: if LJP criteria not met and ≥4 teeth (of which ≥2 were second molars, cuspids or premolars) with ≥3 mm AL; ILA: if neither LJP nor GJP criteria met but ≥1 teeth with ≥3 mm AL; bivariate and multivariate analysis	Population estimates: LJP 0.53%; GJP 0.13%; ILA 1.61%; all 2.27% representing almost 300 000 adolescents; Blacks at much higher risk for all forms of early-onset disease than Caucasians Males more likely (4.3:1) to have GJP than females, after adjusting for other variables; Black males 2.9 times as likely to have LJP than Black females; Caucasian females more likely to have LJP than Caucasian males by the same odds
Bhat (1991) USA	A sample of 11 111 schoolchildren, 14–17 years old; probing assessments at mesial and buccal surfaces of all teeth; multistage cluster sampling stratified by age, sex, seven geographic regions, and rural or urban residence; not stratified by race or ethnicity	22% of children with ≥1 site with AL of ≥2 mm, 0.72% of ≥4 mm, and 0.04% of ≥6 mm Supra- and subgingival calculus in 34% and 23% of children, respectively
van der Velden *et al*. (1989) The Netherlands	4565 subjects, 14–17 years old examined; randomization among high school students; probing assessments at the mesio- and distofacial surfaces of first molars and incisors; one bacterial sample from the dorsum of the tongue and one subgingival plaque sample from the site with maximal attachment loss obtained from 103 of the 230 subjects with AL and cultured for identification of *Aggregatibacter actinomycetemcomitans*	Overall, AL occurred in 5% of the sample and was more frequent in males; 16 subjects (0.3%) had ≥1 site with AL of 5–8 mm; female : male ratio in this group 1.3 : 1 *A. actinomycetemcomitans* identified in 17% of the sampled subjects with AL
Lopez *et al*. (1991) Chile	2500 schoolchildren in Santiago (1318 male, 1182 female), aged 15–19 years; clinical and radiographic assessments; three-stage screening: (1) clinical assessments of PD at incisors and molars, (2) children with ≥2 teeth with PD of ≥5.5 mm subjected to a limited radiographic examination, and (3) children with alveolar bone loss of ≥2 mm invited for a full-mouth clinical and radiographic examination	After screening, 27 subjects had a tentative diagnosis of LJP, of which 8 were confirmed (7 female, 1 male); overall prevalence of LJP 0.32%, 95% CI 0.22– 0.42%; LJP significantly more frequent in the low socioeconomic group

Table 6-3 (*Continued*)

Authors/country	Sample/methodology	Findings
Ben Yehouda *et al*. (1991) Israel	1160 male Israeli army recruits, aged 18–19 years; panoramic radiography; JP diagnosed on the basis of bone loss involving ≥30% of the root length adjacent to first molars or incisors	10 recruits (0.86%, 95% CI 0.84–0.88%) had a bone loss pattern consistent with localized juvenile periodontitis
Melvin *et al*. (1991) USA	5013 military recruits, aged 17–26 years; panoramic radiography followed by full-mouth clinical examination; diagnosis of JP if bone loss and attachment loss was greater at first molars and/or incisors than at other teeth	Overall prevalence of JP 0.76%, female : male ratio 1.1 : 1 Prevalence in Blacks: 2.1%, female : male ratio 0.52 : 1 Prevalence in Whites: 0.09%, female : male ratio 4.3 : 1
Tinoco *et al*. (1997) Brazil	7843 schoolchildren, aged 12–19 years; two-stage screening: (1) clinical assessment of PD at first molars, (2) children with ≥1 tooth with PD ≥5 mm examined further; LJP diagnosed if a person with no systemic disease presented with AL >2 mm at ≥1 sites with radiographic evidence of bone loss and ≥1 infrabony defects at molars/incisors	119 subjects identified at initial screening; 25 confirmed cases of LJP; overall prevalence 0.3% Ethnic origins and gender ratios not reported
Lopez *et al*. (2001) Chile	A random sample of 9162 high school students, aged 12–21 years; probing assessments of AL at six sites/tooth at all incisors and molars	Prevalence of AL of ≥1 mm was 69.2%, of ≥2 mm was 16%, and of ≥3 mm was 4.5%. AL was associated with older age, female gender, poor oral hygiene, and lower socioeconomic status
Levin *et al*. (2006) Israel	642 army recruits (87.5% men), aged 18–30 years (mean 19.6 years); radiographic and clinical examination of first molars and incisors	Prevalence of *aggressive periodontitis* was 5.9% (4.3% LAP, 1.6% GAP); current smoking and north African origin were significantly related to AP
Holtfreter *et al*. (2009) Germany	587 young adults, aged 20–29 years, participants in the Study of Health in Pomerania (SHIP); half-mouth examination of an upper and lower quadrant at four sites/tooth with respect to PD and AL	12% and 1% of sample were found to suffer from "moderate" or "severe" periodontitis, respectively, according to the CDC/AAP criteria; 5% of sample exhibited AL ≥4 mm, 2% ≥5 mm and 1% ≥6 mm
Eres *et al*. (2009) Turkey	3056 students (1563 female and 1493 male) in ages 13–19 years, recruited in public schools in an urban area; clinical periodontal examination using CPTIN; 170 students with code 3 or code 4 sextants were examined radiographically and received a full mouth examination	The prevalence of LAP was 0.6% with a female : male ratio of 1.25 : 1
Elamin *et al*. (2010) Sudan	1200 students, 13–19 years old, selected through multistage, stratified sampling form 38 public and private high schools in Sudan; full-mouth exam at 6 sites per tooth	3.4% of the sample was diagnosed with aggressive periodontitis that was found to be more prevalent in male (4.9%) than female students (2.0%); 16.3% of the students had ≥1 tooth with CAL ≥ 4 mm, and 8.2% had ≥1 tooth with CAL ≥ 5 mm, with no difference in prevalence between male and female students

AL, attachment level; CEJ, cemento-enamel junction; CDC/AAP, Centers for Disease Control/American Academy of Periodontology; CI, confidence interval; CPITN, Community Periodontal Index of Treatment Needs; GAP, generalized aggressive periodontitis; GJP, generalized juvenile periodontitis; ILA, incidental loss of attachment; JP, juvenile periodontitis; LAP, localized aggressive periodontitis; LJP, localized juvenile periodontitis; PD, probing depth.

128 periodontally healthy children aged 7–9 years, in order to define a threshold value that, if exceeded, would indicate a high probability of periodontal pathology around the deciduous teeth. Having set this threshold value at 2 mm, Sjödin *et al*. (1993) retrospectively examined radiographs of the deciduous dentition from 118 patients with *juvenile periodontitis* and 168 age- and gender-matched periodontally healthy controls. The patients were divided in two groups, one comprising those with only one affected site (45 subjects) and another (73 subjects) including those with 2–15 sites with bone loss in their permanent dentition. It was found that 52% of the patients in the latter group, 20% of those in the former group, and only 5% of the controls exhibited at least one site with bone loss in their primary dentition. The authors concluded that, at least in some young subjects with destructive disease, the onset of the disease may manifest in the primary dentition. Similar results were reported by Cogen *et al*. (1992) from a study in the USA. Among systemically healthy young Black subjects with *aggressive periodontitis* and available radiographs of the primary dentition, 71% showed alveolar bone loss adjacent to one or several primary teeth. Finally, an interesting radiographic study of the mixed dentition in Australian children aged 5–12 years by (Darby *et al*. 2005) investigated the prevalence of alveolar bone loss around first

permanent molars, and first and second deciduous molars. Based on radiographs of 542 children, 13% were found to display definite bone loss, that is, bone levels >3.0 mm from the CEJ. Half of all sites with definite bone loss were on the second deciduous molars and, in the vast majority, on distal tooth surfaces. In other words, this study showed that the tooth surface of the deciduous dentition most frequently affected by bone loss was the one in close proximity to the most frequent localization of destructive periodontitis in young age groups, namely the mesial surface of the first permanent molar.

Periodontitis and tooth loss

Tooth loss may be the ultimate consequence of destructive periodontal disease. Teeth lost due to the sequelae of the disease are obviously not amenable to registration in epidemiologic surveys and may, hence, lead to an underestimation of the prevalence and the severity of the disease. The well-established epidemiologic concept of *selection bias* (also referred to as the *healthy survivor effect*, indicating that the comparatively healthier subjects will present for an examination while the more severely affected may refuse participation or fail to present because of the morbidity itself) is in this context applicable at the individual tooth level, since the severely affected teeth may have already been extracted/lost. Aspects related to tooth loss on a population basis have been addressed in numerous publications. Important questions that were analyzed included the relative contribution of periodontitis to edentulism (Eklund & Burt 1994; Takala *et al*. 1994) or to tooth extractions in subjects retaining a natural dentition (Reich & Hiller 1993; McCaul *et al*. 2001; Susin *et al*. 2005; Thorstensson & Johansson 2010; Hirotomi *et al*. 2011).

Typically, surveys addressing the first topic have utilized questionnaire data obtained from general practitioners instructed to document the reasons why teeth were extracted over a certain time period. The results indicate that the reason underlying the vast majority of extractions in ages up to 40–45 years is dental caries. However, in older age cohorts, periodontal disease is about equally responsible for tooth loss. Overall, periodontitis is thought to account for 30–35% of all tooth extractions, while caries and its sequelae for up to 50%. In addition, caries appears to be the principal reason for extractions in cases of total tooth clearance. Finally, identified risk factors for tooth loss include smoking, poor dental health, poverty and other socio-behavioral traits, and poor periodontal status.

Obviously, it is not feasible to "translate" tooth loss data into prevalence figures of periodontal disease. An evaluation, however, of the periodontal status at the population level, and in particular in older age cohorts, must weigh the information provided by tooth loss data, otherwise underestimation of the occurrence and the sequelae of the disease is inevitable (Gilbert *et al*. 2005).

Risk factors for periodontitis

Introduction: definitions

The discipline of epidemiology has been central to causal inquiry for health outcomes in humans since the beginning of the nineteenth century. However, despite numerous historical examples of causal discovery in the health sciences using core epidemiologic methods, a number of surprising and/or inconsistent findings, particularly in regard to complex chronic disease etiology, have weakened confidence in the causal models that helped to vanquish infectious diseases during the early twentieth century. For a more thorough overview of this debate see Demmer and Papapanou (2020).

A careful review of the definition of a "cause" is necessary to understand the underlying logic and models used to identify causal relationships in the health sciences. The following is a popular definition of a cause: "any factor without which the disease event would not have occurred, at least not when it did, given that all other conditions are fixed" (Rothman *et al*. 2008). To test causal hypotheses and identify causes, epidemiologists utilize a conceptual approach referred to as a "potential outcomes" or – synonymously – a "counterfactual framework". A counterfactual framework observes the disease experience in a group of individuals exposed to a hypothesized cause and then inquires what the disease experience in that same group would have been, had they – counter to fact – *not* been exposed to the hypothesized cause during the same time-period, with all other factors held constant. The observations from this theoretical experiment would then yield a causal effect, which is defined as the ratio (or difference) between: (1) the proportion of exposed individuals who develop disease during a given time period; and (2) the proportion of the same exposed individuals that would have developed disease, had they been unexposed during the same observation period. Unfortunately, this thought experiment is untenable in reality. Therefore, a cornerstone of etiologic epidemiological designs is the use of group comparisons. All etiologic epidemiological study designs, including observational designs and randomized interventions, have been developed precisely to enable valid group comparisons that can approximate the counterfactual ideal, and estimate causal effects.

Measures of disease occurrence

As implicitly alluded to above, the use of group comparison to estimate causal effects requires scientists to use measures of disease occurrence. In its simplest form, disease frequency can be captured via counts of diseased individuals (ideally in a clearly defined population during a precise time period). While absolute disease counts are suitable in some instances, they are often inappropriate in the context of group comparison because the groups being compared are almost

always of unequal size. In the setting of unequal group size, the observations at the group level might not enable logical inference at the individual level. For example, if group 1 has 1000 members and 100 cases of disease while group 2 has 100 members and 50 cases of disease the conclusion that group 1 has greater counts of disease is in conflict with the fact that individuals in group 2 have greater probability of disease.

To address this, the concept of risk has served as a fundamental tool for causal inquiry in epidemiology. In the context of a counterfactual (or potential outcomes) framework, risk is a proportion that is numerically equivalent to the probability of disease occurrence defined as follows: the number of people who develop a condition over a specified time period divided by the number of at-risk individuals in the source population under study. In more precise epidemiological terms, risk is often referred to as cumulative incidence (CI); a visual representation of CI and the explicit formula is presented in Fig. 6-3a. It is worth noting that this definition of risk explicitly requires the passage of time such that disease develops during a follow-up period among a subset of initially disease-free individuals. In contrast to cumulative incidence, prevalence reflects the probability of current disease. Prevalence is defined as a ratio of the number of existing cases at a point in time (or during a specific time period) over the total number of individuals in the population under study. For example, if the prevalence of periodontitis is 50% in a particular country, this tells us that the probability of any randomly selected inhabitant having periodontitis is 0.50 (or approximately one in two people). Alternatively, if the cumulative incidence (or risk) of periodontitis in 2020 is 5%, this tells us that during the 2020 calendar year, the probability of developing periodontitis among the initially periodontitis-free population is approximately one in 20. Another commonly used measure of disease occurrence is odds, which is defined as the probability of having the disease over the probability of being disease-free (i.e., 1 - probability of disease). Finally, the concept of incidence rate (or incidence density) is also of central importance to epidemiological inquiry and is closely related to the concept of risk. The incidence rate simply incorporates time explicitly into the denominator as follows: the number of people who develop a condition divided by the person time contributed by initially disease-free individuals during the study period. Person time is calculated for each individual as the amount of time that passes between entry into the study and either: (1) the development of disease; (2) the end of the observation period; or (3) death or loss-to-follow-up.

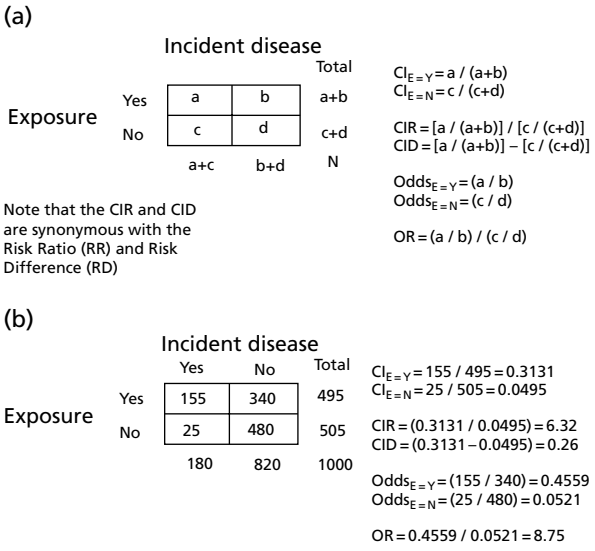


Fig. 6-3 Contingency tables describing the association between a particular exposure and incident disease and the definitions of cumulative incidence (CI), cumulative incidence ratio (CIR), cumulative incidence difference (CID), and odds ratio (OR). (a) describes the definitions and (b) provides a numerical example.

Measures of association

While measures of disease frequency, such as risk (i.e. cumulative incidence), are valuable for a number of reasons, risk is frequently used to assess the evidence for causal associations. This is usually done by comparing risk of disease between two different groups of individuals defined by variation in an "exposure" (i.e. a hypothesized cause of disease). For example, consider a hypothetical situation where exposure to a potential cause, "Z" is studied in a longitudinal cohort study of 1000 subjects (Fig. 6-3b). In this example, the association between exposure and disease can be expressed by the *cumulative incidence ratio* (CIR), also known as the *risk ratio* (RR), which is defined by the ratio of the probability of disease occurrence in the exposed to the probability of disease occurrence in the unexposed. For the data in Fig. 6-3b, the RR is calculated as [(155/495)/(25/505)] = 6.32. This indicates that the probability of disease among individuals exposed to Z was 6.32 times higher than the probability of disease among individuals unexposed to Z. If several important assumptions hold (beyond the scope of this chapter), this risk ratio is an estimate of the causal effect of Z on disease occurrence. Similarly, many investigators often choose to calculate the cumulative incidence difference, also known as the risk difference (RD), which is simply the difference in disease probabilities between exposed and unexposed, or [(155/495) - (25/505)] = 0.26. This concept described for RRs and RDs can be applied to other measures of disease frequency such as odds or incidence density (for examples, please see Demmer & Papapanou 2020). A note of caution is in order with regard to the interpretation of odds ratios (OR). Specifically, the OR is frequently misinterpreted to be synonymous with the RR, although this assumption only holds when the disease is rare (<10% is commonly used as a guide for designating a disease as

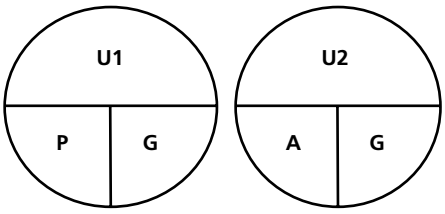
rare). As shown in Fig. 6-3b, since the overall cumulative incidence of disease is 18%, the OR of 8.75 substantially overestimates the RR of 6.32.

Causal inference and causal models

The use of group comparisons to approximate the ideal counterfactual knowledge under investigation is of critical importance but still fails to provide an explicit causal model linking exposures to disease outcomes. For epidemiological designs to yield meaningful causal inferences, coherent causal models of disease etiology are necessary.

A now classic model for causal inference was proposed by Rothman *et al*. (2008) using a "*sufficient cause*" model of causation. A sufficient cause (SC) is defined as "a complete causal mechanism that inevitably produces disease". The SC model visually represents causal hypotheses using causal "pies" as shown in Figs. 6-4 and 6-5. Causal pies are represented as full circles (i.e. sufficient causes) comprised of individual slices termed "*component causes*", each of which is required to complete a sufficient cause and, thus, for disease to occur. According to the main premise of the conceptual model, once all component causes of a sufficient causal pie are in place, disease will inevitably occur. The example in Fig. 6-4 provides a hypothetical sufficient component causal model for the development of human periodontitis in which there are two sufficient causes. In this example, sufficient cause 1 involves the presence of microbial dysbiosis triggered by a particular microorganism (*Porphyromonas gingivalis*) (P), a set of genetic polymorphisms (G) and the additional presence of a number of unknown factors (U1). Sufficient cause 2 is comprised of a different dysbiotic microbial profile, namely dysbiosis triggered by *Aggregatibacter actinomycetemcomitans* (A), the same set of genetic polymorphisms as in SC 1 (G), and another set of unknown factors (U2) which are distinct from U1. In the example visualized in Fig. 6-4, G represents a *necessary cause* – that is, G is a component cause that is present in all sufficient causes of disease and is therefore necessary to be present for periodontitis to occur. However, while G is necessary for the development of periodontitis, G alone is not sufficient to produce periodontitis without the presence of G's causal complements (i.e. P + U1, or A + U2). In contrast, P, A, U1 and U2 represent component causes that are neither sufficient nor necessary to cause periodontitis. If any individual in a hypothetical population completes either SC 1 or SC 2, they will develop periodontitis. A second example (Fig. 6-5) provides a hypothetical set of sufficient causes positing translocation of *Fusobacterium nucleatum* (F) from the oral cavity to the pancreas as a cause of type 2 diabetes mellitus development. In this example, there are three distinct sufficient causes comprised of six different component causes. This example demonstrates a scenario in which there are no necessary causes.

Two points should be emphasized from the SC model approach presented in Figs. 6-4 and 6-5. First, in modern epidemiology, the term "component cause" is synonymous with the more commonly used term, "risk factor". In other words, risk factors, are causes of disease that generally work in tandem with other risk factors (i.e. component causes) to produce disease. Note that the term "risk predictor" is generally



Sufficient Cause 1 Sufficient Cause 2

Prevalence of U1 and U2 is 100% in population 1 and 2.

Table B.
Joint distribution of *P. gingivalis* and periodontitis in population 1

	Periodontitis	No Periodontitis	Total
P. gingivalis present	900	900	1800
P. gingivalis absent	50	150	200

Table C.
Joint distribution of *P. gingivalis* and periodontitis in population 2

	Periodontitis	No Periodontitis	Total
P. gingivalis present	600	600	1200
P. gingivalis absent	350	450	800

Table A. Linking risk factor combinations to periodontitis risk according to Sufficient Causes 1 and 2

U1	U2	A	P	G	SC	Risk	Population 1	Population 2
1	1	1	1	1	1,2	1	500	500
1	1	1	1	0	None	0	500	500
1	1	1	0	1	2	1	50	350
1	1	1	0	0	None	0	50	350
1	1	0	1	1	1	1	400	100
1	1	0	1	0	None	0	400	100
1	1	0	0	1	None	0	50	50
1	1	0	0	0	None	0	50	50

Estimates of the causal effect of *P. gingivalis* on periodontitis in two separate populations

CIR = (900/1800) / (50/200) = 2.0

CID = (900/1800) – (50/200) = 0.25

CIR = (600/1200) / (350/800) = 1.14

CID = (600/1200) – (350/800) = 0.06

Fig. 6-4 Hypothetical sufficient component causal model for the development of human periodontitis in which there are two sufficient causes. Sufficient cause (SC) 1 involves the presence of microbial dysbiosis triggered by a particular microorganism (*Porphyromonas gingivalis*) (P), a set of genetic polymorphisms (G) and the additional presence of a number of unknown factors (U1). Sufficient cause 2 is comprised by dysbiosis triggered by *Aggregatibacter actinomycetemcomitans* (A), the same set of genetic polymorphisms as in SC 1 (G), and another set of unknown factors (U2) which are distinct from U1. CID, Cumulative Incidence Difference; CIR, Cumulative Incidence Ratio.

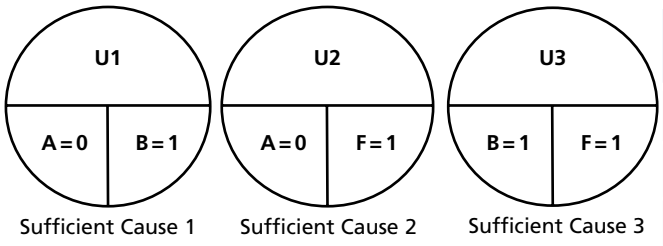


Table A. Linking risk factor combinations to diabetes risk according to Sufficient Causes 1 and 2

A	B	F	SC	Risk	Population 1	Population 2
1	1	1	3	1	900	100
1	1	0	None	0	900	100
1	0	1	None	0	100	900
1	0	0	None	0	100	900
0	1	1	1,2,3	1	100	900
0	1	0	1	1	100	900
0	0	1	2	1	900	100
0	0	0	None	0	900	100

Table B. Joint distribution of *F. nucleatum* and diabetes in population 1

Population 1	Diabetes present	Diabetes absent	Total
F. nucleatum present	1900	100	2000
F. nucleatum absent	100	1900	2000

CIR = (1900/2000) / (100/2000) = 19
CID = (1900/2000) – (100/2000) = 0.9

Table C. Joint distribution of *F. nucleatum* and diabetes in in population 2

Population 2	Diabetes present	Diabetes absent	Total
F. nucleatum present	1100	900	2000
F. nucleatum absent	900	1000	2000

CIR = (1100/2000) / (900/2000) = 1.22
CID = (1100/2000) / (900/2000) = 0.1

Fig. 6-5 Hypothetical sufficient component causal model for the development of type 2 diabetes mellitus involving translocation of *Fusobacterium nucleatum* (F) from the oral cavity to the pancreas. Three distinct sufficient causes are depicted, comprising a total of six different component causes (U1, U2, U3, A, B, and F). Note the absence of any necessary causes. CID, Cumulative Incidence Difference; CIR, Cumulative Incidence Ratio.

used to refer to a variable that predicts risk but for which causality is not assumed (e.g. grey hair is a risk predictor of mortality but not a causal risk factor). Second, and building on the first point, a somewhat obvious conclusion from the SC model is that there are multiple pathways that lead to the development of a given disease and each pathway involves multiple component causes that work together synergistically. This synergy precisely represents the concept of interaction (or effect measure modification) in statistics and epidemiology. In the specific context of SC models, when causal factors interact, any one component cause can only cause disease in the presence (or possibly in the absence) of the other component cause(s) in the same SC.

A careful review of the examples in Figs. 6-4 and 6-5 demonstrates another important concept that helps us understand why an exposure can cause disease even if the strength of association is weak or varies greatly across different studies (for example, as often observed in a meta-analysis). It is apparent that the CIR, that is, the ratio of the proportion of individuals with a certain risk factor that have completed a sufficient cause (i.e. have developed the disease) over the proportion of individuals without the risk factor that have completed a sufficient cause, and the cumulative incidence difference (CID), that is, the difference between the above two proportions, vary across populations in which the distribution of component causes are not equal. This raises a profoundly important point about causal inquiry that is often not appreciated in the health sciences: specifically, the strength of association (using absolute measures) is dependent upon the prevalence of causal complements in the population. The causal complement of a risk factor is defined as the set of all other component causes in all sufficient causes in which a risk factor participates. In the case of Fig. 6-5, the causal complements of F are A=0 and U2, or B=1 and U3. As the prevalence of these causal complements increases, the strength of association between F and diabetes becomes stronger.

What are then the implications of the above causal models for epidemiological research and the ability to identify causes of disease in humans? When we explore risk factors in isolation using reductionist approaches, there can be great variation in the strength of association between a causal factor and a disease outcome across populations. In populations with a low prevalence of causal complements, the strength of association for the main component cause (i.e. risk factor) under investigation will be weak when compared with that in a population with a higher prevalence of causal complements.

In contrast, in disease models where there are multiple sufficient causes in the population, and there is a high prevalence of component causes in sufficient causes where the risk factor of interest does not participate, the observed effect for this particular risk factor will be relatively weak or undetectable. In Fig. 6-5, note that an increase in the prevalence of individuals with both A=0 and B=1 would lead to an increase in the prevalence of individuals susceptible to SC 1, yielding weaker associations between F and diabetes because F cannot cause disease in individuals with SC 1 already complete (i.e. in individuals that are already "doomed"). This concept, known as causal redundancy, has been elegantly discussed in a review by Gatto and Campbell (2010).

Another often cited approach to establishing causality is to apply the Bradford Hill (Hill 1971) criteria below that include:

1. *Strength of the association*. The stronger the association between the potential (*putative*) risk factor and disease presence, the more likely it is that the anticipated causal relation is valid.
2. *Dose–response effect*. An observation that the frequency of the disease increases with the dose or level of exposure to a certain factor supports a causal interpretation.
3. *Temporal consistency*. It is important to establish that the exposure to the anticipated causative factor occurred prior to the onset of the disease. This may be difficult in cases of diseases with long latent periods or factors that change over time.
4. *Consistency of the findings*. If several studies investigating a given relationship generate similar results, the causal interpretation is strengthened.
5. *Biologic plausibility*. It is advantageous if the anticipated relationship makes sense in the context of current biologic knowledge. However, it must be realized that the less that is known about the etiology of a given disease, the more difficult it becomes to satisfy this particular criterion.
6. *Specificity of the association*. If the factor under investigation is found to be associated with only one disease, or if the disease is found to be associated with only one factor among a multitude of factors tested, the causal relation is strengthened. However, this criterion can by no means be used to reject a causal relation, since many factors have multiple effects and most diseases have multiple causes.

It is important to realize that the criteria described above are meant as guidelines for the establishment of a causal inference. None of them, however, is either necessary or sufficient for a causal interpretation. Strict adherence to any of them without concomitant consideration of the others may result in incorrect conclusions. We need only heed the explicit advice of Bradford Hill himself (Hill 1971): "None of my viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non [an absolute necessity]."

Interestingly, high variability in measures of association across studies conducted in different populations is often taken to suggest lack of evidence for causality. While consistently strong associations do increase confidence in a causal hypothesis, lack thereof does not necessarily imply no causality. The examples provided above clearly demonstrate that under specific causal hypotheses, not dissimilar to the underlying hypotheses of modern chronic disease etiology, causal effects are *expected* to be inconsistent and at times weak, across different populations, as long as the prevalence of other risk factors varies.

Lastly, in the context of causal inference, some useful applied principles of the *risk assessment process* were discussed by Beck (1994) and consist of the following four steps:

1. The *identification* of one or several individual factors that appear to be associated with the disease.
2. In case of multiple factors, a *multivariate risk assessment model* must be developed that discloses which combination of factors most effectively discriminates between health and disease.
3. The *assessment* step, in which new populations are screened for this particular combination of factors, with a subsequent comparison of the level of the disease assessed with the one predicted by the model.
4. The *targeting* step, in which exposure to the identified factors is reduced by prevention or intervention and the effectiveness of the approach in suppressing the *incidence* of the disease is evaluated.

Thus, according to this process, *potential* or *putative risk factors* (often also referred to as *risk indicators*) are first identified and thereafter tested until their significance as *true risk factors* is proven or rejected.

There are various ways to assess simultaneously the effect of the several putative risk factors identified in step 1 and to generate the *multivariate model* required for step 2. For example, the association between exposure and disease may, for reasons of simplicity, have the form of the following linear equation:

$$y = a + b_1x_1 + b_2x_2 + b_3x_3 + \ldots b_nx_n$$

where y represents occurrence or severity of the disease, a is the intercept (a constant value), x_1, x_2, . . . x_n describe the different exposures (putative risk factors), and b_1, b_2, . . . b_n are *estimates* defining the relative importance of each individual exposure as a determinant of disease, after taking all other factors into account. Such an approach will help to identify factors with statistically and biologically significant effects and may minimize the effect of confounders.

In the third step (*assessment step*), a new population sample that is independent of the one used in the construction of the multivariate model is screened for occurrence of disease and presence of the relevant factors included in the multivariate model of step 2. Alternatively, in the case of a prospective cohort study, exposure to the relevant factors is assessed among the subjects of the new sample, and disease incidence, that is the number of new cases of disease, is determined over a time period after a longitudinal follow-up of the subjects. Subsequently, disease occurrence predicted from the model is compared with the actual disease occurrence, and the *external validity* of the model (i.e. the "behavior" or "fitness" of the model in the new population) is evaluated.

Lastly, during the fourth step (*targeting*), aspects of causality or risk are verified if disease occurrence is suppressed when exposure is impeded. Ideally, such studies should be designed as randomized clinical trials, in which treatment is randomly assigned to one of two groups and the effectiveness of the intervention is assessed in direct comparison to outcomes in an untreated, control group. Additionally, an evaluation of the particular preventive/therapeutic strategy from a "cost–benefit" point of view is also facilitated in such studies. Note that successful fulfillment of the targeting step requires that (1) the factor is amenable to intervention and (2) the intervention is delivered at the appropriate time point. Genetic traits are examples of risk factors not amenable to intervention. Likewise, in cases where a single exposure to a factor results in detrimental and/or irreversible biologic damage (e.g. exposure to a high dose of radiation), interventions protecting against subsequent exposure to the factor (radiation) may not lower the incidence of disease (e.g. cancer).

In the context of periodontitis, it should be realized that few of the putative risk factors for disease development have been subjected to the scrutiny of all four steps. In fact, risk assessment studies in dental research in general have been frequently confined to the first two steps. Numerous cross-sectional studies identifying potential risk factors are available, but a relatively limited number of longitudinal studies involve a multivariate approach to the identification of exposures of interest while simultaneously controlling for the effect of possible confounders. Intervention studies in the form of randomized clinical trials are sparse. In the following text, the issue of risk factors is addressed according to the principles described previously. Results from cross-sectional studies are considered to provide evidence for putative risk factors that may be further enhanced if corroborated by longitudinal studies involving multivariate techniques, or prospective intervention studies. As reviewed by Borrell and Papapanou (2005), distinction is also made between putative factors that are not amenable to intervention (non-modifiable background factors) and modifiable factors (environmental, acquired, and behavioral).

Non-modifiable background factors

Age

The relationship between age and periodontitis is complex. Although it is clear that both the prevalence and the severity of periodontitis increase with age (Albandar & Kingman 1999; Burt 1994; Dye *et al*. 2007; Eke *et al*. 2018), the concept of periodontitis as an inevitable consequence of aging has been challenged over the years (Papapanou *et al*. 1991; Papapanou & Lindhe 1992) and the alleged "age effect" largely represents the cumulative effect of prolonged exposure to true risk factors. Notably, the association between age and periodontitis appears to be different for pocket depth and amount of clinical attachment loss. While there is a pronounced effect of increasing attachment loss with age, the effect on pocket depth appears to be minimal (Albandar 2002; Albandar & Tinoco 2002; Billings *et al*. 2018). Interestingly, the effect of age on attachment loss was found to be attenuated after adjustment for co-variates, such as oral hygiene levels or access to dental care services (Albandar & Tinoco 2002). In addition, epidemiologic studies have often failed to adjust for important co-variates such as presence of systemic diseases, consumption of multiple medications, and co-morbidities related to nutritional disturbances in the older population, all of which could partly account for the increased prevalence and severity of periodontitis in the elderly. On the other hand, age-associated molecular alterations in key phagocytic cells involved in both the protective and destructive immune responses have been shown to affect their ability to carry out efficient antimicrobial functions and to result in a dysregulation of the inflammatory response (Hajishengallis 2010). Since periodontitis is a microbially-associated inflammatory disorder, these alterations in innate immunity likely contribute to more pronounced periodontal pathology in elderly individuals. An age-related, rather than an age-dependent, increased susceptibility to periodontitis in older people is therefore biologically plausible.

Sex

There is no established, inherent difference between men and women in their susceptibility to periodontal disease, although men have been shown to exhibit worse periodontal conditions than women in multiple studies from different populations (Brown *et al*. 1990; Susin *et al*. 2004a; Holtfreter *et al*. 2009; Dye 2012; Eke *et al*. 2016b). This difference has been traditionally considered to reflect the documented better oral hygiene practices (Hugoson *et al*. 1998b; Christensen *et al*. 2003) and/or increased utilization of oral health care services among women (Yu *et al*. 2001; Dunlop *et al*. 2002; Roberts-Thomson & Stewart 2003). On the other hand, there is evidence for sexual dimorphism in elements of both the innate and the acquired immunity that may lead to enhanced pro-inflammatory responses in men (Shiau & Reynolds 2010), which are in line with the epidemiologic evidence of gender-associated disparities in prevalence, extent, and severity of periodontitis.

Race/ethnicity

Differences in the prevalence of periodontitis between countries and across continents have been demonstrated (Dye 2012; Kassebaum *et al*. 2014; Papapanou & Susin 2017), but no consistent patterns across racial/ethnic groups have been documented when co-variates such as age and oral hygiene were

accounted for (Burt & Eklund 1999). National, population representative studies in the USA consistently show a racial/ethnic differential pattern in the prevalence of periodontitis, with Mexican–Americans and African–Americans exhibiting higher prevalence than non-Hispanic Caucasians (Eke *et al*. 2018). However, race/ethnicity is usually a social construct that determines an array of opportunities related to access, status, and resources (Williams 1997, 1999; Hasslanger 2008). As a result, race/ethnicity and socioeconomic status (SES) are strongly intertwined, suggesting that the observed racial/ethnic effect may be partially attributed to confounding by SES due to the unequal meaning of SES indicators across racial/ethnic groups (Williams 1996; Kaufman *et al*. 1997; Krieger *et al*. 1997; Lynch & Kaplan 2000). Corroborating this point, a study reported that African–Americans demonstrated a lower benefit from education and income in terms of periodontal health status than their Mexican–American and Caucasian peers (Borrell *et al*. 2004). These findings confirm that socioeconomic indicators across racial/ethnic groups are not commensurable but, probably, reflect the broad implications of historic unequal opportunities among certain racial groups (Borrell & Crawford 2012; Borrell 2017).

Gene polymorphisms

Evidence that genetic predispositions are significant determinants of periodontitis phenotype was first documented in a number of classic twin (Michalowicz *et al*. 1991) and family studies (Boughman *et al*. 1992; Marazita *et al*. 1994). Aggregate data from genetic studies carried out since then have led to heritability estimates of periodontitis of up to 50% (Michalowicz *et al*. 2000), although a recent systematic review (Nibali *et al*. 2019) reported substantially lower heritability estimates: 38% in twin studies, 15% in other family studies, and only 7% in *genome-wide association studies* (GWAS).

The association of *single nucleotide polymorphisms* (SNPs), that is, of specific variations at defined locations of the genome that occur in least 1% of the population, with different forms of periodontitis has been studied extensively in the literature. Following the study by Kornman *et al*. (1997), who were the first to report an association between a composite genotype based on specific polymorphisms in the interleukin-1 gene cluster and severe periodontitis in non-smokers, there has been an exponential increase in publications examining a plethora of gene polymorphisms as severity markers of periodontitis. These include additional investigations of the particular composite IL-1 gene polymorphism in cross-sectional and case-control studies (e.g. Diehl *et al*. 1999; Armitage *et al*. 2000; Papapanou *et al*. 2001; Li *et al*. 2004; Meisel *et al*. 2004), prospective studies (Ehmke *et al*. 1999; De Sanctis & Zucchelli, 2000; Lang *et al*. 2000; Cullinan *et al*. 2001; Christgau *et al*. 2003; Jepsen *et al*. 2003) as well as studies in which polymorphisms in particular loci of the *IL1A* gene (Ferreira *et al*. 2008; Fiebig *et al*. 2008; Mazurek-Mochol *et al*. 2019), the *IL1B* gene (Lopez *et al*. 2005; Struch *et al*. 2008), and the interleukin-1 receptor antagonist (Berdeli *et al*. 2006; Fiebig *et al*. 2008; Tai *et al*. 2002) were investigated.

In parallel, polymorphisms in additional inflammatory genes have been investigated, including the tumor necrosis factor-alpha gene (Endo *et al*. 2001; Shapira *et al*. 2001; Craandijk *et al*. 2002; Fassmann *et al*. 2003; Shimada *et al*. 2004; Wei *et al*. 2016), the interleukin-6 gene (Holla *et al*. 2004; Nibali *et al*. 2008, 2009; Zhao & Li 2018), the interleukin-4 gene (Kang *et al*. 2003; Holla *et al*. 2008; Jia *et al*. 2017), and the interleukin-10 gene (Kinane *et al*. 1999; Yamazaki *et al*. 2001; Scarel-Caminaga *et al*. 2004; Wang *et al*. 2019). A substantial body of data has accumulated on polymorphisms in genes coding for various receptors, including the leukocyte receptors for the constant part (Fc) of immunoglobulin G (Kobayashi *et al*. 1997; Sugita *et al*. 1999; Meisel *et al*. 2000; Loos *et al*. 2003; Wolf *et al*. 2006; Lavu *et al*. 2016), pattern recognition receptors such as CD14 (Holla *et al*. 2002; Tervonen *et al*. 2007; Zheng *et al*. 2013) and Toll-like receptors (TLRs) 2 and 4 (Folwaczny *et al*. 2004; Fukusaki *et al*. 2007; Noack *et al*. 2008; Zhu *et al*. 2008; Leite *et al*. 2019), and the vitamin D receptor (Nibali *et al*. 2008; Wang *et al*. 2009; Park *et al*. 2019). Additional polymorphisms studied in single studies or a few cohorts have been discussed in a comprehensive review by Laine *et al*. (2012) and a meta-analysis of 53 studies collectively including 4178 cases and 4590 controls (Nikolopoulos *et al*. 2008).

Until fairly recently, the most common study design used for the identification of periodontitis susceptibility genes has been that of a *candidate-gene* association study, and most of the publications listed above fall into that category. However, this approach has several limitations, notably the fact that the hypotheses for the selection of the particular candidate genes are based on current, imperfect knowledge of the molecular mechanisms that govern processes considered to be involved in the disease pathogenesis, while other genes, members of pathways not yet implicated in processes relevant to the disease or of unknown function, are obviously not studied. In addition, (1) most studies have had relatively limited sample size, (2) the frequency of occurrence of the investigated polymorphisms has varied extensively between ethnic groups, (3) the definitions of the outcome variable (periodontitis) has varied considerably across studies, and (4) adequate adjustments for other important co-variates and risk factors have frequently not been carried out (Citterio *et al*. 2019). Notably, a recent comprehensive case-control validation study that involved a fairly large population sample in northern Europe (755 cases of aggressive periodontitis and 3042 periodontitis-free individuals, as well 1437 cases of chronic periodontitis and 1125 controls) attempted to replicate the association of 23 genes that

were repeatedly proposed in the literature to confer risk for severe periodontitis in Caucasian populations (Schaefer *et al*. 2013). However, with the exception of an SNP in the *IL10* gene that was associated with aggressive periodontitis, all other previously proposed associations could not be validated, suggesting the possibility that earlier positive reports were due to type 1 error.

In contrast, GWAS studies adopt a "hypothesis-free" approach to identify genetic loci associated with periodontitis susceptibility by examining polymorphic regions in the entire genome, and are therefore not burdened by the key shortcoming of the candidate gene association approach. However, given the large number of statistical tests required to test the association of every reported polymorphic region with the phenotype under investigation, the obtained *P* values need to be adjusted accordingly and very sample sizes are required to produce reliable findings. To date, only 12 GWAS studies of clinical periodontal status have been published: Five studies involved populations from Europe (Schaefer *et al*. 2010; Teumer *et al*. 2013; Freitag-Wolf *et al*. 2014; Munz *et al*. 2017; Bevilacqua *et al*. 2018), three from Asia (Hong *et al*. 2015; Shimizu *et al*. 2015; Tong *et al*. 2019), and four from the Americas (Divaris *et al*. 2013; Feng *et al*. 2014; Shaffer *et al*. 2014; Sanders *et al*. 2017). However, a meta-analysis of the available GWAS findings (Shungin *et al*. 2019) suggests that there is limited concordance among studies, which can partly be attributable to inherent genetic differences between the populations, but also to inconsistencies in the precise definition of periodontitis "cases" and "controls" across studies. Table 6-4 presents an overview of identified genes associated with poor clinical periodontal status in the available GWAS studies that met a nominal statistical significance level ($P \leq 5 \times 10^{-6}$).

In addition, three publications (Divaris *et al*. 2012; Rhodin *et al*. 2014; Offenbacher *et al*. 2016), all stemming from a single GWAS study in the USA involving participants in the Atherosclerosis Risk in Communities (ARIC) study have investigated whether there is evidence that distinct subgingival colonization patterns, or so-called "periodontal microbial traits", are associated with specific genetic loci. These studies have analyzed subgingival plaque samples using the "checkerboard" DNA-DNA hybridization technique

Table 6-4 Genes mapping to single nucleotide polymorphisms reported to have a suggestive association ($P \leq 5 \times 10^{-6}$) with various periodontitis-associated clinical phenotypes in genome-wide association studies. Genes listed in boldface font have been identified in at least two independent population samples.

Authors/country	Periodontitis-associated clinical phenotypes analyzed	Associated genes
Schaefer *et al*. (2010) Germany, the Netherlands	Aggressive periodontitis	*GLT6D1*
Divaris *et al*. (2013) USA	Chronic periodontitis	*NIN*; ***NPY***; *WNT5A*; ***ERC2***; *NCR2*; *EMR1*; *VAV1*; *GPR113*; *CUGBP*; ***CELF2***
Teumer *et al*. (2013) Germany	Chronic periodontitis	***CELF2***; *EPHA3*; *RAB6C*; *C9orf150*; *IQSEC1*; ***ERC2***; *CAMK4*; *MFSD1*; *LBP*; *ETS2*; *FAM180A*
Freitag-Wolf *et al*. 2014 Germany	Aggressive periodontitis	***NPY***
Shaffer *et al*. (2014) USA	Chronic periodontitis	*HSP90AB2P*; *RAB28*; *BOD1L*; *NKX3-2*; *LAMA2*; *ARHGAP18*
Feng *et al*. (2014) USA, Brazil	Chronic periodontitis	Intergenic, non-coding RNA regions
Hong *et al*. (2015) South Korea	CDC/AAP classification of periodontitis	*TENM2*; *LDLRAD4*
Shimizu *et al*. (2015) Japan	Chronic periodontitis	*KCNQ5*; *GPR141-NME8*
Sanders *et al*. (2017) USA	Chronic periodontitis and CDC/AAP classification of periodontitis	*TSNAX-DISC1*; *ASH1L*; *IRX1*; *LINC01017*; *LINC01019*; *LOC645157*; *RNF144B*; *NELL1*
Munz *et al*. (2017) Germany, the Netherlands	Chronic/aggressive periodontitis	***SIGLEC5***; *DEFA1A3*; *NUDC*; *OSTCP2*; *CTD-2353F22.1*; *PGAM1P2-CCDS6596.2 (PGAM1P2)*; *LINC00961-PGAM1P2 (SPAAR)*; *RP11-128M1.1-TGM3*; *LINC01192-RNU-82P201*; *FCER1G*
Bevilacqua *et al*. (2018) Italy	CDC/AAP classification of periodontitis	*EFCAB4B*
Tong *et al*. (2019) China	Chronic periodontitis	***SIGLEC5***

CDC/AAP, Centers for Disease Control/American Academy of Periodontology.

Table 6-5 Genes mapping to single nucleotide polymorphisms reported to have a suggestive association ($P \leq 5 \times 10^{-6}$) with various microbial or biologically informed complex traits in genome-wide association studies. All three publications listed below originate from the same population sample (the Atherosclerosis Risk in Communities study; ARIC). Genes listed in boldface font were associated with more than one trait.

Authors/country	Periodontitis-associated microbial/biologically informed traits	Associated genes
Divaris *et al*. (2012) USA	High colonization by *Aggregatibacter actinomycetemcomitans*; "high *A.a*. trait"	***KCNK1***; ***KIAA1804***; *FOS*; *DP2*; *ODZ2*; *WWC1*; *GRID1*; *M1346/WAPAL*; *KIAA1715*; *EVX2*; *EXTLP2*
Divaris *et al*. (2012) USA	High colonization by *Porphyromonas gingivalis*; "high *P.g*. trait"	*OTOF*; *C2Orf70*; *CIB4*; *TTLL11*; *ANKRD30A*; *DAB2IP*
Divaris *et al*. (2012) USA	High colonization by "red complex" bacteria (*P. gingivalis, Tanerella forsythia, Treponema denticola*); high "red complex" trait	*PKN2*; *HTR4*; *GLDC*; *TBC1D1*; *PTTG2*; ***KIAA1804***; *FBXO38*; *UHRF2*; ***KCNK1***
Divaris *et al*. (2012) Rhodin *et al*. (2014) USA	High colonization by selected "*orange complex*" bacteria (*Prevotella intermedia, Fusobacterium nucleatum, Parvimonas micra* and *Campylobacter rectus*); high "orange complex" trait	*RUNX2*; *CLIC5*; *TRPS1*; *CSMD3*; *CAMTA1*; *VAMP3*; *WDR59*
Offenbacher *et al*. (2016) USA	Biologically informed complex traits (combinations of bacterial colonization by selected microbial species and gingival crevicular fluid interleukin-1 beta levels)	*RBMS3*; *CLEC19A*; *TRA*; *GGTA2P*; *TM9SF2*; *IFI16*; *C1QTNF7*; *TSNARE*; *HPVC1*; *SLC15A4*; *PKP2*; *SNRPN*

(Socransky *et al*. 1994). Findings from these studies, that is, identified genes associated with these microbial traits that met a nominal statistical significance level ($P \leq 5 \times 10^{-6}$), are summarized in Table 6-5.

The available GWAS studies have involved participants across the age spectrum. Given that periodontitis is more pronounced in older ages, there is significant concern that younger individuals involved in these studies who, at the time of examination, presented with no periodontitis or showed signs of mild disease, may have been misclassified, as they might develop more pronounced disease at later stages of their life. To mitigate this concern, Papapanou *et al*. (2021) carried out an external validation of the findings of the available GWAS studies in a sample of 1130 elderly participants (65–98 years old). In these analyses carried out in a sample with fully developed periodontitis-associated phenotypes, they examined the association of the loci listed in Tables 6-4 and 6-5 with respect to multiple clinical, periodontitis-associated phenotypes, including edentulism, as well as a number of microbial traits. In general, genes previously reported in available GWAS studies to be associated with periodontitis-related clinical phenotypes or periodontal microbial traits replicated rather poorly: out of a total of 92 genes tested, 22 genes met the statistical significance threshold after multiple comparisons, and only two genes were found to be associated with more than one of the phenotypes examined. Notably, no genes were associated with the CDC/AAP classification of periodontitis, and the single gene (*SIGLEC5*) identified by the recent meta-analysis as associated with a composite phenotype of "severe periodontitis/loose teeth" (Shungin *et al*. 2019) did not replicate.

In conclusion, there is insufficient epidemiologic evidence that unequivocally establishes any of the above polymorphisms as true risk factors for periodontitis. Studies employing larger cohorts, strict and biologically informed criteria for periodontitis, and refined analytical methods will enhance our understanding of the role of genetic influences in the pathobiology of periodontitis.

Environmental, acquired, and behavioral factors

Microbial factors

In a classic experiment carried out in the mid-1960s, Harald Löe *et al*. demonstrated the causal association between dental plaque accumulation and gingival inflammation (Löe *et al*. 1965; Theilade *et al*. 1966). A 3-week accumulation of plaque in young, periodontally healthy individuals was paralleled by the development of inflammatory changes in the gingival tissues that were fully reversible after prophylaxis and re-institution of oral hygiene measures. A few years later, Lindhe *et al*. (1973) extended these observations and demonstrated in an experimental model in the Beagle dog that long-standing plaque accumulation, facilitated by the placement of cotton ligatures at the level of the gingival margin, induced an irreversible breakdown of the periodontal apparatus, that is, in loss of connective tissue attachment and alveolar bone. These two landmark studies provided the first experimental evidence of the etiological role of bacteria in the development of periodontal diseases and formed the conceptual foundation for the development of antiplaque strategies in their prevention and treatment.

Until fairly recently, the identities of the organisms associated with periodontal lesions or with periodontal health were limited to those that could be cultured in the laboratory. Several cross-sectional and longitudinal epidemiologic studies published in the 1990s and the first decade of the new millennium (e.g. Grossi *et al*. 1994; Beck *et al*. 1990, 1997; Machtei *et al*. 1997;

Papapanou *et al*. 1997, 2002; Timmerman *et al*. 1998; Van der Velden *et al*. 2006) established the association of certain so called "periodontal pathogens" including *Porphyromonas gingivalis, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans* with deep pocketing, and progressive periodontal lesions. A pivotal publication from the Forsyth group (Socransky *et al*. 1998), collected subgingival plaque samples from 185 subjects, 160 of whom suffered from periodontitis and 25 were periodontally healthy, and determined the presence and levels of 40 subgingival taxa in a total of 13261 plaque samples using whole genomic DNA probes and checkerboard DNA-DNA hybridization. Using various analytical methods to assess community ordination, the investigators identified five major bacterial complexes that were consistently observed using any of the analytical methods, one of which, the so called "red complex" that included *Tanerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola*, related strikingly to clinical measures of periodontal disease, and particularly with pocket depth and bleeding on probing. Notably, the consensus report of the 1996 World Workshop in Periodontics (Consensus Report on Periodontal Diseases: Pathogenesis and Microbial Factors, 1996) had identified three species, *Aggregatibacter actinomycetemcomitans* (termed *Actinobacillus actinomycetemcomitans* at the time), *Porphyromonas gingivalis,* and *Tanerella forsythia* (formerly termed *Bacteroides forsythus*), as *causative agents* for periodontitis.

However, with the advent of culture-independent, molecular methods of bacterial identification and enumeration such as 16S rRNA gene amplification and high-throughput sequencing, our understanding of the bacterial composition of the periodontal region evolved significantly (Chen *et al*. 2010). The study of thousands of plaque samples derived from a variety of clinical periodontal conditions demonstrated that approximately 700 prokaryote species can colonize the oral cavity and approximately 150 species can simultaneously colonize oral sites of an individual host (Dewhirst 2016). In addition to the traditional pathogens mentioned above, newly recognized non-cultivable or poorly cultivable organisms that increase in abundance at diseased sites include the Gram-positive bacteria *Filifactor alocis* and *Peptostreptococcus stomatis*; Gram stain-negative members of the phylum *Firmicutes* including the genera *Dialister*, *Megasphaera*, *and Selenomonas*; and species in the genera *Prevotella*, *Desulfobulbus*, and *Synergistes*.

In recognition of the fact that periodontal pathogens do not fulfill the classic Koch's postulates defining the causal relationship between an infectious agent and a disease, Haffajee and Socransky (1994) introduced a list of revised criteria to be used in the identification of bacterial periodontal pathogens, including: (1) *association*, expressed through high odds ratios in disease; (2) *elimination*, according to which suppression of the pathogens beyond detection results in a conversion of the state of periodontal disease to health; (3) *development of a host response*, in other words the expectation that a true pathogen that gains access to the host tissues and is actively involved in the disease process will elicit a systemic antibody response while a mere colonizer will not; (4) *presence of virulence factors* that can account for the microbe's ability to inflict tissue damage; and (5) *evidence from animal studies* that corroborate the observations in humans and demonstrate development of periodontal pathology after infection by the microorganism. Admittedly, what constitutes a microbial pathogen in the context of periodontal diseases has been a subject of considerable debate in the periodontal literature. The debate has been further fueled by the recognition that presumed "causal pathogens" can be encountered in biofilms of periodontally healthy individuals, casting serious doubt on the earlier proposed postulate that these microorganisms may behave as exogenous pathogens. For example, studies performed in children (Tanner *et al*. 2002; Yang *et al*. 2002) that analyzed plaque from the gingival crevice, tooth surface, and dorsum of the tongue revealed that sizeable proportions of subjects harbored *P. gingivalis*, *T. forsythia*, and *A. actinomycetemcomitans* despite absence of overt gingival inflammation. Likewise, a high carrier state was documented in studies that sampled infants, children, adolescents, and adults with apparently healthy periodontal conditions (Könönen 1993; Lamell *et al*. 2000; Rotimi *et al*. 2010).

Today, it is increasingly recognized that periodontal diseases are not bacterial infections in the classic sense, that is, caused by a single or a limited number of pathogens that are not regular constituents of the resident periodontal microbiota, but are rather driven by dysbiotic bacterial communities that induce a perturbation of the host homeostasis in susceptible individuals. Bacterial constituents of these dysbiotic communities that have disproportionate effects relative to their abundance, the so-called *keystone species* (Hajishengallis *et al*. 2012), exhibit synergistic interactions that enhance colonization, persistence, or virulence of the entire bacterial community. Nevertheless, the association between high levels of colonization by specific bacteria and periodontitis progression has been corroborated by longitudinal data in untreated populations. For example, in the study by Papapanou *et al*. (1997), a discriminant analysis based on quantitative assessments of subgingival bacterial load classified correctly the substantial majority of the subjects with progression of periodontitis over a preceding 10-year period. Indeed, bacterial profiles classified correctly 75% of the subjects with 10 or more sites with longitudinal attachment loss of ≥3 mm, and 85% of those that remained stable over the observation period. In a 7-year follow-up study of Indonesian adolescents (Timmerman *et al*. 2000; Timmerman *et al*. 2001), and in a subsequent 15-year follow-up of the same cohort (Van der Velden *et al*. 2006), it was

shown that the subgingival presence of *A. actinomycetemcomitans* was associated with disease progression, defined as presence of longitudinal attachment loss of ≥2 mm.

Important observations have also been reported with respect to the role of specific bacteria on the onset of periodontitis in young individuals. In a group of 96 primarily African–American and Hispanic schoolchildren followed for at least 2 years and 6 months, Fine *et al*. (2007) reported that eight of 38 *A. actinomycetemcomitans*-positive but none of 38 *A. actinomycetemcomitans*-negative adolescents, all of whom were periodontally intact at the baseline examination, developed bone loss over the observation period. In a 2-year prospective study of clinical periodontal status in adolescents in Morocco, Haubek *et al*. (2008) reported that colonization by a specific clone of *A. actinomycetemcomitans*, namely the highly-leukotoxic JP2 clone, conferred a much higher risk for the onset of aggressive periodontitis in periodontally healthy schoolchildren than concomitant colonization by a variety of clones of the same species, or the total absence of colonization by *A. actinomycetemcomitans*. Indeed, in comparison with schoolchildren who were not colonized by *A. actinomycetemcomitans*, the relative risk for incident disease in those colonized exclusively by JP2 clones was 18.0 (95% CI 7.8–41.2), as compared with 12.4 (95% CI 5.2–29.9) in those colonized by both JP2 and non-JP2 clones, and 3.0 (95% CI 1.3–7.1) in those colonized exclusively by non-JP2 clones of *A. actinomycetemcomitans*. This study underscored the important role of this particular periodontal pathogen in the etiology of early-onset forms of periodontitis, but also demonstrated that within-species variation in virulence is associated with differences in the clinical presentation of the disease. A more recent longitudinal study reported that concomitant detection of *A. actinomycetemcomitans*, *Streptococcus parasanguinis*, and *F. alosis* may signify risk for bone loss in African–American adolescents (Fine *et al*. 2013).

Collectively, data generated in the past 30 years have enhanced our knowledge of the role of periodontal bacteria as risk factors for periodontitis and underscore the fact that, although abundance by specific microbiota in the subgingival plaque has been shown to confer risk for periodontitis, it is the collective decrease of the subgingival plaque burden that consistently results in substantial improvement in clinical periodontal status. Thus, it is primarily the fulfillment of the "targeting" step of the risk assessment process described above that validates the role of the plaque microbiota as risk factors for periodontitis. As demonstrated in systematic reviews, removal of subgingival plaque with or without adjunctive antiseptics or antibiotics followed by adequate maintenance care, is the single most successful and consistent approach in the treatment of periodontitis (Herrera *et al*. 2002; Tonetti & Chapple 2011; Suvan *et al*. 2019).

Cigarette smoking

The biologic plausibility of an association between tobacco smoking and periodontitis has been founded on the broad effects of multiple tobacco-related substances on cellular structure and function. Smoking has been shown to affect the vasculature, the humoral and cellular immune responses, cell signaling processes, and tissue homeostasis (for reviews see Kinane & Chestnutt, 2000; Palmer *et al*. 2005; Zhang *et al*. 2019). Furthermore, while older, culture-based studies that examined only a limited number of species suggested that the composition of the subgingival microbiota in smokers is rather similar to that of non-smokers (Stoltenberg *et al*. 1993), more recent studies that utilized robust, culture-independent methodologies demonstrated that smoking contributes significantly to enhanced subgingival dysbiosis (Camelo-Castillo *et al*. 2015; Coretti *et al*. 2017; Hanioka *et al*. 2019).

Early epidemiologic data provided the first evidence that cigarette smoking is associated with poor periodontal status (Bergström 1989; Locker *et al*. 1991; Jette *et al*. 1993). Data derived from the NHANES III study (Tomar & Asma 2000) suggested that as many as 42% of periodontitis cases in the USA can be attributed to current smoking, and another 11% to former smoking. Similarly, in a study from Brazil, Susin *et al*. (2004) reported that the attributable fraction of clinical attachment loss due to cigarette smoking was 37.7% and 15.6% among heavy and moderate smokers, respectively. An abundance of data from different parts of the world has documented that tobacco smoking is associated with a higher extent and severity of periodontitis after adjustment for multiple covariates (Roberts-Thomson *et al*. 2014; Zhan *et al*. 2014; Eke *et al*. 2015; Lee *et al*. 2016; Eke *et al*. 2018; Zhao *et al*. 2019). Likewise, data from longitudinal studies indicate that smoking confers a statistically significant increased risk for periodontitis progression in multivariate models (Beck *et al*. 1995, 1997; Machtei *et al*. 1999; Norderyd *et al*. 1999; Chen *et al*. 2001; Ogawa 2002; Paulander *et al*. 2004; Mdala *et al*. 2014; Leite *et al*. 2018).

Studies examining the effects of smoking on the outcome of periodontal therapy have demonstrated that treatment responses are impaired by smoking, with current or heavy smokers exhibiting poorer responses than former or never smokers (e.g. Ah *et al*. 1994; Kaldahl *et al*. 1996; Grossi *et al*. 1997; Trombelli *et al*. 2003; Rieder *et al*. 2004; Stavropoulos *et al*. 2004; Angst *et al*. 2019). Notably, these studies have confirmed the negative effect of smoking on the outcome of multiple periodontal treatment modalities, including non-surgical, surgical, and regenerative periodontal therapy. Published meta-analyses of the effects of smoking on the outcome of periodontal therapy support the above conclusions (Garcia 2005; Labriola *et al*. 2005; Patel *et al*. 2012; Kotsakis *et al*. 2015).

Importantly, smoking cessation was shown to have beneficial effects on periodontal status. In a longitudinal study (Bolin *et al*. 1993), 349 subjects with ≥20 remaining teeth were examined on two occasions 10 years apart. Progression of alveolar bone loss was assessed on radiographs at all interproximal tooth surfaces and was shown to be significantly attenuated in individuals who gave up smoking during the observation period. Extending these observations, Krall *et al*. (1997) reported that, over a mean follow-up period of 6 years, subjects who continued to smoke had a 2.4–3.5-fold higher risk of tooth loss when compared with individuals who quit smoking. In a 10-year follow-up study, Bergström *et al*. (2000) observed an increase of periodontally diseased sites concomitant with loss of periodontal bone height in current smokers, as compared with non-smokers; the periodontal condition of the latter group remained unaltered throughout the period of investigation. The periodontal condition in former smokers was similarly stable to that of non-smokers, underscoring the beneficial effects of smoking cessation. In a shorter (12-month) follow-up study evaluating the adjunctive effect of smoking cessation on the outcome of non-surgical periodontal therapy, Rosa *et al*. (2011) showed enhanced gain in clinical attachment in chronic periodontitis patients who quit smoking when compared with their smoker counterparts. Importantly, smoking cessation alone or in conjunction with non-surgical periodontal therapy appears to result in a composition of subgingival microbiota that comprises higher levels of health-associated species and lower levels of periodontal pathogens (Fullmer *et al*. 2009; Delima *et al*. 2010). Lastly, a recent systematic review of the impact of the promotion of healthy lifestyles in patients with periodontitis identified smoking cessation as a key strategy to achieve improvements in periodontal health (Ramseier *et al*. 2020).

In conclusion, cigarette smoking clearly fulfills the risk assessment process criteria stipulated by Beck (1994) and is considered a major risk factor for periodontitis.

Diabetes mellitus

An association between diabetes mellitus (DM) and periodontitis has been reported in the literature since the 1960s (Belting *et al*. 1964). Several biologically plausible mechanisms by which the disease may contribute to impaired periodontal conditions have been identified over the past two decades (for comprehensive reviews see Lalla *et al*. 2000; Mealey & Oates 2006; Lalla & Papapanou 2011; Graves *et al*. 2020).

Early epidemiologic studies in the 1980s and the 1990s provided the first solid evidence that patients with DM show higher extent and severity of periodontitis than individuals free of diabetes. In a limited-sized study from Sweden involving participants with long- or short-duration diabetes and diabetes-free controls, Hugoson *et al*. (1989) were the first to document that diabetes duration was positively associated with the extent of periodontal pocketing. Larger studies involving individuals at the Gila River Indian community in Arizona, USA (Shlossman, Knowler *et al*. 1990; Emrich *et al*. 1991) expanded these observations and confirmed that individuals with diabetes have consistently poorer periodontal status than those without the disease. This accumulating evidence resulted in an influential publication by Löe (1993), who coined periodontal disease as "the sixth complication of diabetes mellitus". Approximately a decade ago, Chávarry *et al*. (2009) examined in a systematic review whether diabetes remains associated with periodontitis of higher severity after adjustment for potential confounders, as well as whether it influences the response to periodontal therapy. Out of 49 cross-sectional studies that fulfilled the inclusion criteria, 27 documented a higher extent and severity of periodontitis in diabetes, and a meta-analysis indicated a statistically significant average estimated difference in clinical attachment loss of 1 mm (95% CI 0.15–1.84 mm) between diabetic and diabetes-free individuals. The difference was primarily documented in patients with type 2 diabetes, while the estimated difference in attachment level between patients with type 1 diabetes and diabetes-free controls was not statistically significant.

The adverse effects of DM on periodontal status appear to be particularly pronounced in subjects with long duration of DM and poor metabolic control (Taylor *et al*. 1996; Grossi & Genco 1998; Taylor *et al*. 1998; Lalla *et al*. 2004). Indeed, studies have provided evidence of a dose–response relationship between poor metabolic control and the severity as well as the progression of periodontitis (Seppälä *et al*.1993; Tervonen & Oliver 1993; Tervonen & Karjalainen 1997; Guzman *et al*. 2003; Bandyopadhyay *et al*. 2010; Demmer *et al*. 2012; Morita *et al*. 2012). Expanding this observed dose–response relationship to include the pre-diabetic state as well, several studies (Saito *et al*. 2004; Lim *et al*. 2014; Song *et al*. 2016; Perez *et al*. 2017) reported that the level of glucose intolerance in non-diabetic individuals correlates positively with the severity of periodontal disease. Indeed, in a recent systematic review, Kocher *et al*. (2018) emphasized that the level of hyperglycemia in a continuous scale, rather than specific cut-off definitions of diabetes, are more meaningful in the quantification of the risk conferred by DM for periodontal pathology.

Interestingly, and in line with the above concepts of a continuous level of risk associated with the level of hyperglycemia, the outcome of periodontal treatment in patients with diabetes and good metabolic control is similar to that of non-diabetic periodontitis patients (Westfelt *et al*. 1996; Christgau *et al*. 1998; Faria-Almeida *et al*. 2006; Navarro-Sanchez *et al*. 2007), while patients with poorly controlled DM

display an inferior treatment outcome (Tervonen & Karjalainen 1997; Santos *et al*. 2009; Kaur *et al*. 2015).

The age of onset of DM manifestations in the periodontal tissues has been addressed in studies examining children and adolescents with type 1 DM (de Pommereau, Dargent-Paré *et al*. 1992; Pinson *et al*. 1995) and both type 1 and type 2 DM (Lalla *et al*. 2006). All three studies documented more pronounced gingival inflammation in subjects with diabetes aged between 6 and 18 years. The case-control study by Lalla *et al*. (2006) further reported that clinical attachment loss was more pronounced in young patients with diabetes after adjustment for age, gender, ethnicity, gingival bleeding, and frequency of dental visits. In a subsequent publication, Lalla *et al*. (2007a) reported data on 350 children with either type 1 or type 2 DM and found a strong positive association between mean HbA1c levels over the 2 years preceding the dental examination and periodontitis. In a report including a total of 700 children, 350 with diabetes and 350 non-diabetic controls, Lalla *et al*. (2007b) documented a statistically increased periodontal destruction in children with diabetes across all disease definitions tested and in both age subgroups of 6–11 and 12–18 years.

Several studies suggest a two-way relationship between DM and periodontitis. Beyond the observed increased severity of periodontal tissue destruction in subjects with DM, studies indicate a higher incidence of DM complications and poorer metabolic control of diabetes in periodontitis patients (for review see Lalla & Papapanou 2011). These findings are discussed in more detail in Chapter 11.

Obesity

The biologic plausibility of a potential link between obesity and periodontitis has been suggested to involve an hyperinflammatory state involving adipose-tissue derived cytokines, an aberrant lipid metabolism prevalent, as well as the pathway of insulin resistance (Saito *et al*. 1998; Nishimura & Murayama 2001; Akram *et al*. 2016), all of which may collectively result in an accelerated breakdown of the periodontal tissues. Indeed, a number of studies have indicated a positive association between obesity, defined as body mass index (BMI) ≥30 kg/m^2, and periodontitis. Four publications have documented such an association in the NHANES III database. Wood *et al*. (2003), using a subset including Caucasian subjects aged 18 years and older, reported that BMI, waist-to-hip ratio, visceral fat, and fat-free mass were associated with periodontitis after adjusting for age, gender, history of diabetes, current smoking, and socioeconomic status. Al-Zahrani *et al*. (2003) reported a significant association between both BMI and waist-to-hip ratio and periodontitis in younger adults, but no association in middle-aged or older adults. Genco *et al*. (2005) reported that overweight subjects in the upper quartile of the insulin resistance index were 1.5 times more likely to have periodontitis compared with their counterparts with a high BMI but a low insulin resistance index. Lastly, Andriankaja *et al*. (2010) demonstrated an association between *metabolic syndrome* (i.e. a combination of hypertension, impaired fasting glucose, large waist circumference, and dyslipidemia) and periodontitis in women, and between abdominal obesity and periodontitis in both genders.

In a longitudinal study of 1038 healthy, Caucasian US male veterans, obesity conferred a 41–72% increased risk for progression of periodontitis, after adjustment for several co-variates (Gorman *et al*. 2012).

Corroborating data have been reported also from countries other than the USA. In a sample of 643 apparently healthy Japanese adults, Saito *et al*. (2001) reported that waist-to-hip ratio, BMI, and body fat were significant risk indicators for periodontitis after adjustments for known risk factors. In a longitudinal study from Japan involving a sample of 3590 individuals, the 5-year incidence of periodontitis was statistically higher for both those with a BMI between 25 and 30 kg/m^2 and those with a BMI of ≥30 kg/m^2, when compared with individuals with a BMI of ≤22 kg/m^2 (Morita *et al*. 2011), establishing a dose–response relationship between overweight/obesity and risk for periodontitis. Finally, in a study involving a nationally representative sample of 7188 subjects in Korea, *metabolic syndrome* was associated with periodontitis (Kwon *et al*. 2011). In contrast, an inverse association between obesity and clinical attachment loss was observed in a study involving 1579 men and women in Denmark (Kongstad *et al*. 2009).

The three most recent systematic reviews that compiled the available evidence linking obesity to periodontitis have all demonstrated a positive association between the two conditions. This appears to be the case both in adolescents and young adults (Khan *et al*. 2018) as well as across the age spectrum (Martinez-Herrera *et al*. 2017; Arboleda *et al*. 2019). However, there is inconclusive evidence on the effects of obesity on the outcomes of periodontal therapy, as evidence from longitudinal studies is sparse (Arboleda *et al*. 2019).

Osteopenia/osteoporosis

Several early cross-sectional studies, of limited sample size and largely confined to postmenopausal women, have suggested that women with low bone mineral density are more likely to have gingival recession and/or pronounced gingival inflammation and clinical attachment loss (von Wowern *et al*. 1994; Mohammad *et al*. 1996, 1997; Tezal *et al*. 2000).

In a radiographic study of 1084 subjects aged 60–75 years, Persson *et al*. (2002) reported a positive association between osteoporosis and periodontitis with an OR of 1.8 (95% CI 1.2–2.5). However, studies that have failed to report such an association have also been published (Weyant *et al*. 1999; Lundström *et al*. 2001).

Based on these observations, it has been hypothesized that the systemic loss of bone density in osteoporosis may, in combination with hormone action, heredity, and other host factors, result in an increased susceptibility to inflammation-associated destruction of the periodontal tissues (Wactawski-Wende 2001). Suggested mechanisms underlying the association also include disruption of the homeostasis concerning bone remodeling, hormonal balance, and inflammation resolution (Wang & McCauley 2016).

In a cross-sectional study of 1329 postmenopausal women in the USA, systemic bone density was positively associated with clinical attachment loss in women with subgingival calculus, but negatively associated in women without calculus (Brennan *et al*. 2007). The data from longitudinal studies are apparently conflicting. Payne *et al*. (1999, 2000) reported an enhanced longitudinal alveolar bone loss in osteoporotic women versus women with normal mineral bone density. Yoshihara *et al*. (2004) reported a significant association between bone mineral density and 3-year longitudinal attachment loss in Japanese subjects aged ≥70 years after adjustment for covariates. In contrast, Reinhardt *et al*. (1999) reported no significant impact of serum estradiol levels on longitudinal attachment loss over a 2-year period. Nevertheless, the most recent systematic reviews available concluded that osteoporosis is indeed a risk factor for periodontitis (Wang & McCauley 2016; Goyal *et al*. 2017) but also emphasize that well-controlled longitudinal and interventional studies are necessary to inform evidence-based clinical guidelines.

Human immunodeficiency virus infection

Early studies published in the late 1980s seemed to indicate that both the prevalence and the severity of periodontitis were exceptionally high in patients with acquired immunodeficiency syndrome (AIDS) (Winkler & Murray 1987), but a more tempered picture emerged in subsequent publications. While it cannot be ruled out that the initial reports included biased samples, it is also possible that the successful control of immunosuppression in human immunodeficiency virus (HIV)-positive subjects by means of high activity antiretroviral therapy (HAART) and other continuously evolving pharmacotherapies has influenced the incidence of periodontal disease progression in HIV-seropositive subjects and has resulted in less severe periodontal manifestations of HIV infection (Chapple & Hamburger 2000). For example, a cross-sectional study of 326 HIV-infected adults (McKaig *et al*. 1998) revealed that, after adjustments for CD4 counts, persons taking HIV antiretroviral medication were five times less likely to suffer from periodontitis than those not taking such medication, underscoring the importance of the host's immunologic competency in this context.

Nevertheless, subsequent publications continued to generate conflicting results. Thus, although a number of studies (Smith *et al*. 1995; Robinson *et al*. 1996; Ndiaye *et al*. 1997; McKaig *et al*. 1998; Nittayananta *et al*. 2010; Stojkovic *et al*. 2011; Groenewegen *et al*. 2019) indicated higher prevalence and severity of periodontitis in HIV-positive subjects when compared with controls, other studies are either not supportive of this notion or indicate that the differences in periodontal status between HIV-seropositive and -seronegative subjects are limited (Cross & Smith 1995; Lamster *et al*. 1997; Scheutz *et al*. 1997; Vastardis *et al*. 2003; Ryder *et al*. 2017; Williams-Wiles & Vieira 2019). Studies investigating the pathobiology of periodontitis in HIV-infected subjects suggested that specific IgG subclass responses to periodontopathic bacteria were similar in HIV-positive and HIV-negative subjects (Yeung *et al*. 1993), while CD4 count levels were not found to correlate with the severity of periodontitis (Martinez Canut *et al*. 1996; Vastardis *et al*. 2003).

The few available longitudinal studies are equally conflicting. Two companion publications, from a short-term follow-up study (Cross & Smith 1995; Smith *et al*. 1995) involving a group of 29 HIV-seropositive subjects who were examined at baseline and at 3 months, reported a low prevalence and incidence of clinical attachment loss. The subgingival microbial profiles of the seropositive subjects resembled those of non-systemically affected subjects, and did not correlate with their CD4 and CD8 lymphocyte counts. Similarly, in a small follow-up study of 12 months' duration, Robinson *et al*. (2000) found no difference in the progression of periodontitis between HIV-positive and HIV-negative subjects. Hofer *et al*. (2002) demonstrated that compliant HIV-positive subjects can be successfully maintained in a manner similar to non-infected controls. However, a 20-month follow-up study of 114 homosexual or bisexual men (Barr *et al*. 1992) revealed a clear relationship between incidence of clinical attachment loss and immunosuppression, expressed through CD4 cell counts. The authors suggested that HIV-infection in combination with older age confers an increased risk for attachment loss. Similar observations were reported by Lamster *et al*. (1997), who concluded that periodontitis in the presence of HIV infection is dependent upon the immunologic competency of the host as well as the local inflammatory response to the subgingival microbiota. A large longitudinal investigation conducted between 1995 and 2002 involving 584 HIV-seropositive and 151 HIV-seronegative women, examined every 6 months, demonstrated no differences in baseline clinical attachment loss or in periodontitis progression between the two groups (Alves *et al*. 2006). Lastly, a 24-month follow-up of 73 HIV-positive individuals who received comprehensive care, the observed resolution of periodontitis was deemed similar to that expected in HIV-uninfected periodontitis patients, and was associated

with improved CD4 counts among those who were initially immunosuppressed (Valentine *et al*. 2016).

As emphasized in a very recent comprehensive review of current trends and developments in HIV research as it pertains to periodontal diseases (Ryder *et al*. 2020), the antiretroviral therapies administered over the last 20 years have had a profound impact on the sequelae of HIV infection, and the almost certain mortality historically associated with them has evolved into a chronic condition compatible with an extended lifespan. However, existing disparities in access to state-of-the art care globally (Geter *et al*. 2018; Ottria *et al*. 2018), combined with emerging comorbidities in ageing HIV-positive individuals (Erlandson & Karris, 2019), necessitate keen awareness of the association between HIV-infection and oral pathologies and additional research.

Psychosocial factors

The mechanisms by which psychosocial stress may affect periodontal status are complex. It has been suggested that one of the plausible pathways may involve behavioral changes leading to smoking and poor oral hygiene that, in turn, may affect periodontal health (Genco *et al*. 1998). In the absence of an unequivocal biologic measure of stress, a limited number of studies have used proxy measures of stress to study its association with periodontitis. In a study of 1426 subjects in Erie County, NY, USA, Genco *et al*. (1999) reported that adults who were under financial strain and exhibited poor coping behaviors were at increased risk of severe periodontitis when compared with subjects who demonstrated good coping behavior patterns under similar financial strain, or with controls under no financial strain. In a sample of 1089 adults in rural Japan, job- and health-related stress was positively associated with clinical attachment loss after adjustments for common risk factors (Akhter *et al*. 2005). War-related stress was found to be associated with poor periodontal conditions in Croatia (Spalj *et al*. 2008). Similar observations were made in a study of an immigrant population from Ethiopia, in which psychological distress was positively associated with deep periodontal pockets (Vered *et al*. 2011). In contrast, a study of 681 subjects carried out in Lithuania (Aleksejuniene *et al*. 2002) could not document an association between psychosocial stress and periodontitis, although the disease was found to correlate with lifestyle factors. In a small prospective study, Linden *et al*. (1996) reported that longitudinal attachment loss was significantly predicted by increasing age, lower socioeconomic status, lower job satisfaction, and type A personality, characterized by aggressive, impatient, and irritable behavior.

Clearly, the role of stress in periodontitis has not been fully explored and multiple gaps in our knowledge exist. Nevertheless, given the established role of the sympathetic, parasympathetic, and peptidergic/sensory nervous systems, as well as that of the hypothalamic–pituitary–adrenal axis on brain-to-immune regulatory pathways, such a role is clearly biologically plausible. Experimental animal studies have begun to shed light on basic mechanisms that may explain the link between psychosocial factors and periodontitis. For example, a study by Breivik *et al*. (2006) demonstrated that experimentally induced depression accelerated tissue breakdown in a ligature-induced periodontitis rat model and that pharmacologic treatment of depression attenuated this breakdown. In a study in humans, salivary cortisol levels (indicative of psychological stress) were positively associated with the extent and severity of periodontitis (Hilgert *et al*. 2006). In a case-control study of 56 patients with periodontitis and 44 periodontally healthy controls (Haririan *et al*. 2018), salivary levels of neuropeptides VIP (vasoactive intestinal peptide) and NPY (neuropeptide Y) were associated with bleeding on probing and the extent and severity of periodontitis. Lastly, a meta-analysis collectively analyzing 573 individuals, including 258 participants with chronic and 72 with aggressive periodontitis demonstrated on average a 53% higher level of salivary cortisol in aggressive periodontitis patients than in periodontally healthy controls (Botelho *et al*. 2018) but emphasized that well-designed longitudinal studies are required to fully elucidate the role of psychological factors on periodontitis and account for possible confounders.

Concluding remarks

The analytical epidemiologic studies described in this chapter are obviously diverse with respect to important elements of design and methodology, such as definitions of disease, sample size, use of full-mouth or partial-mouth recording protocols, length of follow-up in longitudinal studies, adjustment for potential confounders, etc. Nevertheless, despite these apparent shortcomings, a number of conclusions can be made with reasonable certainty:

1. Subgingival bacterial dysbiosis, cigarette smoking, and diabetes mellitus are the major established risk factors for periodontitis. The clinical significance of additional emerging, biologically plausible factors needs to be further investigated in future studies.
2. There is a need to introduce uniform definitions of periodontitis to be used in analytical epidemiologic studies. This will facilitate valid comparisons, establish whether seemingly conflicting data reflect true biologic variation or are exclusively owed to methodologic inconsistencies, and contribute to the correct identification of risk factors. Consistent implementation of the standards for reporting periodontitis prevalence and severity in epidemiologic studies introduced by the joint EU/USA periodontal epidemiology working group (Holtfreter *et al*. 2015) may allow for

meaningful comparisons across populations and better insights into the determinants of global variation. Furthermore, adoption of the definitions introduced by the recent World Workshop for the Classification of Periodontal Diseases and Conditions (Papapanou *et al*. 2018; Tonetti *et al*. 2018) can provide a unifying basis and facilitate collection of comparable data across the globe. Obviously, no definition is devoid of shortcomings and the above proposals are no exception.

3. Studies need to distinguish between risk factors and disease markers and predictors. Although the use of the latter as explanatory variables in multivariate models may increase the coefficient of determination (i.e. the proportion of the variance explained by means of the models), it may also obscure the significance of true etiologic factors. For example, as shown by Ismail *et al*. (1990), factors with biologically plausible etiologic potential (such as dental plaque) may not retain their significance in multivariate models that include alternative expressions of disease such as tooth mobility. It has been demonstrated that baseline levels of disease and morphologic features such as angular bony defects are powerful predictors of future disease progression (Papapanou *et al*. 1989; Papapanou & Wennström 1991). Haffajee *et al*. (1991) demonstrated that age, plaque, and bleeding on probing are related to baseline disease levels as well as to incident disease. In the search of true exposures of significance for disease onset or progression, inclusion of a factor in a model may thus erroneously discredit a co-varying, biologically significant other factor. Likewise, factors associated with the initiation of the periodontitis may be different from the ones involved in its progression (Beck *et al*. 1995), and this distinction between them may have implications for assessment strategies and may improve the accuracy of the risk/prediction models.

One of the issues related to the descriptive epidemiology of periodontitis that is still under debate is whether their worldwide prevalence has been decreasing over the past couple of decades. Unfortunately, the data do not allow a clear answer for a number of reasons. First, no universal conclusion is possible, since the prevalence of periodontal disease appears to vary with race and geographic region. Second, the quality of the data available is not consistent across the globe. While several well-conducted, population-representative epidemiologic studies have been carried out in a number of industrialized countries, the majority of studies in the developing world have used the CPITN system, which produced data of inadequate detail. Moreover, studies using the exact same methodology to evaluate representative samples drawn from the same population over time are sparse. Among the few exceptions where such data are available derive from the USA and the National Health and Nutrition Examination Survey. Indeed, data obtained through a partial recording methodology were interpreted to suggest a trend for decreasing prevalence of periodontitis (Dye *et al*. 2007), although more recent data obtained through a full mouth examination protocol do not seem to corroborate this trend (Eke *et al*. 2018). A series of studies from Sweden (Hugoson *et al*. 1992,1998a, 2005, 2008; Wahlin *et al*. 2018) documented, by clinical and radiographic means, the frequency distribution of various levels of severity of periodontitis in five cross-sectional studies over a 40-year period (in 1973, 1983, 1993, 2003, and 2013). In these studies, subjects were grouped according to the severity of their periodontal conditions into five groups: groups 1 and 2 included subjects who were periodontally healthy or only had gingivitis; group 3 included subjects with moderate periodontitis, that is, whose loss of periodontal tissues support did not extend beyond one-third of the root length; and groups 4 and 5 included subjects with more severe destructive disease. As shown in Fig. 6-6 (Wahlin *et al*. 2018) a clear increase in the frequency of subjects in groups 1 and 2 was noted over the observation period, from 43% in 1983 to 60% in 2013. This increase occurred primarily at the expense of group 3, which declined from 41% in 1983 to 33% in 2013. Nevertheless, the frequency of subjects with severe periodontitis did not decrease statistically significantly over time from 16% in 1983, to 11% in 2013. However, tooth retention increased dramatically in the severe periodontitis group from an average of 14 teeth per person in 1983 to 21 teeth in 2013 (Fig. 6-7). Based on these data derived from a population with access to, arguably, one of the best oral health care systems in the world, we may conclude that (1) the fraction of the population which is apparently most susceptible to severe periodontitis remains substantial, although (2) there is a clear benefit from improved oral health awareness, access to care, and increased utilization of therapeutic resources, as expressed by higher tooth retention in all groups.

It has also been well documented in these and other studies that the rate of edentulism has decreased substantially over the past 30 years, with elderly groups retaining their natural dentition and higher mean numbers of teeth than their counterparts a generation ago (Kassebaum *et al*. 2014). This fact *per se* should contribute to an increased prevalence of periodontal disease in older age cohorts, since retained teeth in the elderly are more likely to experience substantial cumulative attachment loss which forms the basis of the assessment of prevalence (Douglass & Fox 1993; Eke*et al*. 2016). Additional research is clearly required to further elucidate these issues, and an adequate and consistent epidemiologic methodology is essential for generating valid comparative data. Arguably, one

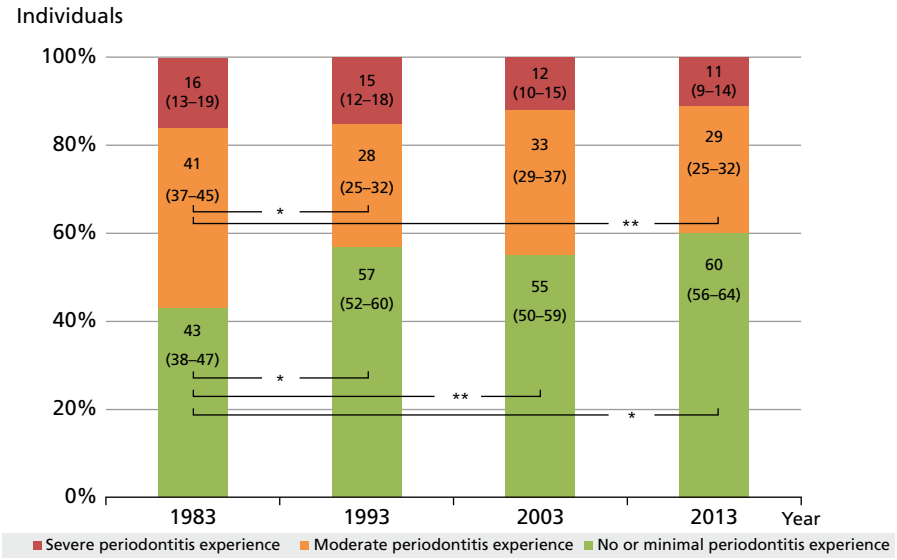


Fig. 6-6 Frequency distribution of subjects with healthy periodontal conditions or gingivitis (no/minimal; groups 1+2), moderate (group 3), and severe periodontitis (groups 4+5), in a Swedish cohort in 1983, 1993, and 2003 and 2013. For definitions, see text. (Source: Wahlin *et al*. 2018, reproduced with permission.)

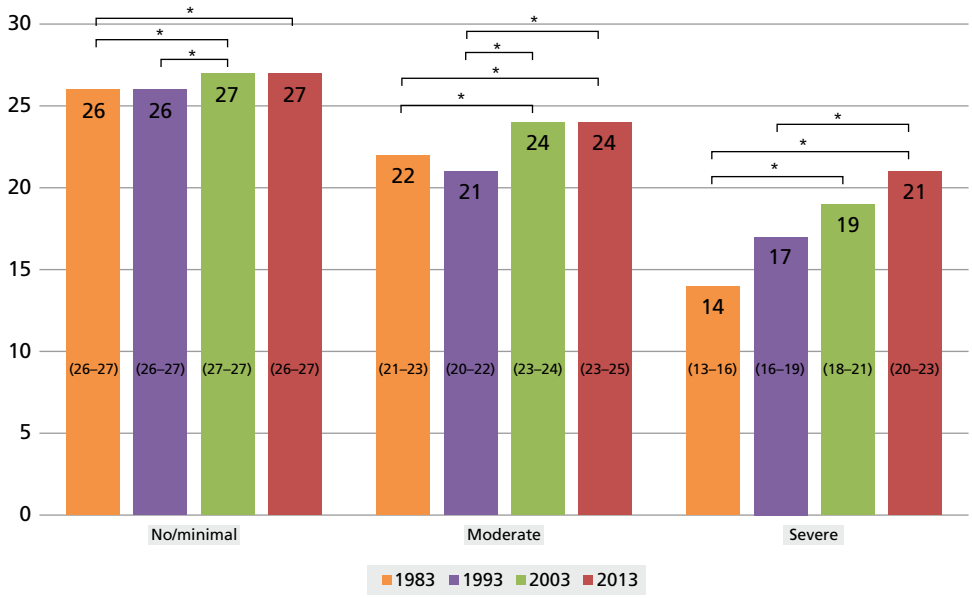


Fig. 6-7 Mean number of teeth present (range in parenthesis) in subjects with healthy periodontal conditions or gingivitis (no/minimal; groups 1+2), moderate (group 3), and severe periodontitis (groups 4+5), in a Swedish cohort in 1983, 1993, and 2003 and 2013. For definitions, see text. (Source: Wahlin *et al*. 2018, reproduced with permission.)

of the important tasks for future epidemiologic research is to identify determinants of susceptibility to severe periodontitis, prior to the development of irreversible tissue damage (Papapanou 2012; Papapanou & Susin 2017). Although several risk factors have been established and a wide array of disease markers has been recognized, the impact of interventions targeting these factors on the state of periodontal health on the population level has yet to be fully appreciated. To assess the magnitude of the clinical benefit achieved by such modulation, prospective, long-term epidemiologic studies must be conducted.

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Chapter 7

Epidemiology of Peri-Implant Diseases

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Introduction

Epidemiology includes evaluation of the prevalence and risk factors of diseases in populations at risk. Epidemiological findings may generate hypotheses regarding etiology and pathogenesis. Ultimately, understanding the dynamics of diseases can assist in creating prophylactic and therapeutic strategies, and influence the allocation of resources in medical care and directions in education.

Because an implant device is involved, epidemiology of peri-implant diseases differs from epidemiology of, for example, periodontal diseases (see Chapter 6); outcomes may be considered as complications of an intervention rather than occurrence of a natural disease. This puts a specific focus on the target population, which, in this context are subjects provided with implant-supported restorative therapy. While epidemiological data on periodontal diseases have a broad applicability, the validity of similar data on peri-implant diseases may be less obvious, because, from a global perspective, populations at risk do not necessarily share the same characteristics. One important aspect is the variation in levels of implant therapy in different countries. Registry data from Sweden suggest that about 8% of subjects aged ≥70 years currently have at least one dental implant (SKaPa 2018). Given the widespread use of dental implants in many parts of the world, an epidemiological approach towards peri-implant diseases is justified.

Disease definition

Peri-implant diseases include two entities: peri-implant mucositis and peri-implantitis, and their typical characteristics were summarized at the 2017 World Workshop on Classification of Periodontal and Peri-implant Diseases and Conditions (Berglundh *et al*. 2018a). Thus, peri-implant mucositis constitutes an inflammatory lesion in the peri-implant mucosa surrounding an endosseous implant without loss of supporting peri-implant bone. Further, peri-implantitis is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and progressive loss of supporting bone. Marginal bone loss is a distinctive feature of peri-implantitis.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

Case definition

A disease definition provides descriptive information on the characteristics of a condition, and detailed information on etiology and pathogenesis of peri-implant mucositis and peri-implantitis is presented in Chapter 20. Case definitions, on the other hand, offer specific points of measurement, which are prerequisites for the diagnosis of a disease and studies of its prevalence, incidence, and risk factors. In addition to case definitions, guidelines for the description of severity of the disease are also important. To facilitate interpretation and comparison of data, researchers should adhere to accepted case definitions, which should ideally be clinically relevant and evidence based.

Tomasi and Derks (2012) reviewed the methodology of clinical research on the incidence, prevalence, and risk factors of peri-implant diseases. The authors found a significant heterogeneity between relevant studies in terms of case definitions. Thus, six publications on peri-implant mucositis presented six different case definitions, which varied in terms of thresholds of probing pocket depth and the detection of "absence of bone loss" in radiographs. Case definitions for peri-implantitis were reported in 12 studies. While the clinical criteria for soft tissue inflammation were largely consistent, the thresholds for the assessment of bone loss in radiographs varied extensively. In all, seven different levels of bone loss were used, and the thresholds ranged from 0.4 mm to 5 mm. It is obvious that the inconsistency in terms of case definitions contributed to the variation in prevalence of peri-implant diseases observed in the current literature (Derks & Tomasi 2015).

In a consensus report from the 2017 World Workshop on Classification of Periodontal and Peri-implant Diseases and Conditions, case definitions were proposed for peri-implant health, peri-implant mucositis, and peri-implantitis. These were adapted for use in day-to-day clinical practice and in epidemiological studies (Berglundh *et al*. 2018a). The most important clinical tool to distinguish between peri-implant health and disease is bleeding/suppuration on probing (BoP), while the distinction between peri-implant mucositis and peri-implantitis is made by assessment of bone loss in radiographs. The consensus report emphasized that bone loss in this context should exceed possible crestal bone level changes resulting from initial bone remodeling after implant placement. A summary of the case definitions for peri-implant health, peri-implant mucositis, and peri-implantitis established at the 2017 World Workshop is presented in Table 7-1.

Peri-implant health

Clinical and histological features of the healthy peri-implant mucosa were reviewed by Araujo and Lindhe (2018) and details are also described in Chapter 4. Distinctive for peri-implant health is the absence of BoP and visual signs of inflammation, such as swelling and redness. As peri-implant mucosal dimensions may vary between, for example, posterior and anterior locations, it is not possible to define a range of probing depths compatible with health. The consensus report (Berglundh *et al*. 2018a) also underlined that peri-implant health can exist around implants with reduced bone support, as peri-implant health can be achieved at sites successfully treated for peri-implantitis. In addition, implant placement in sites presenting with ridge deficiencies may also result in a "reduced" bone level located apical of the implant margin.

Table 7-1 Case definitions of peri-implant diseases suggested by the 2017 World Workshop on Classification of Periodontal and Peri-implant diseases and Conditions (Source: Data from Berglundh *et al*. 2018a.)

	Peri-implant health	Peri-implant mucositis	Peri-implantitis	
Visual signs of inflammation (e.g. swelling and redness)	No	Yes	Yes	
Bleeding/suppuration on probing	No	Yes	Yes	
Increase in probing pocket depth	No	Possible	Yes (≥6 mm if no previous reference)	
Progressive bone loss (beyond initial bone remodeling)	No	No	**Epidemiological studies**	**Day-to-day clinical practice**
			Yes	Yes
			Baseline documentation available Bone loss exceeding measurement error	*Baseline documentation available* Bone loss (no threshold)
			Baseline documentation not available Bone level ≥3 mm	*Baseline documentation not available* Bone level ≥3 mm

In summary, the case definition of peri-implant health to be used in day-to-day clinical practice and epidemiological studies presented in the consensus report (Berglundh *et al*. 2018a) includes: (1) absence of visual signs of inflammation and bleeding/suppuration on gentle probing; (2) no increase in probing depth compared to previous examinations; and (3) no bone loss (Table 7-1).

Peri-implant mucositis

Clinical and histopathological characteristics, and risk indicators of peri-implant mucositis, were described in a review by Heitz-Mayfield and Salvi (2018). The presence of an inflammatory lesion in the peri-implant mucosa and the absence of loss of supporting bone are the two fundamental features of peri-implant mucositis. The lesion occupies a connective tissue zone lateral, but not apical, of the pocket epithelium (for details see Chapter 20). The main clinical characteristic of peri-implant mucositis is BoP, while visual signs of inflammation, such as swelling and redness, may also occur. Similar to gingivitis around teeth, peri-implant mucositis often presents with an increase in probing pocket depth as a result from swelling or decrease in probing resistance. The consensus report stated that there is strong evidence that plaque is the etiological factor for peri-implant mucositis and that the lesion can resolve after reinstitution of plaque control procedures.

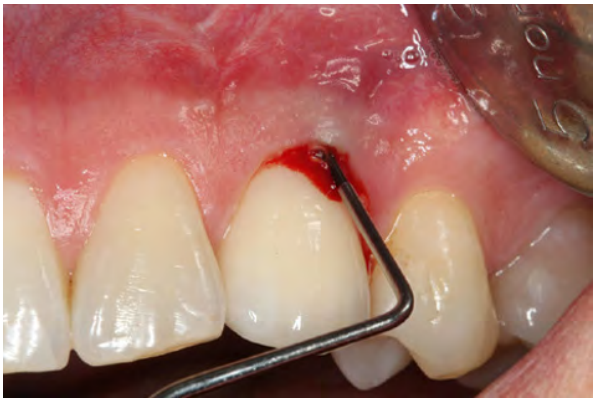
In summary, the case definition of peri-implant mucositis to be used in day-to-day clinical practice and epidemiological studies presented in the consensus report (Berglundh *et al*. 2018a) includes (1) bleeding and/or suppuration on gentle probing and (2) no bone loss (Table 7-1).

Peri-implantitis

Schwarz *et al*. (2018) reviewed the clinical and histopathological characteristics and risk indicators of peri-implantitis. The two main features of peri-implantitis are inflammation in the peri-implant mucosa and loss of supporting bone. Peri-implantitis lesions extend apical of the pocket epithelium into the supracrestal connective tissue (for details see Chapter 20) and are larger than those at peri-implant mucositis and periodontitis sites. Clinical signs of inflammation including BoP, increased probing pocket depths, and/or recession of the mucosal margin are key findings together with radiographic bone loss (Fig. 7-1).

In summary, the case definition of peri-implantitis to be used in day-to-day clinical practice and epidemiological studies presented in the consensus report (Berglundh *et al*. 2018a) includes (1) bleeding and/or suppuration on gentle probing and (2) increased probing pocket depth compared to previous examinations and (3) bone loss. The case definition of peri-implantitis when previous examination data or radiographs are lacking includes (1) bleeding and/or suppuration on gentle probing, (2) probing pocket depths of ≥6 mm and (3) bone levels ≥3 mm apical of the most coronal portion of the intra-osseous part of the implant.

(a)



(b)

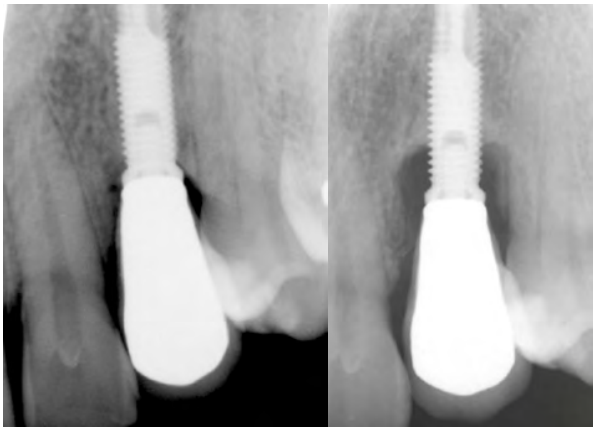


Fig. 7-1 **(a)** Bleeding on probing at an implant installed 11 years earlier. (b) The 11-year follow-up radiograph indicates bone loss relative to baseline, confirming the diagnosis of peri-implantitis.

Examination methods

The case definitions of peri-implant health and diseases highlight the importance of baseline or reference assessments to allow for evaluations of changes in probing pocket depths and marginal bone levels over time. An increase of probing pocket depth may serve as an indicator of disease progression. The clinical assessment of soft tissue inflammation in sites with peri-implant disease relies on visual signs of inflammation and the presence of bleeding/suppuration on probing (Heitz-Mayfield & Salvi 2018). As studies on periodontal disease have shown the consistency between BoP and a histologically detected inflammatory lesion in gingival tissues, there are reasons to suggest a similar association for assessments of peri-implant diseases. This assumption is justified by findings from experimental studies on gingivitis and peri-implant

mucositis demonstrating a similar pattern of the development of an inflammatory lesion following periods of plaque accumulation (Berglundh *et al*. 1992; Ericsson *et al*. 1992; Leonhardt *et al*. 1992) and data from clinical studies showing that plaque accumulation was directly related to the rate of BoP (Pontoriero *et al*. 1994; Salvi *et al*. 2012). In the study on experimental peri-implant mucositis by Salvi *et al*. (2012) the plaque formation phase was followed by an additional period of infection control and the findings on reduction in BoP towards the end of the study underlined the reversibility of the condition.

The importance of BoP in regard to assessment of peri-implant disease was addressed in clinical studies. In an evaluation including 112 implant-carrying patients, Farina *et al*. (2017) showed that the probability of BoP at implant sites was similar to that of corresponding tooth sites. It is important to note that the authors adjusted the comparisons for probing pocket depth. In two longitudinal studies, the predictive value of BoP at implants was evaluated (Carcuac *et al*. 2017; Karlsson *et al*. 2019). Results indicated that, while BoP was a poor predictor for future bone loss, the absence of BoP was a strong predictor for the preservation of marginal bone levels. These observations are in line with data evaluating the value of BoP at teeth and underline its clinical relevance.

The recommendation in the consensus report from the 2017 World Workshop (Berglundh *et al*. 2018a) to obtain baseline or reference measurements is critical for assessments of bone level changes in radiographs during follow-up. Thus, a radiographic evaluation following the completion of the implant-supported prosthesis is indicated. An additional radiograph obtained after an initial (one-year) function period may then serve as an ideal baseline as physiological remodeling will be completed.

In cases where previous examination data or radiographs are lacking, the diagnosis of peri-implantitis is based on the combination of the clinical findings of BoP and a probing pocket depth ≥6 mm together with the assessment of a bone level located ≥3 mm apical of the most coronal portion of the intraosseous part of the implant. This case definition is important for diagnosis in day-to-day clinical practice, as patients may present for the first time and previous records are not available. Epidemiological research on peri-implant diseases, however, should ideally be designed to include data from previous examinations performed after the first year in function of the implant. Another concern regarding epidemiological research on peri-implant diseases is the importance of a valid and relevant threshold for bone loss. Thus, the measurement error of the assessment of bone levels around implants within each study should be considered. Previous studies have reported on mean values of measurement errors of 0.5 mm and below.

Prevalence of peri-implant diseases

The occurrence of peri-implant diseases has predominantly been evaluated in studies using a cross-sectional design. Such analyses provide information on the prevalence of the condition. Thus, little is known about the incidence of the disease, that is, the number of new cases occurring during a given time period. Selected studies on the prevalence of peri-implant mucositis and peri-implantitis are summarized in Table 7-2. Data originating from different countries and patient cohorts are largely in agreement, when taking the specific case definitions or thresholds of measurements into consideration. In general, peri-implant mucositis was found consistently to be more frequent than peri-implantitis. In a meta-analysis, Derks and Tomasi (2015) found a weighted mean prevalence of 43% and 22% for peri-implant mucositis and peri-implantitis, respectively. The confidence intervals of the estimates, however, were large, mostly due to the heterogeneity of case definitions used in the included studies. The majority of reports relied on convenience samples, that is, groups of patients attending a single clinical center, commonly in a university/hospital setting. In the two studies that adopted an epidemiological approach and enrolled random population samples, the reported prevalence of peri-implantitis was 15% (Derks *et al*. 2016) and 34% (Kordbacheh *et al*. 2019), respectively.

In contrast to epidemiological studies on periodontitis, where age of the patient is directly related to the time of exposure (time at risk), the time at risk in studies on peri-implant diseases is determined by the time point of implant installation. Function times for implants vary considerably within and between study samples and need to be considered when evaluating prevalence data. Table 7-2 illustrates the variation in time of function of implants between the studies. As the occurrence of peri-implant diseases accumulates with time, it is reasonable to expect studies with longer follow-up periods to report on higher proportions of disease (Derks & Tomasi 2015).

Extent and severity of peri-implantitis

To describe the burden of a disease, the severity and extent of the condition should be considered in addition to its prevalence. For peri-implant diseases, the interpretation of these characteristics is challenging. Severity of periodontitis at teeth is assessed by the amount of clinical attachment loss or radiographic bone loss relative to the length of the root and the age of the patient (Papapanou *et al*. 2018). A corresponding approach at implants is less feasible as implant length may vary considerably. Different cut-off points in radiographic bone loss expressed in millimeters have therefore been proposed. Thus, Derks *et al*. (2016) used different thresholds of bone loss ranging from 0.5 mm to 4 mm within the same study sample to describe severity of peri-implantitis. While 45% of

Table 7-2 Selection of studies on the prevalence of peri-implant diseases and their respective case definitions.

Study	Function time	Sample	Case definitions	Prevalence of peri-implant diseases (patient level)
Daubert *et al*. (2015), USA	8.9–14.8 years mean: 10.9 years	Convenience sample 96 subjects	*Mucositis* BoP and absence of bone loss *Peri-implantitis* PD ≥4 mm, BoP/SUP and bone loss ≥2 mm	*Mucositis* 48% *Peri-implantitis* 26%
Derks *et al*. (2016), Sweden	mean: 8.9 years	Population sample 596 subjects	*Mucositis* BoP/SUP and absence of bone loss *Peri-implantitis (moderate/severe)* BoP/SUP and bone loss >2 mm from year 1 after loading	*Mucositis* 32.0% *Peri-implantitis* 14.5%
Ferreira *et al*. (2006), Brazil	0.5–5 years mean: 3.5 years	Convenience sample 212 subjects	*Mucositis* BoP and absence of bone loss *Peri-implantitis* PD ≥5 mm, BoP/SUP and bone loss (no threshold)	*Mucositis* 64.6% *Peri-implantitis* 8.9%
Koldsland *et al*. (2010), Norway	1–16 years mean: 8.4 years	Convenience sample 109 subjects	*Mucositis* BoP/SUP and absence of bone loss *Peri-implantitis* BoP/SUP and bone loss >0.4 mm from loading	*Mucositis* 39.4% *Peri-implantitis* 47.1%
Kordbacheh Changi *et al*. (2019), USA	mean: 2.2 years	Population sample 215 subjects	*Peri-implantitis* Clinical signs of inflammation and bone loss >2 mm from implant installation	*Peri-implantitis* 34%
Marrone *et al*. (2013), Belgium	5–18 years mean: 8.5 years	Convenience sample 103 subjects	*Mucositis* PD ≤5 mm, BoP and bone level ≤2 mm *Peri-implantitis* PD >5 mm, BoP and bone level >2 mm	*Mucositis* 31% *Peri-implantitis* 37%
Mir-Mari *et al*. (2012), Spain	1–18 years mean: 6.3 years	Convenience sample 245 subjects	*Mucositis* BoP and bone level <2 threads *Peri-implantitis* BoP/SUP and bone level ≥2 threads	*Mucositis* 38.8% *Peri-implantitis* 16.3%
Rodrigo *et al*. (2018), Spain	5–13 years mean: 9.0 years	Population sample 275 subjects	*Mucositis* BoP and bone level <2 mm *Peri-implantitis* BoP and bone level ≥2 mm	*Mucositis* 27% *Peri-implantitis* 24%
Rokn *et al*. (2017), Iran	1–11 years mean: 4.4 years	Convenience sample 134 subjects	*Mucositis* BoP/SUP and bone level ≤2 mm *Peri-implantitis* BoP/SUP and bone level >2 mm	*Mucositis* 49% *Peri-implantitis* 20%
Roos-Jansåker *et al*. (2006), Sweden	9–14 years mean: 11.0 years	Convenience sample 216 subjects	*Mucositis* PD ≥4 mm, BoP and bone level <1 thread *Peri-implantitis* BoP/SUP and bone loss ≥1.8 mm from year 1 after loading	*Mucositis* 48% *Peri-implantitis* 16%
Wada *et al*. (2019), Japan	≥3 years mean: 5.8 years	Convenience sample 543 subjects	*Mucositis* BoP and absence of bone loss *Peri-implantitis* BoP/SUP and bone loss >1 mm from year 1 after loading	*Mucositis* 24% *Peri-implantitis* 16%

BoP, bleeding on probing; PD, probing pocket depth; SUP, suppuration.

all subjects presented with an overall occurrence of peri-implantitis (≥1 implant with BoP and bone loss >0.5 mm) after 9 years, a smaller group of 15% demonstrated moderate/severe forms (≥1 implant with BoP and bone loss >2 mm) of the disease. The corresponding proportions using similar case definitions reported by Koldsland *et al*. (2010) were 47% and 20%.

The evaluation of the extent of peri-implant diseases is hampered by a pronounced variation in the number of implants within single patients. While the average number of implants per individual in the cross-sectional analysis by Derks *et al*. (2016) was 4.0, a range of one to 12 implants was observed. These numbers should be viewed in regard to the average number of >20 teeth per patient that is commonly reported in surveys on periodontal disease. In two separate reports, an extent of peri-implantitis of 40% was observed (Mir-Mari *et al*. 2012; Derks *et al*. 2016). It should be noted, however, that patients with single implants were excluded from these analyses.

Peri-implantitis and implant loss

Untreated peri-implantitis may lead to implant loss with obvious consequences in terms of discomfort, loss of function, and cost. Implant loss has been evaluated as the primary outcome measure in the majority of studies on implant therapy (Needleman *et al*. 2012). While early implant loss may be related to the failure to achieve osseointegration, late implant loss constitutes a failure to maintain integration and may therefore be a consequence of progressive bone loss. Karlsson *et al*. (2020) observed that 42% of patients diagnosed with moderate/severe peri-implantitis after 9 years of function also had experienced implant loss. This clustering suggests that peri-implantitis represents a major cause of implant loss. This assumption is further supported by data from other evaluations, in which either all implant loss (Rosenberg *et al*. 2004; Roccuzzo *et al*. 2010, 2014; Dvorak *et al*. 2011; Malò *et al*. 2014) or the majority of implant loss (Romeo *et al*. 2004; Daubert *et al*. 2015; Jemt *et al*. 2017) was attributed to peri-implantitis. Longitudinal data on patients with peri-implantitis also indicate that progression of the disease leads to implant loss. Thus, Karlsson *et al*. (2019) in a 3.3-year follow-up study on patients previously diagnosed with moderate/severe peri-implantitis reported that 12 out of initially 133 implants in nine patients (out of 70) were lost during the observation time, all due to progression of the disease. These observations underline the importance of early diagnosis, prevention, and treatment of peri-implant diseases.

Etiology of peri-implant diseases

The term etiology implies a causal association between an exposure and an outcome. Hence, the etiological factor needs to be present and precede the occurrence of the event of interest. A risk factor, on the other hand, modifies the probability of the occurrence of the outcome but is not an absolute prerequisite. Criteria for scientific evidence supporting causation have been suggested and critically discussed (Hill 1965; Rothman & Greenland 2005). Causal associations have to be confirmed in prospective and interventional studies.

In analogy with periodontal diseases, bacterial plaque has been identified as the etiological factor of peri-implant diseases. In the consensus report from the 2017 World Workshop on Classification of Periodontal and Peri-implant Diseases and Conditions, it was stated that strong evidence is available identifying plaque as the etiological factor for peri-implant mucositis (Berglundh *et al*. 2018a). Data from human studies support the cause-and-effect relationship between plaque and the development of the disease. Thus, in a series of studies emulating the experimental gingivitis model (Löe *et al*. 1965), accumulation of plaque at implants in humans was allowed to occur over 21 days (Pontoriero *et al*. 1994; Zitzmann *et al*. 2001; Salvi *et al*. 2012; Meyer *et al*. 2017). During this period, peri-implant sites consistently developed visual and other clinical signs of peri-implant mucositis, that is, swelling, redness, and BoP (Heitz-Mayfield & Salvi 2018). Further, the inflammatory condition could be reversed or reduced after reinstating plaque control measures over an additional 3-week period (Salvi *et al*. 2012; Meyer *et al*. 2017).

Because peri-implant mucositis is the precursor of peri-implantitis (Jepsen *et al*. 2015), it is reasonable to evaluate the evidence supporting plaque as the cause of peri-implantitis. Experimental studies in humans evaluating plaque as the etiological factor for peri-implantitis are, for ethical reasons, not feasible. Preclinical models, however, have shown that the disruption of the supracrestal soft tissue barrier by means of a ligature together with plaque formation results in (1) downgrowth of the bacterial biofilm, (2) soft tissue inflammation, and (3) loss of marginal bone support (Zitzmann *et al*. 2004; Albouy *et al*. 2008; Carcuac *et al*. 2020) (for details, see Chapter 20). Epidemiological evidence on etiological factors for peri-implantitis may be obtained from retrospective evaluations. Thus, Schwarz *et al*. (2018) analyzed data from observational studies and found that patients exhibiting poor plaque control and not attending regular maintenance therapy were at higher risk of developing peri-implantitis (see Table 7-4 for more details). Further evidence on plaque as the etiological factor stems from studies evaluating long-term outcomes of therapy of peri-implantitis. Thus, using treatment strategies targeted at removal of bacterial deposits on implant surfaces and patient-performed plaque control, levels of soft tissue inflammation, and continued marginal bone loss were suppressed (Carcuac *et al*. 2017; Roccuzzo *et al*. 2017; Schwarz *et al*. 2017b; Berglundh *et al*. 2018b).

Risk factors for peri-implant diseases

The use of the terms "risk factor" or "risk indicator" depends on data quality and study design. For simplicity, the term "risk factor" will be used in this chapter. Risk factors for peri-implantitis can be grouped according to the patient or the implant. While potential etiological factors are ideally studied in prospective and longitudinal research, risk factors may be evaluated through a variety of study designs, such as cross-sectional analyses or retrospective cohort studies.

Peri-implant mucositis

Selected studies on potential risk factors for peri-implant mucositis are presented in Table 7-3. In general, the available evidence on risk factors in this context is limited. In line with the description on the etiological factor, analysis of data from cross-sectional studies consistently revealed associations between poor plaque control and lack of compliance to supportive therapy and the condition peri-implant mucositis. As an example, Wada *et al*. (2019) reported on a significantly elevated risk for patients with plaque scores >20% to present with an implant with peri-implant mucositis. The design of the implant-supported supraconstruction was also found to be a factor consistently associated with peri-implant mucositis, as illustrated in the interventional study by de Tapia *et al*. (2019). The authors evaluated the effect of treatment of mucositis and observed a greater improvement at sites, at which supraconstructions had been adjusted in order to facilitate access for oral hygiene. The ability of patients to perform plaque control measures has been demonstrated to be associated with the dimensions of the keratinized mucosa. Thus, Souza *et al*. (2016) reported that in patients with a reduced dimension of keratinized mucosa (<2 mm) plaque scores were higher and patients reported more frequently on pain during brushing. The evidence on the potential association between the width of keratinized mucosa and peri-implant mucositis, however, is conflicting. This fact may be explained by the variation in terms of patient groups, perception of discomfort, and case definitions.

Table 7-3 Selection of studies on potential risk factors for peri-implant mucositis.

Independent variable	Studies	Comment
Poor plaque control/lack of compliance to supportive therapy	Ferreira *et al*. (2006) Roos-Jansåker *et al*. (2006) Konstantinidis *et al*. (2015) Wada *et al*. (2019)	Consistent evidence of association
Design/extent of the implant-supported prostheses	Heitz-Mayfield *et al*. (2011) Konstantinidis *et al*. (2015) Tapia *et al*. (2019) Wada *et al*. (2019)	Consistent evidence of association
Dimensions of keratinized peri-implant mucosa	Adibrad *et al*. (2009) Bouri *et al*. (2008) Boynueğri *et al*. (2013) Crespi *et al*. (2010) Frisch *et al*. (2013) Konstantinidis *et al*. (2015) Lim *et al*. (2019) Roos-Jansåker *et al*. (2006) Schrott *et al*. (2009) Wada *et al*. (2019) Zigdon & Machtei (2008)	Inconsistent evidence of association
Smoking	Karbach *et al*. (2009) Konstantinidis *et al*. (2015) Rinke *et al*. (2011) Roos-Jansåker *et al*. (2006) Wada *et al*. (2019)	Inconsistent evidence of weak association
Systemic diseases	Ferreira *et al*. (2006) Karbach *et al*. (2009) Konstantinidis *et al*. (2015) Roos-Jansåker *et al*. (2006) Wada *et al*. (2019)	Inconsistent evidence of weak association

Peri-implantitis: risk factors related to the patient

Selected studies on potential risk factors for peri-implantitis related to the patient are presented in Table 7-4. Information on risk factors on peri-implantitis is more extensive when compared with peri-implant mucositis. There is convincing evidence that subjects who are susceptible to periodontitis, as assessed by current or history of periodontitis, are at high risk for peri-implantitis. This is illustrated by findings from two cross-sectional studies originating from Scandinavia. Thus, in a study on 109 patients with a mean follow-up period of 8.4 years, Koldsland *et al*. (2010, 2011) noted an elevated risk for peri-implantitis in periodontitis-susceptible subjects (odds ratio 6). Likewise, Derks *et al*. (2016) examined 596 individuals after a similar follow-up period and reported on the same strength of association between periodontitis and peri-implantitis.

In line with findings related to peri-implant mucositis, poor plaque control and lack of compliance to supportive therapy were also consistently identified as risk factors for peri-implantitis. In a 5-year follow-up evaluation on patients initially diagnosed with mucositis, Costa *et al*. (2012) found

Table 7-4 Selection of studies on potential risk factors for peri-implantitis related to the patient.

Independent variable	Studies	Comment
History/presence of periodontitis	Canullo *et al*. (2016) Casado *et al*. (2013) Costa *et al*. (2012) Dalago *et al*. (2017) Daubert *et al*. (2015) de Araújo Nobre *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Ferreira *et al*. (2006) Karoussis *et al*. (2003) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Marrone *et al*. (2013) Renvert *et al*. (2014) Roccuzzo *et al*. (2010, 2012) Rokn *et al*. (2017) Roos-Jansåker *et al*. (2006) Schwarz *et al*. (2017) Wada *et al*. (2019)	There is strong evidence from longitudinal and cross-sectional studies that a history of periodontitis constitutes a risk factor for peri-implantitis (Schwarz *et al*., 2018)
Poor plaque control/lack of compliance to supportive therapy	Aguirre-Zorzano *et al*. (2015) Canullo *et al*. (2016) Costa *et al*. (2012) de Araújo Nobre *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Ferreira *et al*. (2006) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Marrone *et al*. (2013) Monje *et al*. (2017) Rinke *et al*. (2011) Roccuzzo *et al*. (2010, 2012) Rodrigo *et al*. (2018) Rokn *et al*. (2017) Roos-Jansåker *et al*. (2006) Schwarz *et al*. (2017)	There is evidence that poor plaque control and lack of regular maintenance therapy constitute risk factors for peri-implantitis (Schwarz *et al*., 2018)
Age	Aguirre-Zorzano *et al*. (2015) Daubert *et al*. (2015) Derks *et al*. (2016) Ferreira *et al*. (2006) Marrone *et al*. (2013) Renvert *et al*. (2014) Roos-Jansåker *et al*. (2006)	Inconsistent evidence of weak association

Table 7-4 (*Continued*)

Independent variable	Studies	Comment
Gender	Casado *et al*. (2013) Derks *et al*. (2016) Ferreira *et al*. (2006) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Kordbacheh Changi *et al*. (2019) Renvert *et al*. (2014) Rodrigo *et al*. (2018) Roos-Jansåker *et al*. (2006)	Inconsistent evidence of weak association
Systemic diseases	Casado *et al*. (2013) Canullo *et al*. (2016) Dalago *et al*. (2017) Daubert *et al*. (2015) de Araújo Nobre *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Ferreira *et al*. (2006) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Marrone *et al*. (2013) Renvert *et al*. (2014) Rodrigo *et al*. (2018) Rokn *et al*. (2017) Roos-Jansåker *et al*. (2006) Wada *et al*. (2019)	Available evidence is inconclusive as to whether diabetes is a risk factor for peri-implantitis. Evidence suggesting systemic conditions (other than diabetes) to be risk factors for peri-implantitis is limited (Schwarz *et al*., 2018)
Smoking	Aguirre-Zorzano *et al*. (2015) Canullo *et al*. (2016) Casado *et al*. (2013) Daubert *et al*. (2015) Dalago *et al*. (2017) de Araújo Nobre *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Marrone *et al*. (2013) Renvert *et al*. (2014) Rinke *et al*. (2011) Rokn *et al*. (2017) Roos-Jansåker *et al*. (2006) Schwarz *et al*. (2017) Wada *et al*. (2019)	There is no conclusive evidence that smoking constitutes a risk factor for peri-implantitis (Schwarz *et al*., 2018)

that supportive therapy had a significant impact in preventing the progression of mucositis into peri-implantitis. Thus, while 18% of patients with regular maintenance care developed peri-implantitis, the corresponding proportion among subjects without regular supportive care was more than twice as high.

While associations between periodontitis and systemic disorders have been identified (see Chapter 6), similar links between peri-implantitis and systemic conditions have not been demonstrated. This lack of association also applies to cigarette smoking. In this context, however, it should be noted that smoking as an independent factor may not easily be identified in a statistical analysis due to the strong effect of other parameters such as periodontitis (Derks *et al*. 2016; Dalago *et al*. 2017).

Peri-implantitis: risk factors related to the implant

The only implant-related factor that has been consistently associated with the risk for peri-implantitis is the design and extent of the prosthetic reconstruction (Table 7-5). This observation is in line with findings previously discussed for peri-implant mucositis. As an example, Serino and Ström (2009) evaluated the accessibility of implant-supported restorations for oral hygiene measures in patients diagnosed with peri-implantitis. The authors noted that only few sites with access for oral hygiene were affected (18%), while 65% of the non-cleansable sites showed peri-implantitis. In addition, Rodrigo *et al*. (2018) observed an elevated risk for peri-implantitis at

Table 7-5 Selection of studies on potential risk factors for peri-implantitis related to the treatment, site, or implant.

Independent variable	Studies	Comment
Jaw	Aguirre-Zorzano *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Rodrigo *et al*. (2018) Rokn *et al*. (2017) Wada *et al*. (2019)	Inconsistent evidence of weak association
Design/extent of the implant-supported prostheses	Dalago *et al*. (2017) Daubert *et al*. (2015) Derks *et al*. (2016) Konstantinidis *et al*. (2015) Marrone *et al*. (2013) Rodrigo *et al*. (2018) Serino & Ström (2009)	Consistent evidence of association. Higher risk for more extensive restorations and for restorations without access for oral hygiene measures
Dimensions of keratinized peri-implant mucosa	Canullo *et al*. (2016) Daubert *et al*. (2015) Koldsland *et al*. (2011) Konstantinidis *et al*. (2015) Rokn *et al*. (2017) Roos-Jansåker *et al*. (2006)	Inconsistent evidence of association
Type of retention	Canullo *et al*. (2016) Dalago *et al*. (2017) Daubert *et al*. (2015) Derks *et al*. (2016) Kordbacheh Changi *et al*. (2019) Marrone *et al*. (2013) Wada *et al*. (2019)	Inconsistent evidence of association
Type of implant	Daubert *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Kordbacheh Changi *et al*. (2019) Marrone *et al*. (2013) Rodrigo *et al*. (2018) Wada *et al*. (2019)	Inconsistent evidence of association
Augmentation	Canullo *et al*. (2016) Daubert *et al*. (2015) Derks *et al*. (2016) Dvorak *et al*. (2011) Konstantinidis *et al*. (2015) Rokn *et al*. (2017) Wada *et al*. (2019)	No evidence of association

implants that were not accessible for cleaning (odds ratio 4.9). In addition to the design, the extent of therapy, expressed by the number of implants, has been implicated as a risk factor. Individual studies have shown an association between the risk for peri-implantitis and other factors such as type of retention (screw-retained or cemented) of the prosthetic reconstruction or the dimension of the keratinized mucosa. A comprehensive analysis of the literature, however, failed to identify a consistency in these relationships (Schwarz *et al*. 2018), as the results from a number of reports are in conflict. The reasons for this discrepancy are unclear.

Concluding remarks

Epidemiology in the field of peri-implant diseases is an emerging area of research with obvious shortcomings and limitations. Nevertheless, some conclusions can be made based on the available data:

- Sound and commonly accepted case definitions of peri-implant diseases are essential for diagnosis in day-to-day clinical practice and to support a reliable epidemiological evaluation.
- The 2017 World Workshop on Classification of Periodontal and Peri-implant Diseases and

Conditions suggested clear case definitions for peri-implant health, peri-implant mucositis, and peri-implantitis that may be applied in epidemiological research as well as in day-to-day clinical practice.

- Peri-implant probing assessments and subsequent radiographic examinations are essential tools for diagnosis.
- Peri-implant mucositis and peri-implantitis are common conditions in patients provided with dental implants.
- There is evidence to support bacterial plaque as the etiological factor of peri-implant diseases.
- Peri-implantitis is preceded by peri-implant mucositis, which highlights the importance of preventive measures aiming at resolution of soft tissue inflammation.
- The main risk factors for peri-implant mucositis are poor plaque control and lack of compliance to supportive therapy as well as the design of the implant-supported prostheses.
- The main risk factors for peri-implantitis are history of periodontitis, poor plaque control, and lack of compliance to supportive therapy as well as the design and extent of the implant-supported prostheses.

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Part 3: Microbiology

Chapter 8

Dental Biofilms and Calculus

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Introduction

Dental biofilms develop on the hard surfaces of the mouth, such as teeth, dentures, and implants. These dental biofilms form part of the oral microbiome, which in turn is part of the human microbiome. Contemporary studies show that the human microbiome plays an essential role in the health and well-being of their host. Humans have evolved to have an intimate and largely beneficial relationship with these microorganisms; however, this relationship is dynamic and fragile, and a number of intrinsic and extrinsic factors can damage this exquisite balance, and such events can lead to disease.

The human microbiome

The human body is estimated to be composed of approximately 10^{14} cells, of which only half are mammalian (Sender *et al*. 2016). The other 50% are the microorganisms that form the human microbiome, which has been defined as the microbes and their collective genomes that are living in or on our body (Cho & Blaser 2012). The human microbiome plays a fundamental role in the normal development of the body and confers significant benefits to the host. For example, the human microbiome contributes to the differentiation and maturation of the host mucosa and its immune system, to the breakdown of dietary components and the generation of energy, and to the exclusion of exogenous microbes, many of which could be pathogenic (Cho & Blaser 2012; Kilian *et al*. 2016). In general, this relationship is mutually beneficial (i.e. *symbiotic*) in that the microorganisms gain a warm and nutritious environment in which to grow while delivering the benefits described above to the host. On occasions, the balance of the microbiome at a site can be disrupted which can result in this synergistic relationship breaking down, and disease can be a consequence (a process termed *dysbiosis*).

The composition of the microbiome varies at distinct surfaces on the body (e.g. the skin, mouth, digestive and reproductive tracts) despite the frequent

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

transfer of organisms between these sites; their characteristic composition reflects the significant differences in the biological and physical properties of each habitat (Wilson 2005). These properties determine which microorganisms are able to colonize successfully, and which will predominate or be only a minor component of the established microbiome. These resident microorganisms function as an interactive *microbial community* resulting in the properties of the microbiome being greater than the sum of those of the constituent species (see later). The largest and most diverse microbiomes in the human body are found in the gut, followed by the mouth. Features of the oral microbiome will now be described.

The oral microbiome

The mouth is similar to other habitats within the body in having a characteristic microbial community that provides benefits for the host. The mouth is warm and moist, and is able to support the growth of a wide range of microorganisms, including viruses, mycoplasma, bacteria, *Archaea*, fungi, and protozoa, but in which bacteria are the most numerous (Dewhirst *et al*. 2010; Marsh *et al*. 2016b). These microorganisms colonize mucosal and dental surfaces in the mouth to form three-dimensional, structurally organized multispecies communities that are termed *biofilms* (Marsh *et al*. 2011). The biofilms that form on teeth are referred to as dental plaque; dental plaque that becomes calcified is termed *calculus* (see later). The cultivable portion of the microbiome is also referred to as the *oral microbiota*. In general, desquamation ensures that the microbial load on mucosal surfaces is kept relatively low. In contrast, the mouth is a unique site in the body in that it provides non-shedding surfaces (teeth, dentures, implants) for microbial colonization. This can result in the accumulation of large numbers of microorganisms, particularly at stagnant and hard-to-clean sites, unless patients practice effective oral hygiene. Over 770 different types of microorganism (taxa or phylotypes) have been detected in samples from the mouth; of these, 57% are officially named, 13% unnamed but cultivable, and 30% are known only as currently "uncultivable" phylotypes. A single individual may harbour between 100 and 300 species. It is beyond the scope of this chapter to describe the properties of members of the resident oral microbiome, and the reader is recommended to refer to specialist texts for more detail (for example, Marsh *et al*. 2016b) or to the two curated oral 16S rRNA databases: the Human Oral Microbiome Database (HOMD; http://www.homd.org) or the Core Oral Microbiome Database (CORE; http://microbiome.osu.edu).

An appreciation of the relationship between the host and oral microbiome is critical to understand the factors that can lead to dental diseases, and for the effective clinical management of dental patients.

The mouth as a microbial habitat

The mouth supports the growth of a diverse oral microbiome; however, the composition and metabolic activity of the biofilm found on distinct surfaces in the mouth varies substantially due to differences in the biological and physical properties of each site (Fig. 8-1a). The primary source of nutrients for the oral microbiome is provided by the host, and include the proteins and glycoproteins present in saliva and gingival crevicular fluid (GCF). The metabolism of these complex host molecules requires the concerted action of consortia of bacteria (see later), in which their metabolic capabilities are combined in order to achieve complete breakdown (Marsh & Zaura 2017; Miller *et al*. 2019). The mouth is maintained at a temperature of around 35–37 °C, which is suitable for the growth of a broad range of microbes, though temperature does increase at subgingival sites during inflammation, which can favor the growth and metabolism of some putative periodontal pathogens. Although the mouth is overtly aerobic, the majority of oral bacteria are facultatively or obligately anaerobic (Marsh *et al*. 2016b). As oral bacteria exist as members of microbial communities, some anaerobic species survive in more aerobic habitats by existing in close partnership with oxygen-consuming species.

pH is a major determinant of bacterial distribution and metabolism in the mouth. The buffering activity of saliva plays a major role in maintaining the intraoral pH at around neutrality, which favors the growth of the resident oral microbiome. The pH in dental biofilms falls rapidly to below pH 5.0 following the intake of dietary sugars due to the production of acidic fermentation products (Marsh *et al*. 2016b). Many health-associated bacteria can tolerate brief conditions of low pH but are inhibited or killed by more frequent or prolonged exposures to acidic conditions (Svensater *et al*. 1997). This can result in the enrichment of acid-tolerant species, especially mutans streptococci, bifidobacteria, and lactobacilli, which are normally only minor components of dental biofilms at healthy sites, and increases the risk of dental caries. Inflammation raises the flow of GCF in the subgingival habitat; GCF introduces not only components of the host defenses, but if these fail to clear the microbial challenge, then host proteins in GCF can be exploited as a potential novel nutrient supply by some fastidious and proteolytic bacteria, giving them a competitive advantage, and this can drive deleterious shifts in the balance of the subgingival biofilm. The pH of the healthy gingival crevice is approximately 6.9, but this rises to pH 7.4 or higher during inflammation (Eggert *et al*. 1991) because of the catabolism of host proteins. Bacterial metabolism in mature oral biofilms results in sharp gradients of oxygen and pH, thereby generating a mosaic of microenvironments suitable for the growth of a variety of bacteria, enabling the coexistence of species that would otherwise be incompatible with one another.

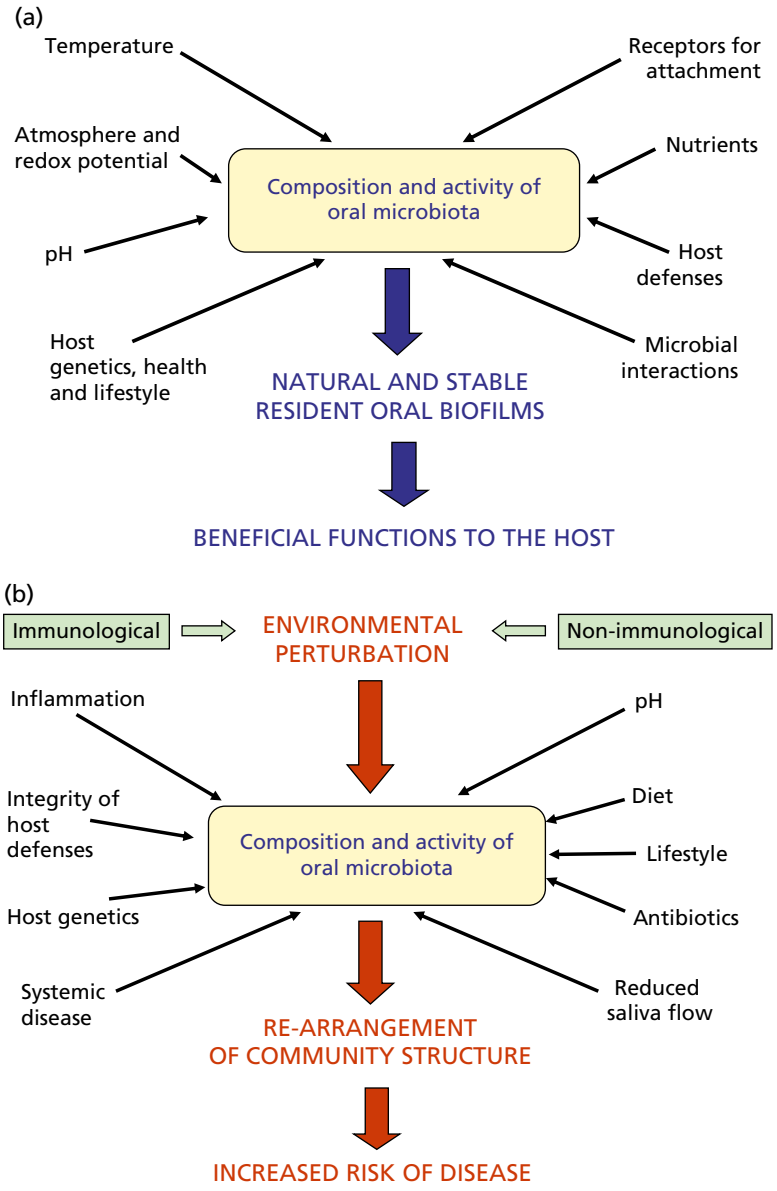


Fig. 8-1 Host factors that influence the microbial composition, activity and stability of the resident oral microbiota. (a) A number of host factors help to determine the composition and activity of the natural and beneficial oral microbiota. (b). A perturbation in a key environmental factor can disrupt the natural stability (microbial homeostasis) of the resident microbiota at a site and result in a re-arrangement of the composition and activity of the resident microbial community; such a change might predispose the site to disease. (Source: Adapted from Marsh et al. 2011.)

The mouth is richly endowed with components of both the innate (e.g. lysozyme, lactoferrin, sialoperoxidase, host defence peptides, etc.) and adaptive (secretory IgA, IgG, complement, neutrophils, etc.) immune response (Marsh *et al*. 2016a, b). The persistence of these microbial communities involves some members of the resident oral microbiota engaging in active cross-talk with the host to downregulate potential damaging proinflammatory responses (Hasegawa *et al*. 2007; Cosseau *et al*. 2008).

The lifestyle of an individual can affect the distribution and metabolism of the oral microbiota. The impact of a diet with a high frequency of intake of fermentable carbohydrates has been discussed above. Smoking may select for potential periodontal pathogens in dental biofilms, and diabetics have a higher frequency of some Gram-negative periodontal pathogens. The composition of the oral microbiome can also change with age. This can be as a consequence of a number of host-related events, including tooth eruption in early life, hormonal changes in puberty, or the waning of the immune response in old age (Marsh *et al*. 2016).

In general, once established, the microbial composition of the biofilm at a site remains stable over time (Hall *et al*. 2017), but this is a dynamic relationship. A major perturbation to the host environment, such as a substantial change in diet or an alteration to the immune status of the host, can drive deleterious shifts in the balance of the oral microbiota, and increase the risk of disease (Fig. 8-1b). Importantly, this stability, termed *microbial homeostasis*, stems

not from any biological indifference by the resident microbiota, but reflects a highly dynamic state in which the relative proportions of individual species are held in balance due to the numerous interactions, both synergistic and antagonistic (see later) (Marsh & Zaura 2017). This natural balance is maintained despite continual surveillance by the host defenses and the regular exposure of the mouth to a variety of modest environmental stresses, such as the diet, changes in saliva flow, oral hygiene, and lifestyle practices such as smoking (Fig. 8-1a). However, microbial homeostasis can breakdown on occasions if one of the key parameters affecting growth is perturbed and is sufficiently robust or regular to result in the reorganization of the composition of the biofilm, with the outgrowth of previously minor components (Fig. 8-1b). Such perturbations can be due to immunological (e.g. neutrophil dysfunction, immune suppression, etc.) or non-immunological (e.g. xerostomia, diet change, etc.) factors, and can predispose a site to disease (Marsh *et al*. 2011), and forms the basis of the "ecological plaque hypothesis" that describes the dynamic relationship between the oral microbiota and the host in health and disease (Marsh 2003).

Methods to determine the composition and function of the oral microbiome

The traditional way to determine the composition of the oral microbiome has been to use conventional culture techniques, in which samples are collected, dispersed, and then inoculated onto a range of agar plates. These agar plates can be formulated to grow the majority of bacterial or fungal species present or designed to be selective to support only specific groups of microbes. The agar plates have to be incubated at a relevant temperature (usually 37 °C), for an appropriate length of time, before the resultant microbial colonies are examined, and further tests are conducted to determine the identity of the isolate (Marsh *et al*. 2016b). This process is time consuming and relatively expensive, and it is now appreciated that <50% of the organisms present in a sample are cultivable.

Contemporary approaches use molecular (i.e. culture-independent) methods to detect and identify microorganisms (Wade & Prosdocimi 2020). These rely on detecting the nucleic acid signatures that are specific to each species, and range from targeted approaches such as PCR, DNA-DNA checkerboard systems, or microarrays, to more open-ended approaches in which all of the microbial DNA in a sample is digested, amplified, sequenced, re-assembled, and finally mapped against a reference database of relevant genomes, so that the whole diversity of the microbiota is revealed. These approaches are not without their own bias, as it can be more difficult to lyse and extract DNA from some organisms, while the primers used for amplification are not optimized for all species (Wade & Prosdocimi 2020). However, the introduction of these culture-independent approaches has changed our awareness of the richness and diversity of the oral microbiome in health and disease (Marsh *et al*. 2016b; Wade *et al*. 2016), and will lead to chairside kits and services to help diagnose oral diseases and monitor the outcome of treatment (Belibasakis *et al*. 2019).

Rather than just cataloguing the types of microorganism that are present at a site, complementary molecular approaches are also being used to monitor gene expression so as to determine the metabolic and functional activity in a sample (e.g. transcriptomics, proteomics, metabolomics). In the future, more emphasis may be placed on what microorganisms are "doing" (i.e. their function and activity) rather than providing a list of "who" is present (Takahashi 2015; Espinoza *et al*. 2018). It is likely that different combinations of species within a microbial community will perform similar tasks, and this might explain why there is not always a clear consensus when comparing the composition of dental biofilms in health and disease from different studies.

The development and composition of the oral microbiome

The mother is the main source of the oral microbiome in the newborn baby. It was originally thought that the fetus was sterile, but evidence has been emerging that some microbes (and microbial DNA) can be detected in the placenta and amniotic fluid (see Tuominen *et al*. 2019). The mode of delivery, and whether the baby is breast or formula fed, can influence the initial oral microbiome. Over time, the properties of the mouth dictate which bacteria predominate, and so a characteristic oral microbiome develops and, once teeth erupt, dental biofilms form and the microbiota becomes more diverse with increased numbers of obligate anaerobes (Mason *et al*. 2018).

Analysis of large numbers of subjects has identified a "core oral microbiome", which includes Gram-positive genera such as *Actinomyces*, *Corynebacterium*, *Gemella*, *Granulicatella*, *Rothia*, and *Streptococcus*, and Gram-negative genera including *Capnocytophaga*, *Fusobacterium*, *Haemophilus*, *Neisseria*, *Porphyromonas*, *Prevotella*, and *Veillonella* (Zaura *et al*. 2009; Chen & Jiang 2014; Diaz *et al*. 2016; Hall *et al*. 2017).

The microbial composition of dental biofilms varies at distinct sites on a tooth (fissures, approximal surfaces, gingival crevice) due to inherent differences in their anatomy and biology (Papaioannou *et al*. 2009; Marsh *et al*. 2016b) (Fig. 8-2). Fissures are influenced by saliva and the diet, and support a relatively sparse microbiota consisting of mainly saccharolytic Gram-positive bacteria, such as streptococci, while obligately anaerobic, and especially Gram-negative species, are rarely recovered (Espinoza *et al*. 2018). In contrast, the microbiota found in the healthy gingival crevice is heavily

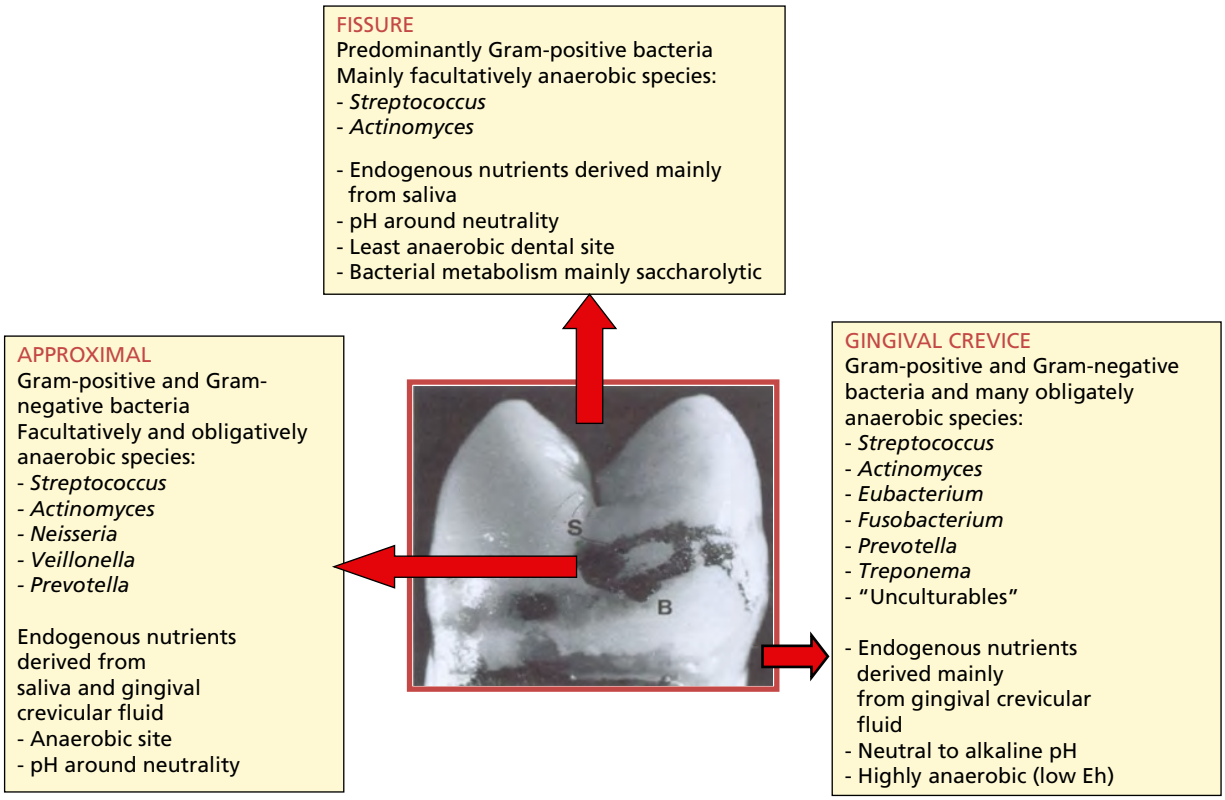


Fig. 8-2 Predominant groups of bacteria found at, and the key features of, distinct sites on the tooth surface.

influenced by GCF and has greater proportions of proteolytic and obligately anaerobic species, many of which are Gram-negative, although *Actinomyces* and *Streptococcus* spp. are also present (Abusleme *et al*. 2013). Highly nutritionally fastidious bacteria are found, including spirochetes, and many novel species are present, some of which cannot currently be grown in pure culture, and are referred to as being "unculturable". These latter bacteria have evolved to coexist with other species, and some can now be grown in co-culture with a partner organism that provides essential co-factors (Wade *et al*. 2016). Black pigmented anaerobes (e.g. *Prevotella* and *Porphyromonas* species) have an absolute requirement for hemin for growth, and these organisms can obtain this co-factor from the degradation of heme-containing host molecules present in GCF. Approximal surfaces have a microbiota that is intermediate in composition between that of fissures and the gingival crevice, and this site also harbors many obligately anaerobic species.

Dental biofilm formation

The most diverse collections of oral microorganisms are found in the biofilms on teeth (previously referred to as dental plaque) (Aas *et al*. 2005; Papaioannou *et al*. 2009; Dewhirst *et al*. 2010; Abusleme *et al*. 2013; Marsh *et al*. 2016b). Dental biofilms form via an ordered sequence of events, resulting in a structurally and functionally organized, species-rich microbial biofilm (Socransky & Haffajee 2002; Kolenbrander *et al*. 2006) (Fig. 8-3). Distinct stages in dental biofilm formation can be discerned and will now be described in more detail. It should be noted that these stages are arbitrary, as the attachment, growth, removal, and reattachment of microorganisms are continuous processes, and biofilms can undergo continual reorganization over time.

Conditioning film formation

Microorganisms rarely colonize clean enamel. Within seconds of eruption, or following cleaning, tooth surfaces become coated with a conditioning film of molecules (biologically active proteins, phosphoproteins, and glycoproteins) derived mainly from saliva (but also from GCF and bacteria) (Hannig *et al*. 2005). The properties of this conditioning film (also referred to as the "acquired pellicle") dictate which species are able to colonize.

Reversible and more permanent attachment

Initially, bacteria can be held reversibly near to the surface by weak, long-range, physicochemical forces between the electrical charge on the molecules on the pellicle-coated surface and those on the microbial cell. This reversible adhesion creates the opportunity for stronger and more permanent attachment. Molecules (adhesins) on these early bacterial colonizers (mainly streptococci such as *Streptococcus mitis*, *Streptococcus oralis*) can bind to complementary receptors in the acquired pellicle to make the

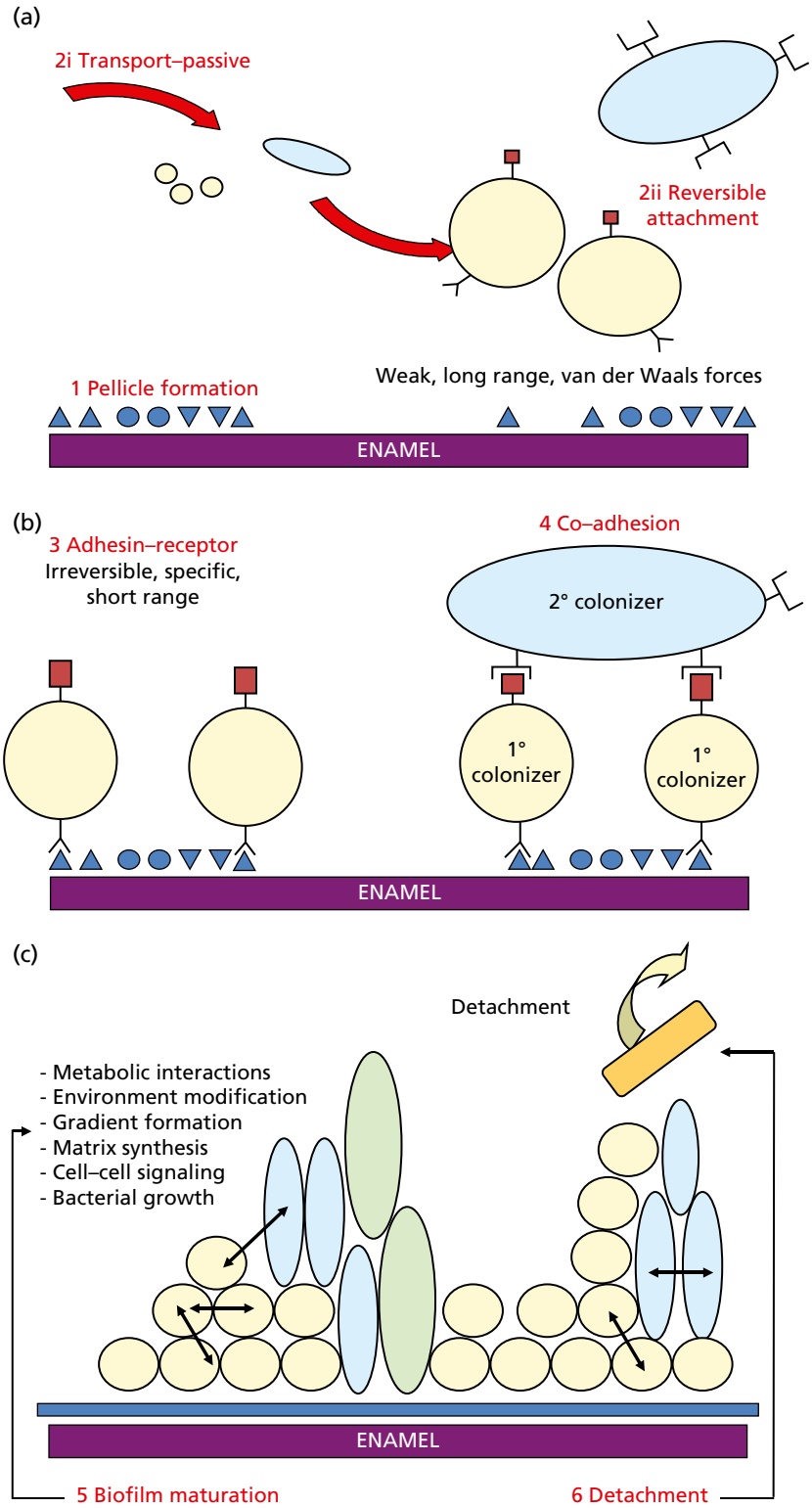


Fig. 8-3 The different stages in the formation of dental biofilms. (a) A conditioning film (the acquired pellicle) forms on a clean tooth surface (1). Bacteria are transported passively to the tooth surface (2i), where they may be held reversibly by weak, long-range forces of attraction (2ii). (b) Attachment becomes more permanent by specific stereo-chemical molecular interactions between adhesins on the bacterium and complementary receptors in the pellicle (3), and secondary colonizers attach to the already attached primary colonizers by molecular interactions (co-adhesion) (4). (c) Growth results in biofilm maturation, facilitating a wide range of intermicrobial interactions (synergistic and antagonistic) (5). On occasions, cells detach to colonize elsewhere (6). (Source: Marsh *et al*. 2016b. Reproduced with permission from Elsevier.)

attachment stronger (Busscher *et al*. 2008; Nobbs *et al*. 2011). Individual species can use multiple adhesins. In Gram-positive bacteria, several families of surface proteins can act as adhesins, including serine-rich repeat, antigen I/II, and pilus families, while in Gram-negative bacteria, autotransporters, extracellular matrix-binding proteins, and pili function as adhesins (Nobbs *et al*. 2011).

Co-adhesion

Once attached, the pioneer colonizers start to multiply. The metabolism of these early attached bacteria modifies the local environment, for example, by making it more anaerobic following their consumption of oxygen and the production of "reduced" end products of metabolism. Molecules on the surface of the attached pioneer species can act as receptors for the more fastidious secondary (and even later) colonizers, by a process termed co-adhesion or co-aggregation. Over time, waves of co-adhesion results in the composition of the biofilm becoming more diverse (microbial succession) (Kolenbrander *et al*. 2006) (Fig. 8-4). A key organism in dental biofilm development is *Fusobacterium nucleatum*. This species can co-adhere to most oral bacteria, and acts as an important bridging organism between early and later colonizing species. Co-adhesion may also ensure that bacteria are co-located with other organisms with complementary metabolic functions.

Plaque maturation

Some attached bacteria synthesize extracellular polymers (the biofilm matrix) that can consolidate the attachment of cells to the dental surface and to each other. These polymers include soluble and insoluble glucans, fructans, proteins, and extracellular DNA. This matrix is more than a mere scaffold for the biofilm; the matrix can bind and retain molecules, including enzymes, and also retard the penetration of charged molecules into the biofilm (Allison 2003; Vu *et al*. 2009; Marsh *et al*. 2011). The close proximity of different species provides the opportunity for numerous interactions (Marsh & Zaura 2017) that can be synergistic or antagonistic; some examples of these include:

- *Nutritional interactions*. Food chains develop between different species (in which the end product of metabolism of one organism is used as a primary nutrient by secondary feeders), and these interactions can increase in complexity to form "food webs" among numerous species (Marsh & Zaura 2017). The catabolism of structurally complex host macromolecules such as glycoproteins found in saliva and GCF requires metabolic cooperation by several species. These interactions increase the metabolic efficiency of the microbial community, and also create numerous interdependencies (Periasamy & Kolenbrander 2010; Marsh *et al*. 2011) which promote stability and resilience in the composition of the biofilm (Rosier *et al*. 2018).
- *Cell–cell signaling and gene transfer*. Bacteria in biofilms communicate with one another using a variety of systems including by quorum sensing in a cell density-dependent manner via small diffusible molecules (Miller & Lamont 2019). For example, Gram-positive bacteria secrete small peptides to coordinate gene expression among cells of a similar species (Suntharalingam & Cvitkovitch 2005), while other bacterial species communicate using autoinducer-2 (AI-2) (Kolenbrander *et al*. 2002), which may function across both Gram-positive and Gram-negative bacteria. Several putative periodontal pathogens (*F. nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*) secrete a signal related to AI-2 (Fong *et al*. 2001; Frias *et al*. 2001). In *Streptococcus mutans*, quorum sensing is mediated by a competence stimulating peptide (CSP) (Li *et al*. 2002), which also increases the transformation frequency of recipient cells. Lysed cells in biofilms could act as donors of DNA, thereby increasing the opportunity for horizontal gene transfer in dental plaque. The recovery of resident and pathogenic bacteria from the nasopharynx with penicillin resistance genes showing a common mosaic structure confirms that gene transfer occurs among streptococci and between *Neisseria* species.
- *Antagonism*. Bacteria produce molecules that can be inhibitory to neighboring cells, thereby providing an organism with a competitive advantage when competing for space and nutrients. The molecules include hydrogen peroxide, bacteriocins organic acids, and enzymes (Marsh *et al*. 2016b).

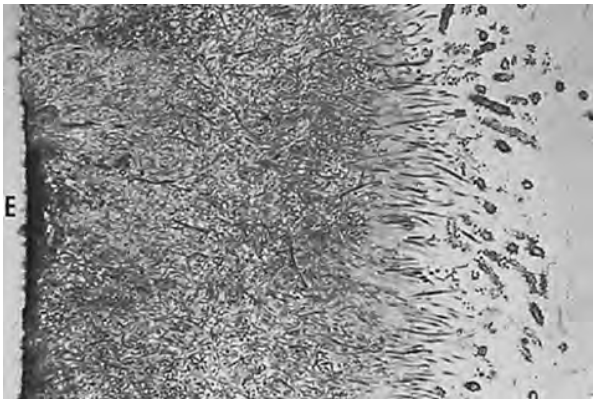


Fig. 8-4 Semi-thin section of a supragingival biofilm on enamel (E) which has been dissolved prior to sectioning. Magnification ×750. (Source: Listgarten 1976.)

As the dental biofilm grows and matures, it becomes spatially and functionally organized (Zijnge *et al*. 2010; Mark Welch *et al*. 2016, 2019). The metabolism of bacteria creates gradients in factors that are critical to microbial growth resulting in a mosaic of microenvironments. Such vertical and horizontal stratification can explain how organisms with apparently contradictory growth requirements can coexist at the same site. Oxygen-consuming species may be located in the outer regions of the biofilm with obligate anaerobes persisting in deeper layers, and consumers and producers of certain metabolites, such as lactate, tend to be near each other (Mark Welch *et al*. 2016, 2019). Clear structural features can be observed microscopically as the biofilm develops.

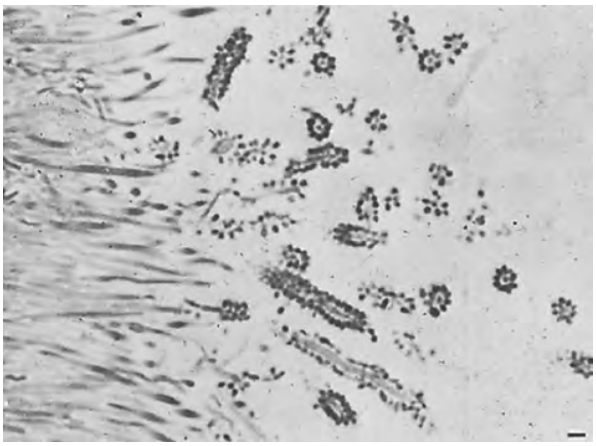


Fig. 8-5 "Corn-cob" formations seen at the biofilm surface in Fig. 8-4. Magnification ×1300. Bar 1 µm. (Source: Listgarten 1976.)

Initially, microcolonies of probably single species develop, and these merge with other species. These structures can grow to form "stacks" and "palisades" of cells, and channels have been observed that penetrate from the outer surface into the depths of the biofilm, which may aid movement of molecules in and out of the biofilm. These channels are often filled with extracellular polymers. Subgingival biofilms have a complex architecture, with distinct tooth-associated and epithelial cell-associated biofilms, with a less dense zone of organisms between the two (Socransky & Haffajee 2002). Characteristic cell associations can be seen in mature dental biofilms, such as "corn-cob" (in which coccal-shaped cells attach along the tip of filamentous organisms; Fig. 8-5) and "test-tube brush" (rod-shaped bacteria protruding perpendicularly from bacterial filaments) formations (Zijnge *et al*. 2010). Corn-cobs can form between diverse groups of microorganisms, including streptococci adhering to a central axis of yeast cells or hyphae, and of streptococci attached to *Corynebacterium matruchotii*, and between *Veillonella* spp. and *Eubacterium* spp. Lactobacilli formed the central axis of some of the "test-tube brushes", with organisms such as *Tannerella*, *F. nucleatum*, and *Synergistes* spp. radiating from this central cell.

Detachment

Bacteria can detect adverse changes in environmental conditions and detach from biofilms so as to be able to colonize more favorable environments elsewhere. Some species produce proteases that degrade the adhesin that is retaining them within the biofilm.

The significance of a biofilm and community lifestyle for microorganisms

The vast majority of microorganisms in nature, including in the mouth, are found attached to surfaces as biofilms. The ability to attach to, and be retained at a surface, is a fundamental survival strategy for most microorganisms, as otherwise they would be lost from habitats such as the mouth by the flow of saliva and swallowing. There would be little scientific or clinical interest if the properties of (1) biofilms were similar to those of conventional planktonic (liquid culture) cells, and (2) if the capabilities of microbial communities were merely the sum of those of the constituent species. However, bacterial gene expression alters markedly when cells form a biofilm, resulting in a radically different phenotype, while the binding of bacteria to specific host receptors can trigger significant changes in host cell gene expression (Marsh 2005).

Furthermore, several potential benefits arise when species interact to function as a microbial community (Caldwell *et al*. 1997; Shapiro 1998; Marsh & Bowden 2000) including:

- a broader habitat range for growth. For example, the metabolism of early colonizers alter the local environment, making conditions suitable for attachment and growth of later (and more anaerobic) species;
- an increased metabolic diversity and efficiency, so that complex host molecules that are recalcitrant to catabolism by individual organisms can be broken down by microbial consortia;
- an enhanced tolerance of environmental stress, antimicrobial agents, and the host defenses. Neighboring cells of a different species can produce neutralizing enzymes (β-lactamase, IgA protease, catalase, etc.) that protect inherently susceptible organisms from inhibitors (Brook 1989). As mentioned earlier, horizontal gene transfer is also more efficient in multispecies biofilms (Molin & Tolker-Nielsen 2003; Wilson & Salyers 2003). Microbial communities can also afford physical protection from phagocytosis for cells deep within a spatially organized consortium (Costerton *et al*. 1987; Fux *et al*, 2005);
- an enhanced ability to cause disease. Abscesses are examples of polymicrobial infections whereby organisms that individually cannot cause disease are able to do so when they are present as a consortium (pathogenic synergism) (van Steenbergen *et al*. 1984); this property is pertinent to periodontal diseases where individual species may play particular roles in overcoming the host defenses and driving inflammation.

In this way, microbial communities display emergent properties, i.e. the properties of the community are more than the sum of its component populations.

An important clinical consequence of both the structural and functional organization of multispecies biofilms is their reduced susceptibility to antimicrobial agents (Gilbert *et al*. 1997, 2002; Ceri *et al*. 1999; Stewart & Costerton 2001). An organism

growing on a surface can be many times more tolerant of an antimicrobial agent than the same cells grown planktonically (Stewart & Costerton 2001), with older biofilms being most recalcitrant. Several mechanisms contribute to the reduced susceptibility of biofilms to antimicrobial agents (Stewart & Costerton 2001; Gilbert *et al*. 2002). Microorganisms conventionally become resistant due to mutations affecting the drug target, to the presence of efflux pumps that prevent accumulation of the agent, or to the production of neutralizing enzymes, etc., but, significantly, even sensitive bacteria become less susceptible to antimicrobials when growing on a surface. The structure of a biofilm may restrict the penetration of the antimicrobial agent; charged inhibitors can bind to oppositely charged polymers that make up the biofilm matrix (diffusion-reaction theory), and so only inhibit organisms at the surface, leaving cells relatively unaffected in deeper layers. The biofilm matrix can also bind and retain neutralizing enzymes (e.g. β-lactamase) at concentrations that could inactivate an antibiotic or inhibitor (Allison 2003). Bacteria growing as a biofilm display a novel phenotype, and this could reduce their sensitivity to inhibitors because the drug target may be modified or not expressed, or the organism may use alternative metabolic strategies for growth. Bacteria grow only slowly under nutrient-depleted conditions in an established biofilm and, as a consequence, are much less susceptible than faster dividing cells. In addition, it has also been proposed that the environment in the depths of a biofilm may be unfavorable for the optimal action of some drugs (Gilbert *et al*. 2002). The increased tolerance of some biofilms to antibiotics may also be due to a subpopulation of "persister" organisms that are specialized survivor cells (Keren *et al*. 2004).

Benefits to the host of a resident oral microbiota.

The host has a sophisticated array of host defenses provided by both the innate and adaptive arms of the immune system, the primary function of which is to protect tissues against microbial colonization and invasion. Despite these host defenses, the host has evolved over millennia to support a complex resident microbiome and, at first sight, this might appear paradoxical (the "commensal paradox") (Henderson & Wilson 1998). It is now apparent that the resident microbiome confers considerable benefit to the host, and that these natural microbial residents are essential for the normal development of the physiology, nutrition, and defenses of the host (Marsh 2000; Wilks 2007) (Fig. 8-6).

Complex biological mechanisms permit a synergistic coexistence between the host and the resident microbiota, while enabling the host to retain the capacity to respond to exogenous microbial challenges. The host is not indifferent to the presence of the diverse microbial communities that reside on its surfaces. There is active cross-talk between the resident microbiome and host in order to effectively maintain this constructive relationship. The host has evolved to tolerate resident microorganisms without initiating a damaging inflammatory response, while also being able to mount an efficient defense against pathogens (Devine *et al*. 2015). Pathogenic and non-pathogenic bacteria may initiate different intracellular signaling pathways and innate immune responses in epithelial cells (Canny & McCormick 2008; Hooper 2009; Neish 2009). Certain oral streptococci have been shown to suppress epithelial cell cytokine expression (Hasegawa *et al*. 2007; Peyret-Lacombe *et al*. 2009). *Streptococcus salivarius*

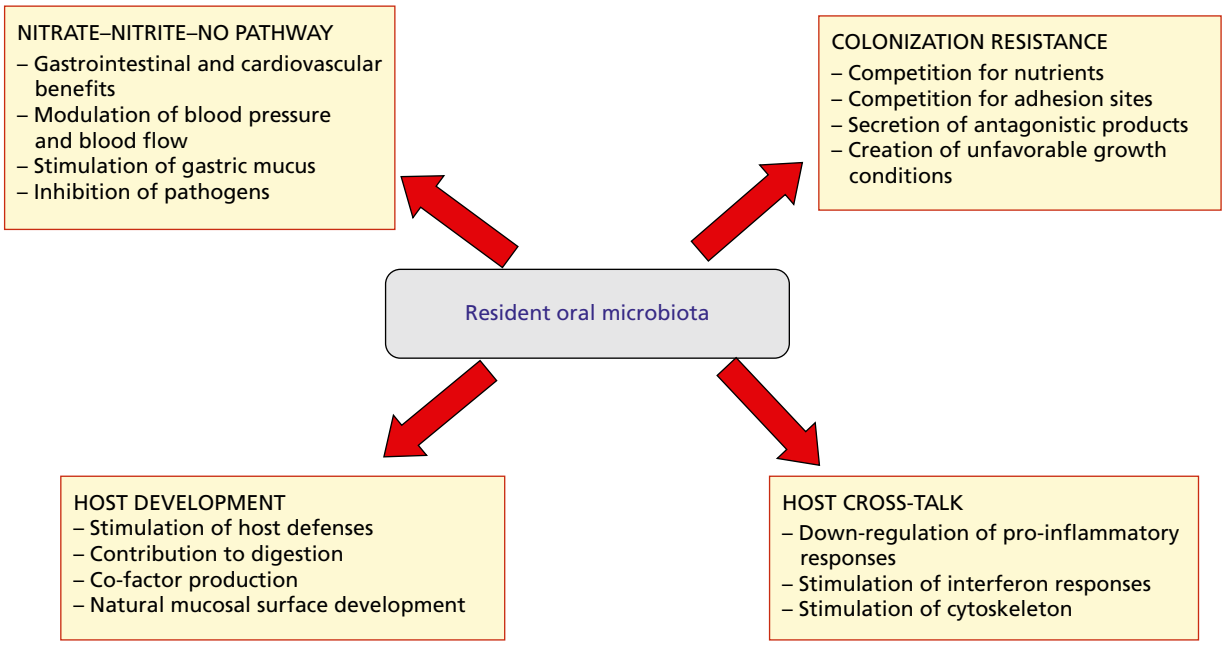


Fig. 8-6 Beneficial functions of the resident oral microbiota. (Sources: Marsh & Bowden 2000; Wilks 2007.)

K12 not only downregulated epithelial cell inflammatory responses by inhibiting the NF-κB pathway, but also actively stimulated beneficial pathways, including type I and II interferon responses, and exerted significant effects on the cytoskeleton and adhesive properties of the host cell (Cosseau *et al*. 2008). The "commensal communism" paradigm proposes that our oral microbiome and mucosa form a unified "tissue" in which host-microbe "cross-talk" is finely balanced to ensure microbial survival and prevent the induction of damaging inflammation (Henderson & Wilson 1998).

One of the principal benefits of the existence of a resident and beneficial microbiota at a site is the ability to prevent colonization by exogenous (and often pathogenic) microorganisms. This property, termed "colonization resistance" (Van der Waaij *et al*. 1971) or "pathogen exclusion", is due to various properties of resident microbes including their: (1) more effective attachment to host receptors; (2) greater efficacy to catabolize and grow on endogenous nutrients; (3) creation of unfavorable growth conditions to discourage attachment and multiplication of invading organisms; and (4) production of antagonistic substances (hydrogen peroxide, bacteriocins, etc.) that are inhibitory to exogeneous species. Colonization resistance can be impaired by factors that compromise the integrity of the host defenses or perturb the stability of the resident microbiota, such as the side-effects of cytotoxic therapy, lifestyle issues, or the long-term use of broad spectrum antibiotics (Johnston & Bodley 1972). For example, the latter can suppress the resident bacterial oral microbiota permitting overgrowth by previously minor populations of oral yeasts. Attempts to boost colonization resistance using replacement therapy (in which resident organisms are deliberately re-implanted), for example, after periodontal therapy (Teughels *et al*. 2007), or by the use of probiotics (Devine & Marsh 2009) or prebiotics (molecules that improve the growth of members of the beneficial resident microbiome) (Slomka *et al*. 2017), are being explored.

Resident oral bacteria play an important role in maintaining many important aspects of the gastrointestinal and cardiovascular systems, via the metabolism of dietary nitrate. Approximately 25% of ingested nitrate (present in beets and green vegetables) is secreted in saliva where facultatively anaerobic oral resident bacteria (such as *Rothia* and *Neisseria* species) reduce nitrate to nitrite. Nitrite affects a number of key physiological processes including the regulation of blood flow, blood pressure, gastric integrity, and tissue protection against ischemic injury. Nitrite can be further converted to nitric oxide in the acidified stomach, and this has antimicrobial properties, and contributes to defenses against enteropathogens and in the regulation of gastric mucosal blood flow and mucus formation (Hezel & Weitzberg 2015; Vanhatalo *et al*. 2018).

Biofilms on implant surfaces

In the oral cavity, biofilms with a distinct composition may be encountered attached to different solid oral surfaces, including teeth, prosthetic devices, and dental implants (Belibasakis *et al*. 2015). The formation and maturation of biofilms on dental implant surfaces can trigger inflammation of the peri-implant tissues and lead to peri-implant diseases, such as mucositis and peri-implantitis, in a similar manner as the subgingival biofilm is associated with gingivitis and periodontitis (Lang *et al*. 2011). The use of experimental multispecies *in vitro* and *in vivo* biofilm models has shown that biofilm formation on implant titanium surfaces follows similar kinetics as on tooth surfaces, with an initial formation of an acquired pellicle due to adsorption of salivary components, mainly proteins, followed by specific adherence by *Streptococcus*, *Veillonella*, and *Actinomyces* species, and then by progressive colonization of secondary and tertiary colonizers, such as *F. nucleatum* and *P. gingivalis*, respectively (Schmidlin *et al*. 2013; Sanchez *et al*. 2014).

Despite the similarities between biofilms on tooth and implant surfaces, some specific features might be attributed to the specific implant surface characteristics. The current knowledge on biofilms on implant surfaces is mainly based on experiments under controlled conditions, where bacterial populations are known. These conditions, however, are very different from those found in the oral cavity, where the microbial communities may vary according to the different specific microenvironments and hence, the effect of implant surfaces on biofilm development *in vivo* still needs to be elucidated.

With the aim of improving the dynamics of osseointegration, different modifications in the implant surface microtopography increased its predictability and reduced the time to achieve implant stability and clinical success. These modifications have involved changes in their surface physicochemical characteristics, mainly its roughness, hydrophobicity, surface free energy and wettability, resulting in most of the currently commercialized implant systems with titanium or titanium alloys having a moderately rough microsurface topography (Albrektsson & Wennerberg 2004).

These complex surface topographies, which clearly enhance implant osseointegration, may also facilitate the development of complex biofilms and impair their cleanability. Recent *in vivo* (Xing *et al*. 2015; Al-Ahmad *et al*. 2016; Ribeiro *et al*. 2016; de Melo *et al*. 2017) and *in vitro* biofilm models (Schmidlin *et al*. 2013; Sanchez *et al*. 2014; Violant *et al*. 2014) have studied the impact of implant surface characteristics on biofilm formation, demonstrating that the physicochemical properties of the surface, and mainly its roughness, significantly affected early bacterial colonization, biofilm formation, and maturation. Studies evaluating biofilms on implants and abutments,

with different surface composition and topography, have shown that there is a correlation between surface roughness and viable biomass within the biofilm (Hahnel *et al*. 2015) as well as increased bacterial colonization and diversity (Teughels *et al*. 2006; Xing *et al*. 2015). Other studies, however, have reported that surface free energy or the biomaterial manufacturing, rather than roughness, may be the key factor determining initial bacterial adhesion (Mabboux *et al*. 2004; Violant *et al*. 2014). Using an *in vitro* multibacterial species biofilm (Fig. 8-7), significant differences in biofilm thickness and three-dimensional structure, were reported when comparing titanium and zirconium surfaces (Sanchez *et al*. 2014). In most of these experimental studies, however, although the early bacterial colonization is significantly influenced by different implant surface characteristics, once developed on the implant surface, mature biofilms are quite similar, in terms of the number of bacteria and thickness or three-dimensional structures when comparing different surface microtopographies (Schmidlin *et al*. 2013; Zhao *et al*. 2014; Sanz *et al*. 2017) (Fig. 8-8).

Most of these experimental models did not use dental implants but rather specimens, such as discs or slabs reproducing the implant surface microtopography, but lacking the macroscopic and topographic characteristics such as the threads that may also influence bacterial colonization. Recent studies (Bermejo *et al*. 2019a) have demonstrated different patterns of bacterial colonization and biofilm deposition depending on whether the biofilm is in the peak of the thread or the valley between threads (Fig. 8-8).

The use of scanning electron microscopy (SEM) has shown the presence of mature biofilms in moderate-roughness titanium implant surfaces with bacterial communities forming large stacks or towers distributed between broad channels, all surrounded with a

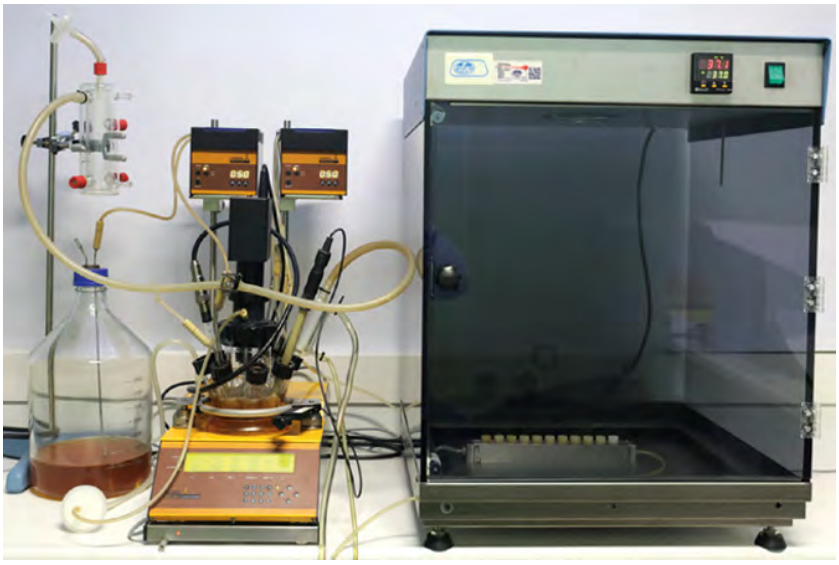


Fig. 8-7 *In vitro* biofilm system consisting of a bio-generator, gas pumps, and the Robbins-device where implants are tested.

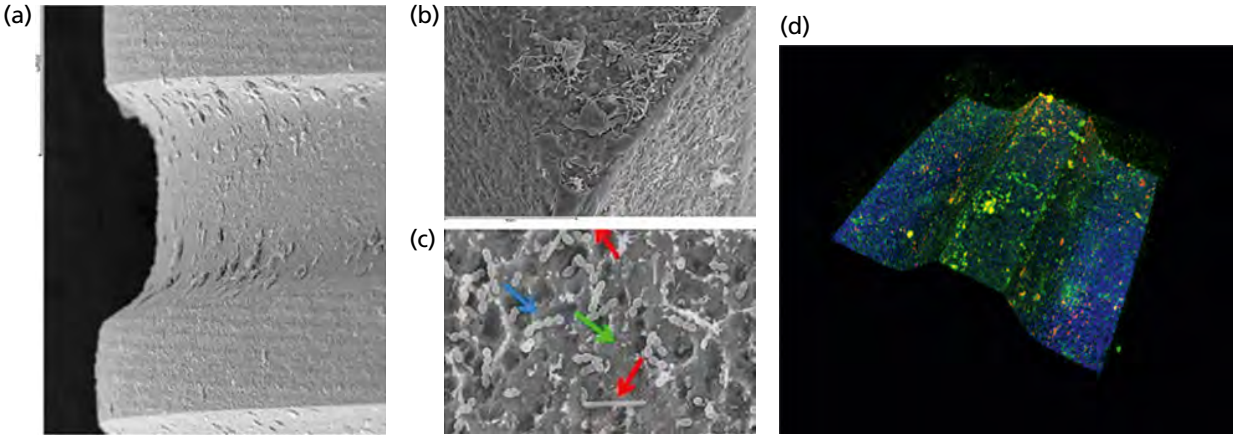


Fig. 8-8 (a) SEM image depicting biofilm deposition on the implant surface. (b) Biofilm deposits with a higher density in the valleys between threads. (c) Higher magnification demonstrating different bacterial morphotypes deposited on the implant surface (arrows). (d) Confocal laser microscope image depicting higher density of viable bacteria (stained green) in the valleys between threads on the implant.

thick extracellular matrix covering the whole implant surface. When compared with smooth titanium surfaces or zirconia surfaces, the main difference is the presence of higher numbers of bacteria within their characteristic pores, which may have implications, not only for the accumulation of larger numbers of bacteria, but also with the likely greater difficulty for their removal (Schmidlin *et al*. 2013; Ferreira Ribeiro *et al*. 2016; Bermejo *et al*. 2019b) (Fig. 8-9).

Dental calculus

Dental calculus or tartar represents mineralized bacterial biofilm, although calculus formation can be induced in germ-free animals as a result of precipitation of mineral salts originating from saliva (Theilade 1964). Supragingival calculus is located coronal to the gingival margin (Fig. 8-10a), whereas subgingival calculus is found apical to the gingival

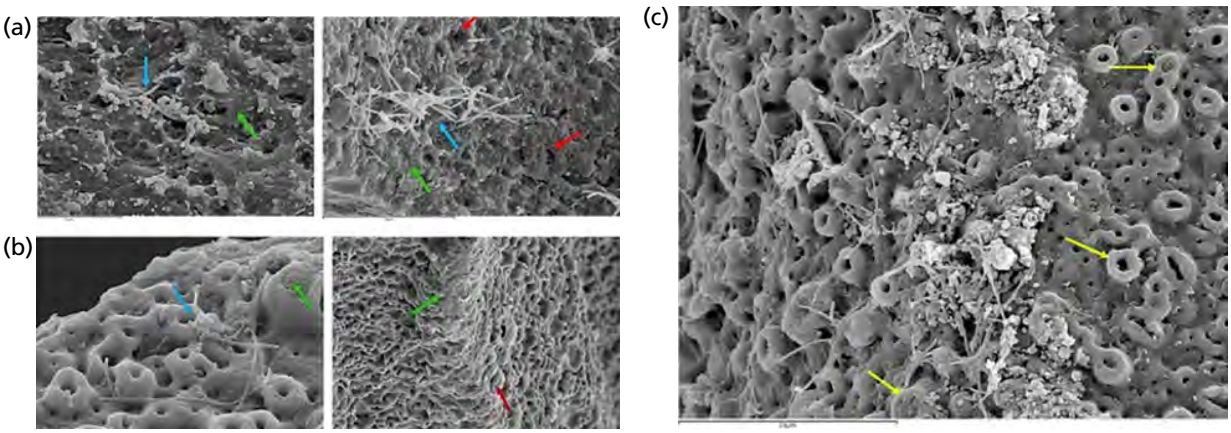


Fig. 8.9 (a) SEM images depicting biofilm deposition on the implant surface in implants with minimal roughness microtopography. (b) SEM images depicting biofilm deposition on the implant surface in implants with moderate roughness microtopography. (c) Higher magnification demonstrating different bacterial morphotypes inside the highly porous microtopography on implants with moderate roughness.

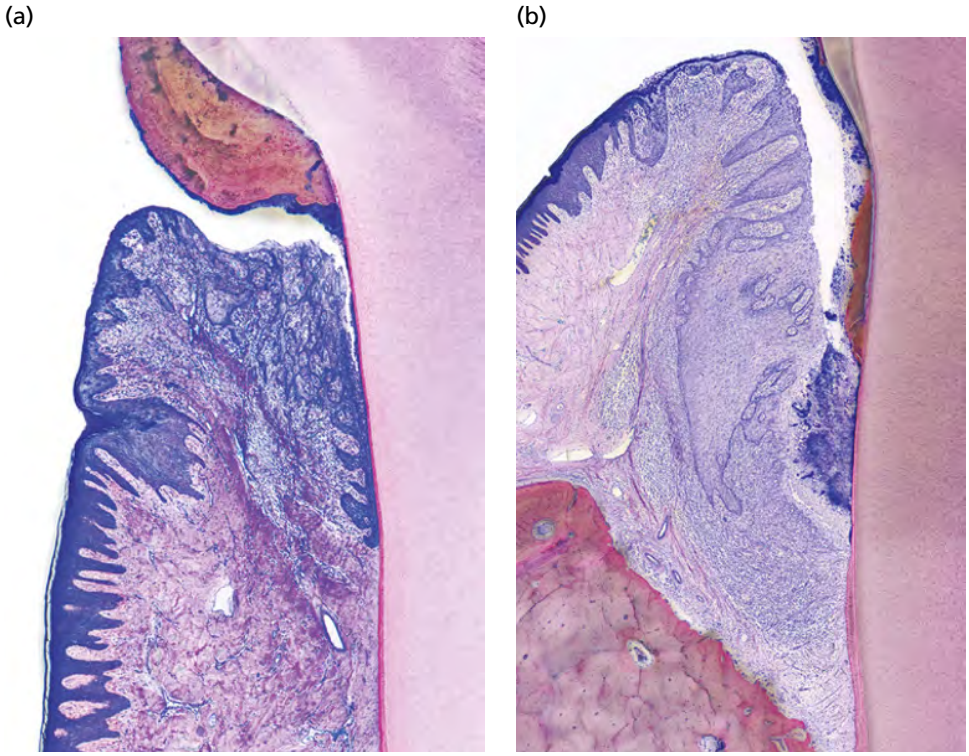


Fig. 8-10 (a) Supragingival calculus adhering to enamel and the root surface of a tooth from a dog. An initial gingival pocket and a slight gingival inflammation has developed. (b) Subgingival calculus on the root of a tooth from a dog with a periodontal pocket. Note the inflamed gingival tissue and bone loss. For both supra- and subgingival calculus, uncalcified dental biofilm extends apically and forms a calculus-free zone between the apical termination of calculus and the apical extension of the pockets. Undecalcified ground sections.

margin (Fig. 8-10b). Supra- and subgingival calculus both have characteristic features. It should be noted that calculus continually harbors a viable bacterial biofilm (Zander *et al*. 1960; Theilade 1964; Schroeder 1969).

Clinical appearance and distribution

Supragingival calculus appears as a creamy-whitish to dark yellow or even brownish mass of moderate hardness (Fig. 8-11). The degree of calculus formation is not only dependent on the amount of bacterial biofilm present, but also on the secretion of the salivary glands. Hence, supragingival calculus is predominantly found adjacent to the excretion ducts of the major salivary glands, such as the lingual aspect of the mandibular anterior teeth for the submandibular glands and the buccal aspect of the maxillary first molars, whereas the parotid gland ducts open into the oral vestibule.

Subgingivally, calculus may be found by tactile exploration only, since it is usually not visible to the naked eye. Occasionally, subgingival calculus may be visible on dental radiographs provided that the deposits are of sufficient mass (Fig. 8-12). Small deposits or residual deposits following root instrumentation may barely be visualized radiographically. If the gingival margin is pushed open by a blast of air or retracted by a dental instrument, a brownish-to-black calcified hard mass with a rough

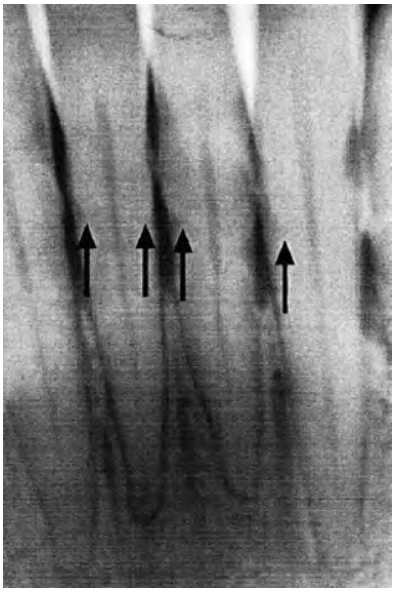


Fig. 8-12 Subgingival calculus may be visible (arrows) on radiographs if abundant deposits are present.

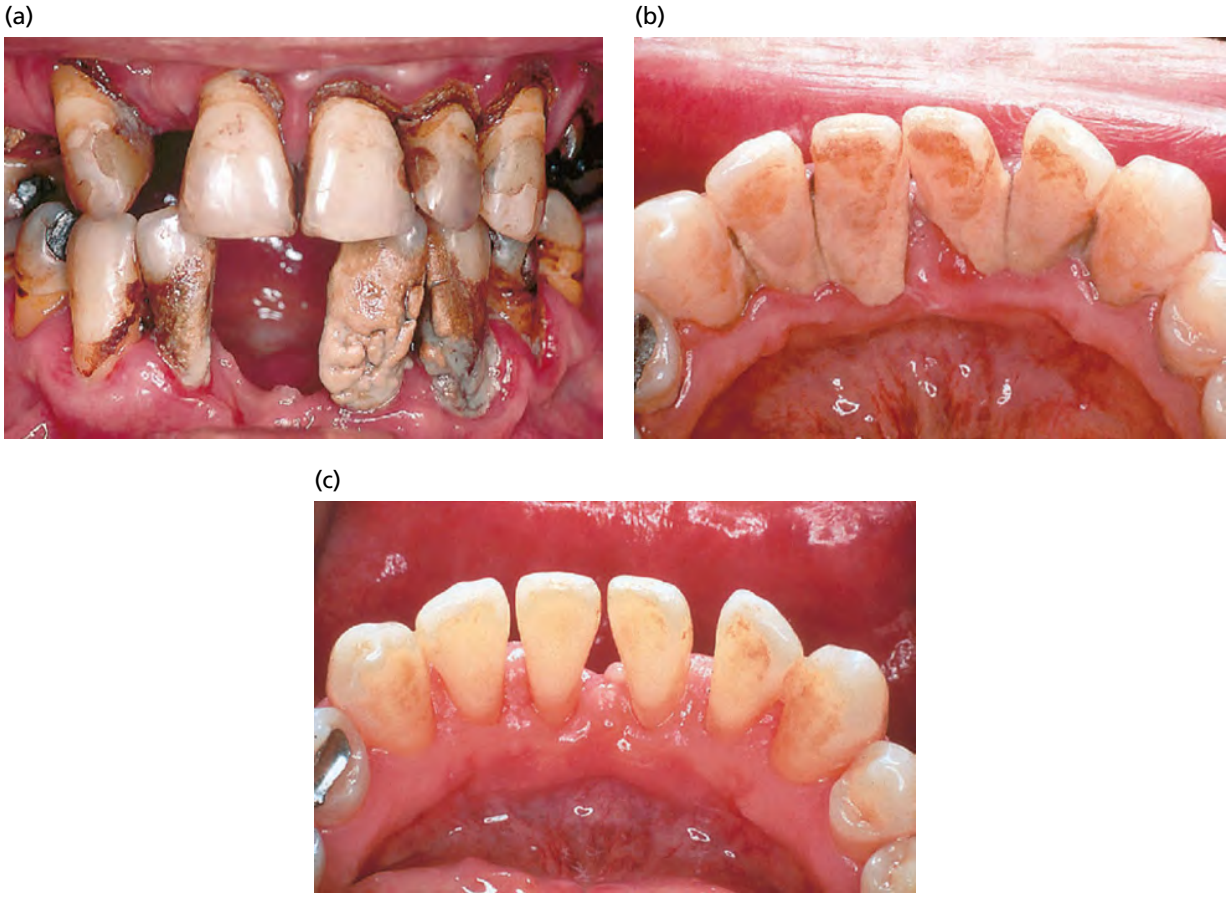
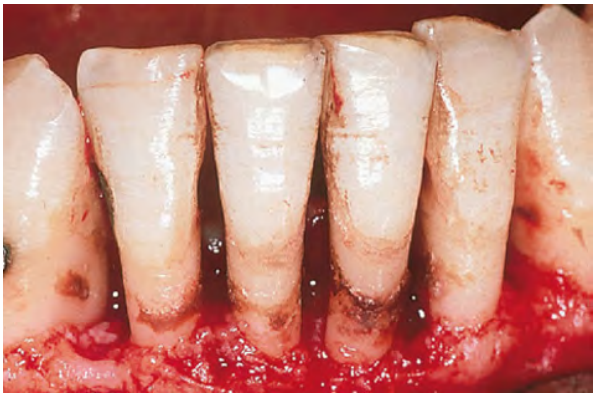


Fig. 8-11 Abundance of supragingival calculus deposits. (a) Gross deposits as a result of long-term neglect of oral hygiene. Two mandibular incisors have been exfoliated. (b) Supragingival biofilm usually covering the lingual aspect of mandibular incisors. Note the intense inflammatory reaction adjacent to the deposits. (c) Same patient and region as in (b) following removal of the calculus. The gingival tissues demonstrate healing.

surface may become visible (Fig. 8-13). Again, this mineralized mass reflects predominantly bacterial accumulations mixed with products from GCF and blood. Consequently, subgingival calculus is found in most periodontal pockets, usually extending from the cementoenamel junction to close to the bottom of the pocket. However, a band of approximately 0.5 mm is usually found coronal to the apical extension of the periodontal pocket (Fig. 8-14). This zone appears to be free of mineralized deposits owing to the fact that GCF is exuding from the periodontal soft tissues and acting as a gradient against microbial accumulation. This calculus-free zone can also be seen in histological sections (see Fig. 8-10a, b). Like supragingival calculus, subgingival calculus also provides an ideal substrate for bacterial adhesion (Zander *et al*. 1960; Schroeder 1969).

Biofilm mineralization varies greatly between and within individuals and also within the different regions of the oral cavity. There is great variability in the formation rate of both bacterial biofilm and in dental calculus. In some subjects, the time required for the formation of supragingival calculus is 2 weeks, at which time the deposit may already contain approximately 80% of the inorganic material found in mature calculus (Fig. 8-15) (Mühlemann & Schneider 1959; Mandel 1963; Mühlemann & Schroeder 1964). In fact, evidence of mineralization may already be present after a few days (Theilade 1964). Nevertheless, the formation of dental calculus with the mature crystalline composition of old calculus may require months to years (Schroeder & Baumbauer 1966).

(a)



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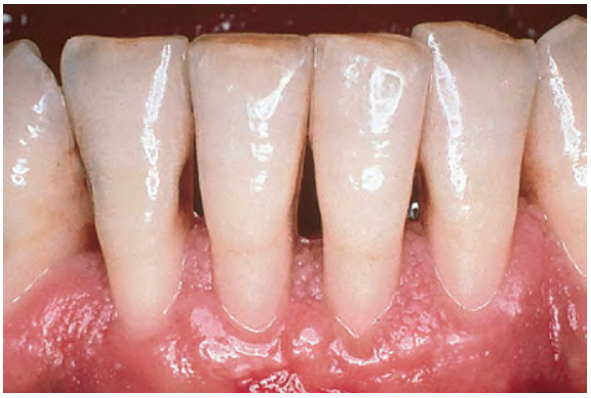

Fig. 8-13 (a) Subgingival calculus presents as a black–brownish hard mass if the gingival margin is retracted or reflected during a surgical procedure. (b) Healing of the site following removal of all hard deposits.

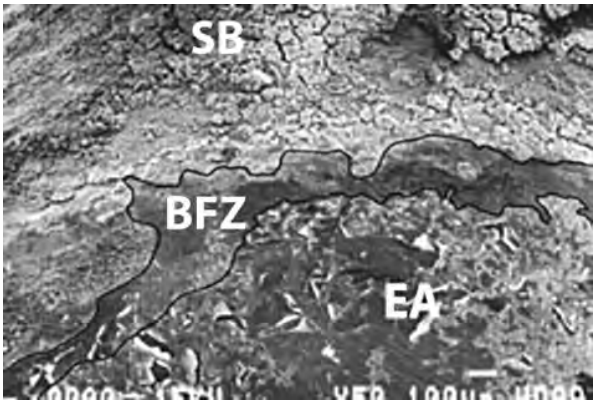

Fig. 8-14 Biofilm- and calculus-free zone coronal to the epithelial attachment. BFZ, biofilm-free zone; EA, remnants of junctional epithelium; SB, subgingival bacterial biofilm.

Calculus formation and structure

In humans, the formation of calculus is always preceded by the development of a bacterial biofilm. The intermicrobial biofilm matrix and the bacteria themselves provide the matrix for calcification, which is driven by the precipitation of mineral salts. Supragingival biofilm becomes mineralized due to the precipitation of mineral salts present in saliva, whereas subgingival biofilm mineralizes due to the presence of mineral salts in the inflammatory exudate passing through the pocket. It is, therefore, evident that subgingival calculus represents a secondary product of infection and not a primary cause of periodontitis.

Mineralization starts at crystallization foci in the intermicrobial (intercellular) matrix and on the bacterial walls (Fig. 8-16), and eventually proceeds inside the bacteria (Fig. 8-17) (Zander *et al*. 1960). The detection of lactate dehydrogenase, alkaline and acid phosphatase activities, and various extracellular matrix proteins in the biofilm suggests that

Fig. 8-15 Seven-day-old calcified biofilm. Observe the isolated calcification centers indicated by the black areas (von Kossa stain).

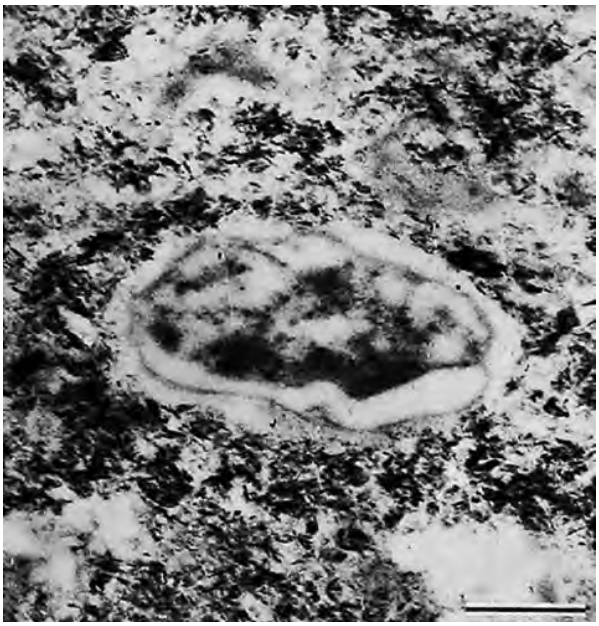

Fig. 8-16 Thin section of old biofilm. A degenerating organism is surrounded by intermicrobial matrix in which initial mineralization has begun with the deposition of small needle-shaped electron-dense apatite crystals. Magnification ×26 500. Bar: 0.5 µm. (Source: Zander *et al*. 1960. Reproduced with permission from Sage.)

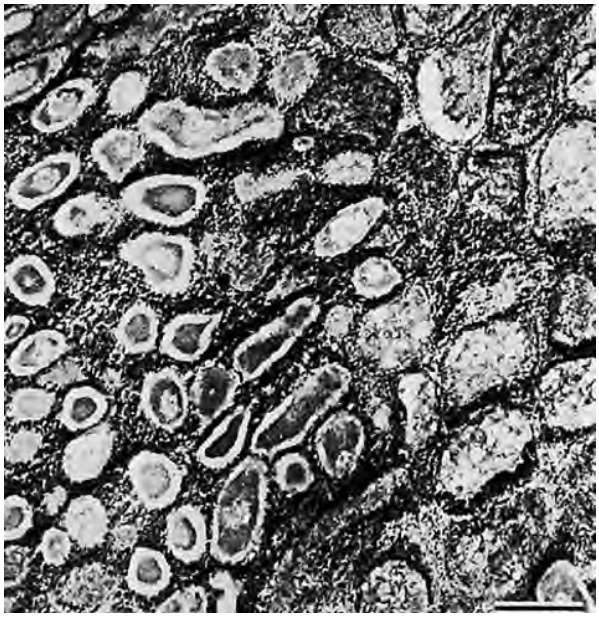

Fig. 8-17 Thin section of old mineralizing biofilm. The intermicrobial matrix is totally calcified, and many microorganisms show intracellular crystal deposition. Magnification ×9500. Bar: 1 µm. (Source: Theilade 1964.)

calculus formation is not merely a passive mineralization process. Bacterial enzymes (Friskopp & Hammarström 1982), calcium phosphate supersaturation, cell membrane-associated constituents, and inactivation of nucleation inhibitors (Jin & Yip 2002) may all be involved in the initiation and regulation of biofilm calcification. Osteopontin and bone sialoprotein (Fig. 8-18), two non-collagenous extracellular matrix proteins involved in the mineralization of bone and cementum, have been immunodetected in human calculus, but not in the unmineralized dental biofilm. Osteopontin and bone sialoprotein are present in blood plasma, and osteopontin has been identified in GCF and saliva (Ogbureke & Fisher 2004; Sharma & Pradeep 2007). Their presence in the biofilm matrix and at the surface of bacteria suggests an involvement in the regulation of mineralization.

The progression of mineralization in an incremental pattern from the inner zones of the bacterial biofilm outward may produce concentric rings, called Liesegang rings, that reflect successive phases of mineralization. Furthermore, the presence of numerous mineralization foci, from which mineralization spreads and which partially coalesce, may leave some unmineralized areas and thus account for the porous nature of calculus, whose cavities and channels are filled with uncalcified biofilm (see Fig. 8-15).

Attachment to tooth surfaces and implants

Dental calculus generally adheres tenaciously to tooth surfaces; consequently, the removal of subgingival calculus may be difficult. The reason for this firm attachment to the tooth surface is the fact that the pellicle beneath the bacterial biofilm also calcifies. This, in turn, results in an intimate contact with enamel (Fig. 8-19), cementum (Fig. 8-20), or dentin crystals (Fig. 8-21) (Kopczyk & Conroy 1968; Selvig 1970). In addition, the surface irregularities are also penetrated by calculus crystals and, hence, calculus is virtually locked onto the tooth. This is particularly the case on exposed cementum, where small pits and irregularities occur at the sites of the previous insertion of Sharpey's fibers (Bercy & Frank 1980). Uneven root surfaces may be the result of carious lesions and small areas of cementum may have been lost due to resorption, when the periodontal ligament was still invested into the root surface (Moskow 1969). Under such conditions, it may become extremely difficult to remove all calculus deposits without sacrificing some hard tissues of the root.

Although some irregularities may also be encountered on dental implant surfaces, the attachment to commercially pure titanium is generally less intimate than to root surface structures. This in turn means that calculus may be chipped from dental implants (Fig. 8-22) without detriment to the implant surface (Matarasso *et al*. 1996). Excess cement at the crown–abutment interface has been associated with peri-implant disease (Pauletto *et al*. 1999; Gabski *et al*. 2008; Wilson 2009). The rough surface of the cement may provide a biofilm/calculus retention site, which can lead to peri-implant disease (Lang *et al*. 2004). Overhang at such sites (Fig. 8-23) may impede calculus removal. After removal of excess cement, clinical and endoscopic signs of peri-implant disease disappear in the majority of cases (Wilson 2009).

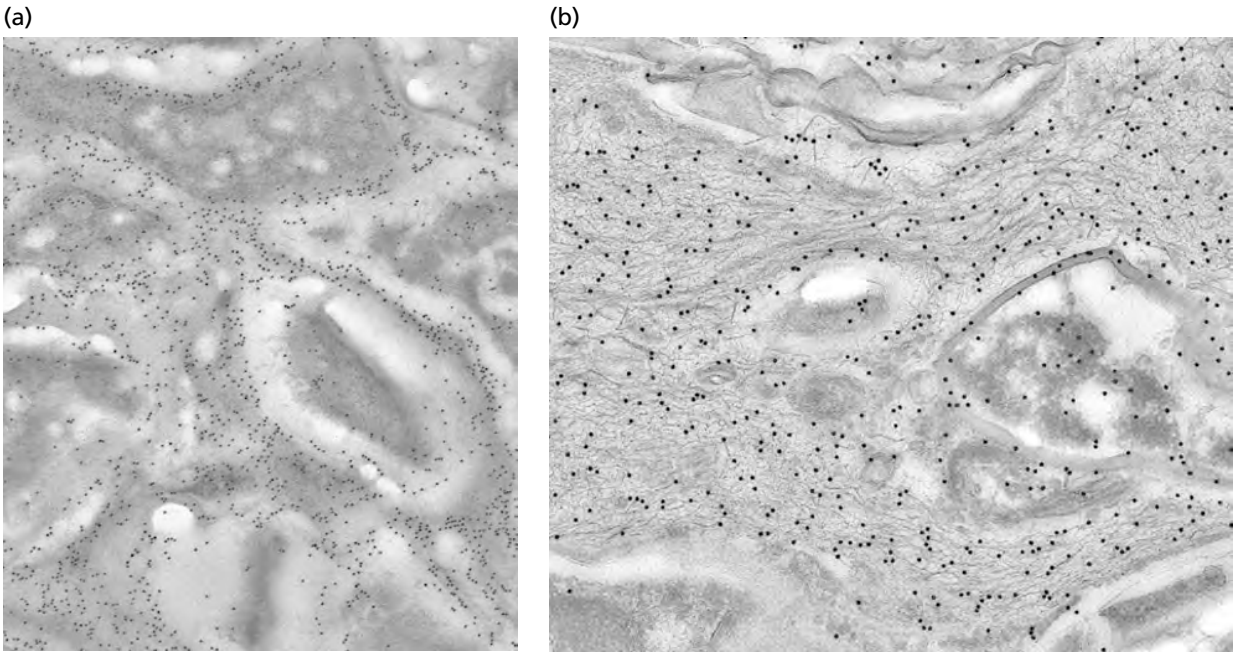

Fig. 8-18 Immunolabeling of calculus on a human tooth root with an antibody against bone sialoprotein. (a) Predominant gold particle labeling of the bacterial cell walls in the inner portion of calculus. (b) Labeling over extensive intermicrobial filamentous matrix. Ultrathin sections viewed under the transmission electron microscope.

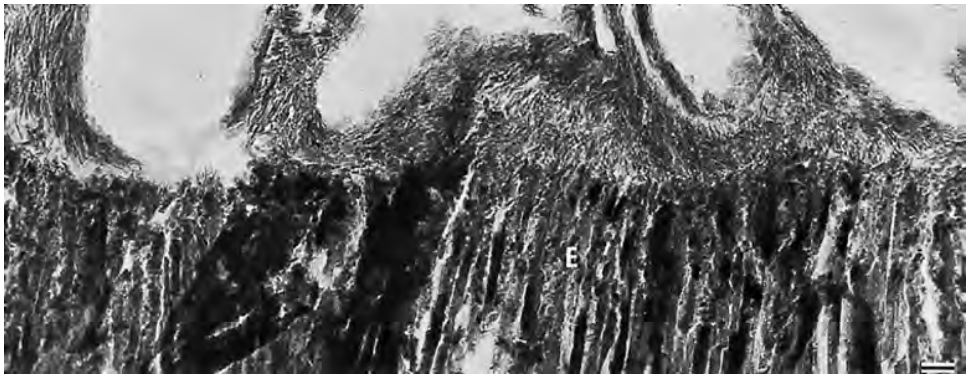

Fig. 8-19 Thin section of enamel surface (E) with overlying calculus. The enamel and calculus crystals are in intimate contact, and the latter extends into the minute irregularities of the enamel. Magnification × 37 500. Bar: 0.1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

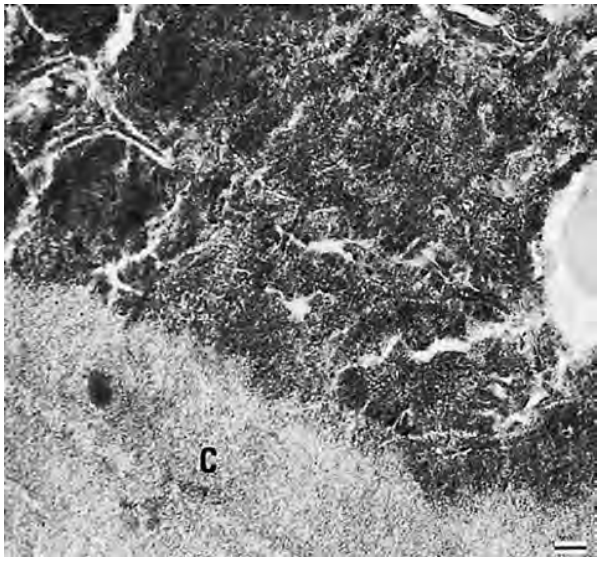

Fig. 8-20 Thin section of cementum surface (C) with overlying calculus. The calculus is closely adapted to the irregular cementum and is more electron dense and therefore harder than the adjacent cementum. To the right, part of an uncalcified microorganism. Magnification ×32 000. Bar: 0.1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

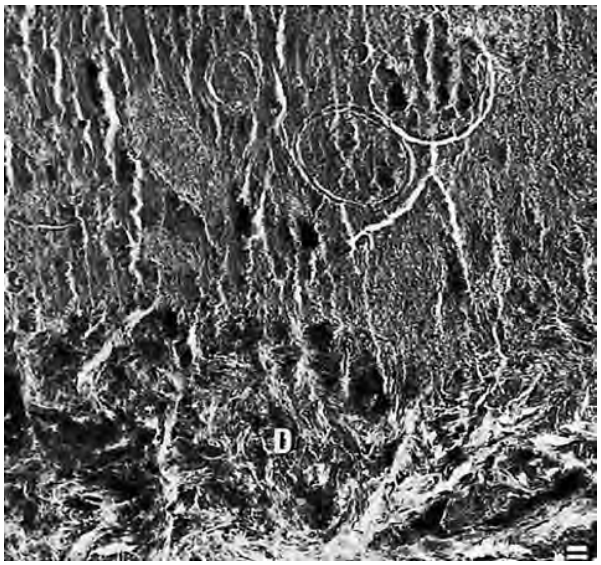

Fig. 8-21 Thin section of dentin (D) surface with overlying calculus. The interface between the calculus and dentin cannot be precisely determined because the calculus crystals fill the irregularities of the dentin surface, which is devoid of cementum as a result of a previous scaling of the root surface. The circular profiles in the calculus completely surround calcified bacteria. Magnification ×19 000. Bar: 1 µm. (Source: Selvig 1970. Reproduced with permission from John Wiley & Sons.)

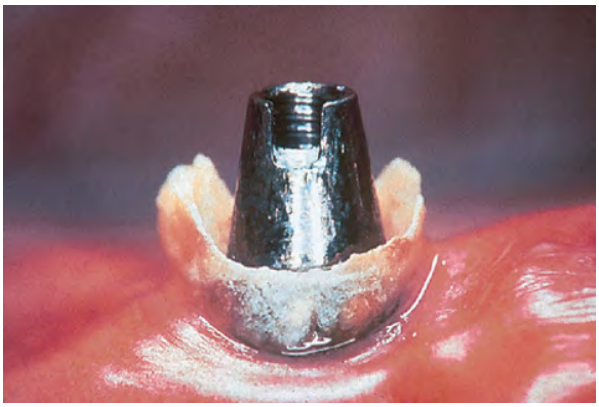

Fig. 8-22 Calculus deposit on an oral implant in a patient without regular maintenance care.

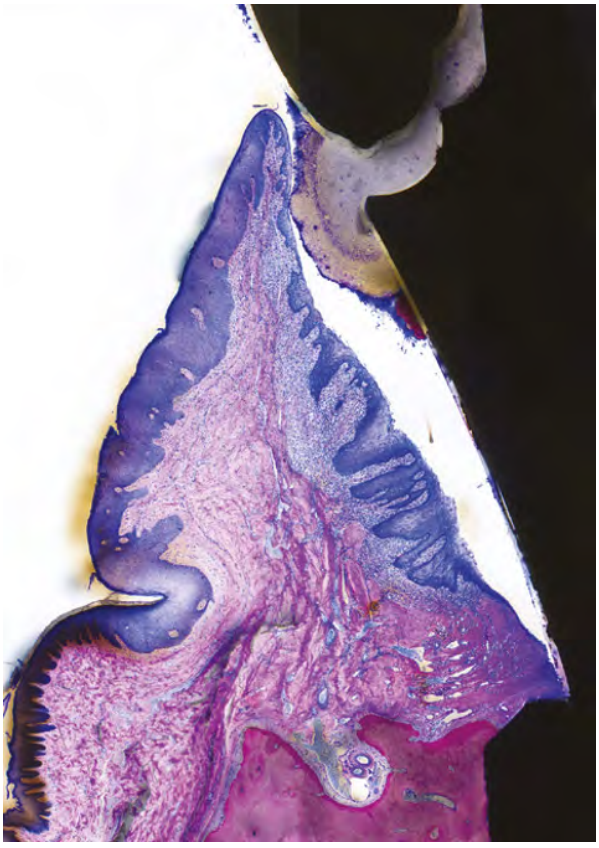

Fig. 8-23 Excess cement at the abutment–crown interface provides an ideal substrate for biofilm and calculus deposition and retention. Bacterial biofilm covers the entire surface of the cement, whereas calculus is present apical to the cement overhang. Detachment of the epithelium indicates pocket formation. The detachment of the apical-most portion of the epithelium, however, may represent an artifact due to histologic processing. Undecalcified ground section.

Calculus composition

Recent and old calculus consists of four different crystals of calcium phosphate (for reviews, see Schroeder 1969; Jepsen *et al*. 2011):

1. $CaH(PO_4) \times 2H_2O$ = brushite (B)
2. $Ca_4H(PO_4)_3 \times 2H_2O$ = octa calcium phosphate (OCP)
3. $Ca_5(PO_4)_3 \times OH$ = hydroxyapatite (HA)
4. $\beta\text{-}Ca_3(PO_4)_2$ = whitlockite (W).

X-ray diffraction studies suggest that mineralization begins with the deposition of OCP and dicalcium phosphate dehydrate (DCPD), followed by less soluble HA and W (Rowles 1964; White 1997). Supragingival calculus is clearly built up in layers and shows a great heterogeneity from one layer to another with regard to mineral content (37% on average, range of 16%–51%) (Kani *et al*. 1983; Friskopp & Isacsson 1984; Sundberg & Friskopp 1985). Subgingival calculus appears somewhat more homogeneous, since it is built up in layers of equally high mineral density (58% on average, range of 32%–78%) (Kani *et al*. 1983; Friskopp & Isacsson 1984).

Clinical implications

Although strong associations between calculus deposits and periodontitis have been demonstrated in experimental (Wærhaug 1952, 1955) and epidemiological studies (Lövdal *et al*. 1958), it has to be realized that calculus is always covered by an unmineralized layer of a viable bacterial biofilm. It has been debated whether or not calculus may exert a detrimental effect on the soft tissues owing to its rough surface. However, it has clearly been established that surface roughness alone does not initiate gingivitis (Wærhaug 1956). It could even be observed that a normal epithelial attachment with hemidesmosomes and a basal lamina forms on calculus if its surface was disinfected using chlorhexidine (Fig. 8-24) (Listgarten & Ellegaard 1973). Furthermore, it has been demonstrated that autoclaved calculus may be encapsulated in connective tissue without inducing marked inflammation or abscess formation (Allen & Kerr 1965).

These studies clearly exclude the possibility of dental calculus being a primary cause of periodontal diseases. Calculus seems to have a secondary effect by providing a surface configuration conducive to further biofilm accumulation. Nevertheless, calculus deposits may develop in areas that are difficult to access for oral hygiene or may, depending on their size, jeopardize proper oral hygiene practices. Calculus may also amplify the effects of bacterial biofilm by keeping the bacterial deposits in close contact with the tissue surface, thereby influencing both bacterial ecology and tissue response (Friskopp & Hammarström 1980).

Well-controlled animal (Nyman *et al*. 1986) and clinical (Nyman *et al*. 1988; Mombelli *et al*. 1995) studies have shown that the removal of subgingival biofilm on top of subgingival calculus results in healing of periodontal lesions and the maintenance of healthy gingival and periodontal tissues, provided that the removal is meticulous and performed on a regular basis. One of these studies (Mombelli *et al*. 1995) clearly demonstrated that microbiota composition and clinical parameters following the diligent and complete removal of subgingival biofilm on top of mineralized deposits after chipping off gross

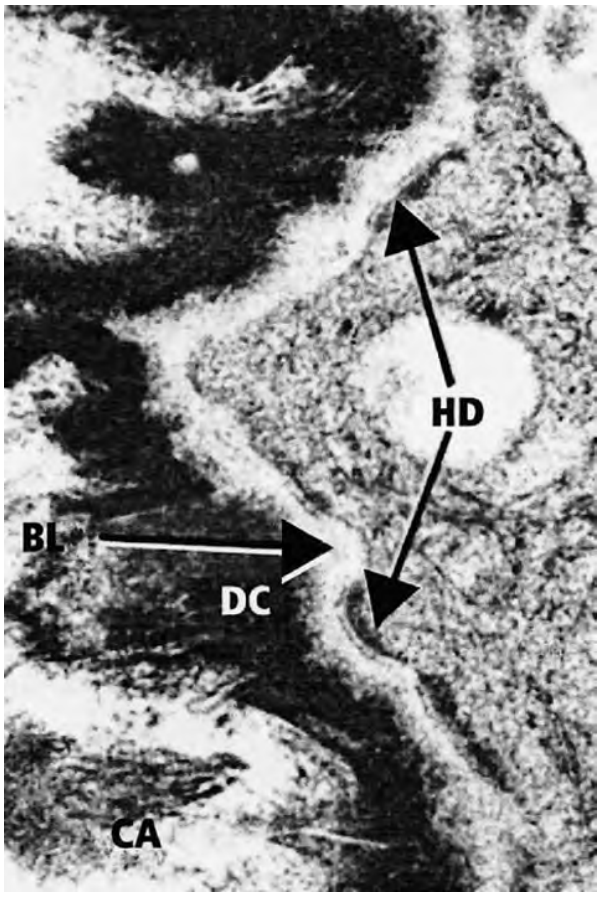

Fig. 8-24 Hemidesmosomal attachment of junctional epithelium on dental calculus in the absence of bacteria following application of chlorhexidine. BL, basement lamina; CA, calculus; DC, dental cuticle; HD, hemidesmosomes. Magnification ×32 000. (Source: Data from Listgarten & Ellegaard 1973.)

amounts of calculus were almost identical to those obtained with routine removal of subgingival calculus by root surface instrumentation. Again, it has to be realized that meticulous supragingival biofilm control guarantees the depletion of the supragingival bacterial reservoir for subgingival recolonization. These studies have clearly elucidated the role of subgingival calculus as a biofilm-retaining factor. Likewise, calculus formation on implant surfaces resulted in the development of peri-implant diseases. Anti-infective surgical peri-implantitis treatment, which included calculus removal, followed by supportive therapy was effective in the long-term in the majority of patients and implants (Berglundh *et al*. 2018; Heitz-Mayfield *et al*. 2018).

The presently available techniques used to remove deposits on the root surface cannot completely eliminate all calculus from diseased root surfaces. Factors such as anatomy, probing depth, instruments, and experience influence the efficacy (Jepsen *et al*. 2011). Some agents have been proven to reduce calculus formation (Jepsen *et al*. 2011). However, their effects appear to be limited to supragingival calculus and complete prevention cannot be achieved with them.

Conclusions

The mouth supports the establishment of diverse communities of microorganisms. These communities, and those present at other habitats in the body, play an active and critical role in the normal development of the host and in the maintenance of health. Clinicians need to be aware of the beneficial functions of the resident oral microbiome, so that treatment strategies are focused on the control rather than the elimination of these natural biofilms. Oral care practices should attempt to maintain plaque at levels compatible with health in order to retain the beneficial properties of the resident oral microbiota while preventing microbial excesses that increase the risk of dental diseases. Dental calculus represents mineralized bacterial biofilm. It is always covered by unmineralized viable bacterial biofilm, and hence, does not directly come into contact with the gingival tissues. Calculus, therefore, is a secondary etiologic factor for periodontitis. Its presence, however, makes adequate biofilm removal impossible and prevents patients from performing proper biofilm control. It is the most prominent biofilm-retentive factor that has to be removed as a basis for adequate periodontal and peri-implant therapies and prophylactic activities.

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Chapter 9

Periodontal and Peri-Implant Infections

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Periodontal infections

Introduction

Our mucosal surfaces are colonized by complex communities of microorganisms, or microbiota, which are uniquely adapted to the different environmental niches in the human body. This microbiota is composed of distinct and specialized microorganisms which are characteristic of the respective niche, for example, the mouth, the gastrointestinal, or the genitourinary tract (Fig. 9-1). Collectively, the microbiota on our mucosal surfaces and other anatomical locations in the body comprise the human microbiome which has become an area of intensive investigation in recent years because of the recognition that the balance between these organisms and the human host plays a fundamentally important role in our biology, the maintenance of our health, and the development of disease.

Of all the environmental niches in the human body, the oral cavity provides an optimal habitat for the growth of bacteria: a stable temperature, constant moisture, an abundant supply of nutrients and, uniquely, the hard surfaces of the teeth which provide a stable site for microbial attachment and accumulation. It is recognized that the different communities of organisms that colonize the distinct anatomical regions of the mouth (the tongue, the buccal and lingual mucosae, the supra- and subgingival surfaces of the teeth and so on) perform an important function in resisting colonization by other, potentially harmful organisms. In addition, recent evidence demonstrates that the oral microbiome may have other, unexpected benefits to the human host.

For example, dietary nitrate, concentrated in saliva to ten-fold the levels in the circulation, is reduced by members of the oral commensal microbiota (e.g. *Neisseriae* and *Rothia* spp.). The resulting microbially produced nitrite is swallowed and either absorbed through the gastrointestinal tract as nitrite or reduced to nitric oxide in the stomach where it contributes to gastric mucosa integrity and provides protection against colonization of the stomach by infectious agents (Kemmerly & Kaunitz 2013). Moreover, the absorbed nitrite in the circulation acts as a substrate for

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

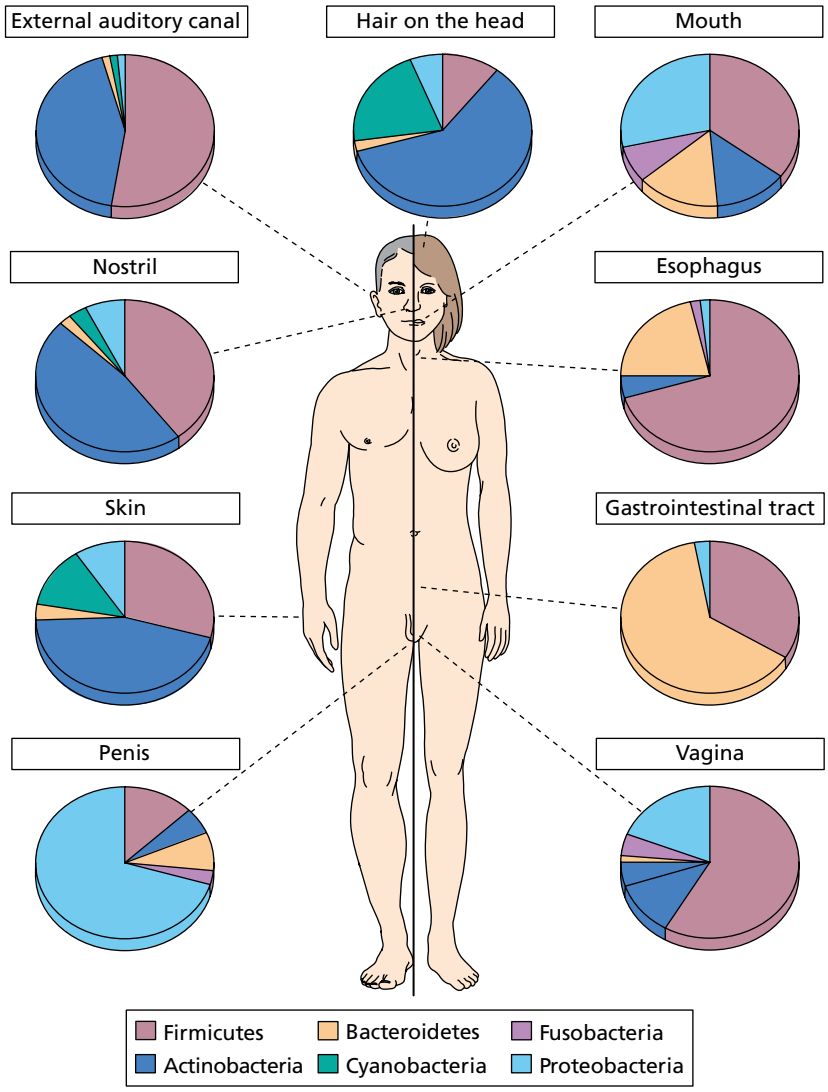


Fig. 9-1 The relative abundances of the six dominant bacterial phyla in each of the different body sites: the external auditory canal, the hair on the head, the mouth, the esophagus, the gastrointestinal tract, the vagina, the penis, the skin, and the nostril. Reprinted from Spor *et al*. (2011) with permission

the production of the potent vasodilator, nitric oxide, which in turn promotes vascular smooth muscle relaxation, lowering of blood pressure, and inhibition of platelet function (Koch *et al*. 2017). As higher-order animals including humans are not capable of reducing nitrate to nitrite, this enzymatic reduction step by the oral microbiome provides a good example of how the bacteria in the human mouth are important contributors to overall health. Indeed, it is suggested that interventionist approaches to positively manipulate this so-called "entero-salivary nitrate system" may provide a convenient means to counteract cardiovascular disease at a population level (Gee & Ahluwalia 2016).

Although there are clear health benefits from a harmoniously balanced oral microbiome and the human host, it is also clear that an imbalance in this relationship occurs in disease (Frank *et al*. 2011) and this is particularly evident in diseases of the periodontium. The evolutionary forces which shaped the development of a calcified dentition of animals have introduced a developmental weak spot from the perspective of infectious disease: nowhere else in the human body is the normally contiguous epithelial barrier of our mucosal surfaces breached by a solid structure which permits the development of a microbial biofilm in direct contact with the adjacent soft tissues. The defense to this challenge, which has co-evolved with the development of teeth, is a sophisticated set of specialized anatomical features supplemented by innate immune and inflammatory responses. The tooth surface at the gingival margin actively develops a dental plaque biofilm which is normally tolerated by the adjacent tissue. However, in disease there are significant alterations to this community of organisms likely driven by and contributing to the enhanced inflammatory conditions. The study of these communities, their transformation from health to disease, so called dysbiosis, and the role of this microbiota in the etiopathogenesis of periodontal pathology are described in the following sections.

Microbiological techniques to study the periodontal microbiota

Our understanding of the periodontal microbiota has undergone sequential stepwise changes over time following the introduction and application of increasingly more sophisticated and higher throughput methods for bacterial characterization and identification (Fig. 9-2). Analysis of the human oral microbiome extends back through history to the very first microscopic observations of bacteria over three centuries ago and continues apace to this day through the application of high throughput DNA sequencing techniques. The more recent techniques provide a description of this microbiota in extraordinary detail which was hitherto impossible. This century old tradition of oral microbiological analysis has placed our knowledge of the bacterial communities of the mouth at the very leading edge of our understanding of the human microbiome. From these investigations, it is now recognized that the oral microbiome is highly complex: approximately 1000 different microorganisms are able to stably colonize the human mouth. Any one individual may harbor 200–300 microbial species and the composition of this community is a personalized signature which differentiates them from other individuals. However, in the case of diseases involving a complex microbial etiology, where the fundamental basis is one of dysbiosis, or perturbation of a normal commensal microbiota, the description of the infectious challenge is more demanding. Here, the accuracy of the description is intimately linked to the effectiveness of the technology available to quantitatively and qualitatively determine the composition of a complex microbial mixture.

The initial description of bacterial cells in the oral cavity was performed by Antonie van Leeuwenhoek, who in 1676 used the newly invented microscope, to describe the "animacules" in the biofilms from human teeth. In the intervening period our understanding of the complexity, site specificity, and environmentally driven nature of these microbial communities has expanded with each technological advance in microbial identification and classification. Advances accompanied the introduction of standardized cultural techniques on solid media, the development of anaerobic culture systems, the introduction of non-cultural techniques for bacterial identification and the use of molecular phylogeny through nucleic acid analyses using DNA:DNA hybridization, the polymerase chain reaction (PCR), Sanger DNA sequencing, and the more recent developments in high throughput pyro-sequencing and metagenomics (Wade 2011). These cultural and non-cultural investigations have now culminated in the development of the Human Oral Microbiome Database (http://www.homd.org) which lists all bacterial species found in the human mouth (Dewhirst *et al*. 2010).

The progress made in describing the etiological agents of infectious diseases in the late nineteenth and early twentieth century naturally led to a search for the causative organisms involved in periodontal infections. However, these investigations were restricted by the techniques available for either visual inspection of subgingival samples or by the relatively primitive cultural techniques that had been developed at this early phase of the discipline of microbiology. As a result of the inability to accurately define the etiological agent(s) of the disease, in contrast to the great strides being made elsewhere in describing the causative organisms in the major, mono-specific infectious diseases, there was a loss of impetus in microbiological research into periodontal infections in the early decades of the 20th century. A summary of these early descriptions was summarized by Socransky and Haffajee (1994).

Introduction of anaerobic techniques

A major breakthrough in our understanding of the complexity of the periodontal microbiota was achieved through the introduction of methods which allowed the laboratory culture of anaerobic microorganisms. The low oxygen levels in the subgingival biofilm are highly permissive for the growth of obligately anaerobic bacteria and hence a significant fraction of the total periodontal microbiota had been largely undetected in previous microbiological investigations conducted under aerobic conditions. This technological advance included the use of anaerobic roll tubes and anaerobic jars which could be flushed with oxygen-free gases and then sealed to prevent the access of air. More latterly, anaerobic chambers were developed which enabled the culture of anaerobic bacteria on both solid and liquid media in a relatively spacious, low oxygen environment periodically flushed with a mixture of nitrogen, carbon dioxide, and hydrogen.

These studies were pioneered by several oral microbiology laboratories throughout the 1970s and 1980s (Socransky 1970; Slots 1976, 1977; Tanner *et al*. 1979; Slots & Rosling 1983; Haffajee *et al*. 1984; Christersson *et al*. 1985; Dzink *et al*. 1985; Loesche *et al*. 1985; Dzink *et al*. 1988; Haffajee *et al*. 1988; van Winkelhoff *et al*. 1988; Zambon *et al*. 1988; Tanner & Bouldin 1989) but, because of the highly labor intensive nature of the methodology, were usually limited to the analysis of relatively few periodontal subjects. Importantly, however, these investigations began to put clear definition to the very significant qualitative differences in the overall microbiota present at periodontally diseased sites compared with control healthy sites and to identify some of the key, characteristic organisms which were frequently associated with disease. The exhaustive investigations conducted in the Virginia Polytechnic Institute laboratories of Holdeman and Moore (Moore 1987) were typical of these investigations and are among the most influential studies of the total, cultivatable, anaerobic microbiota. Studies of this kind began

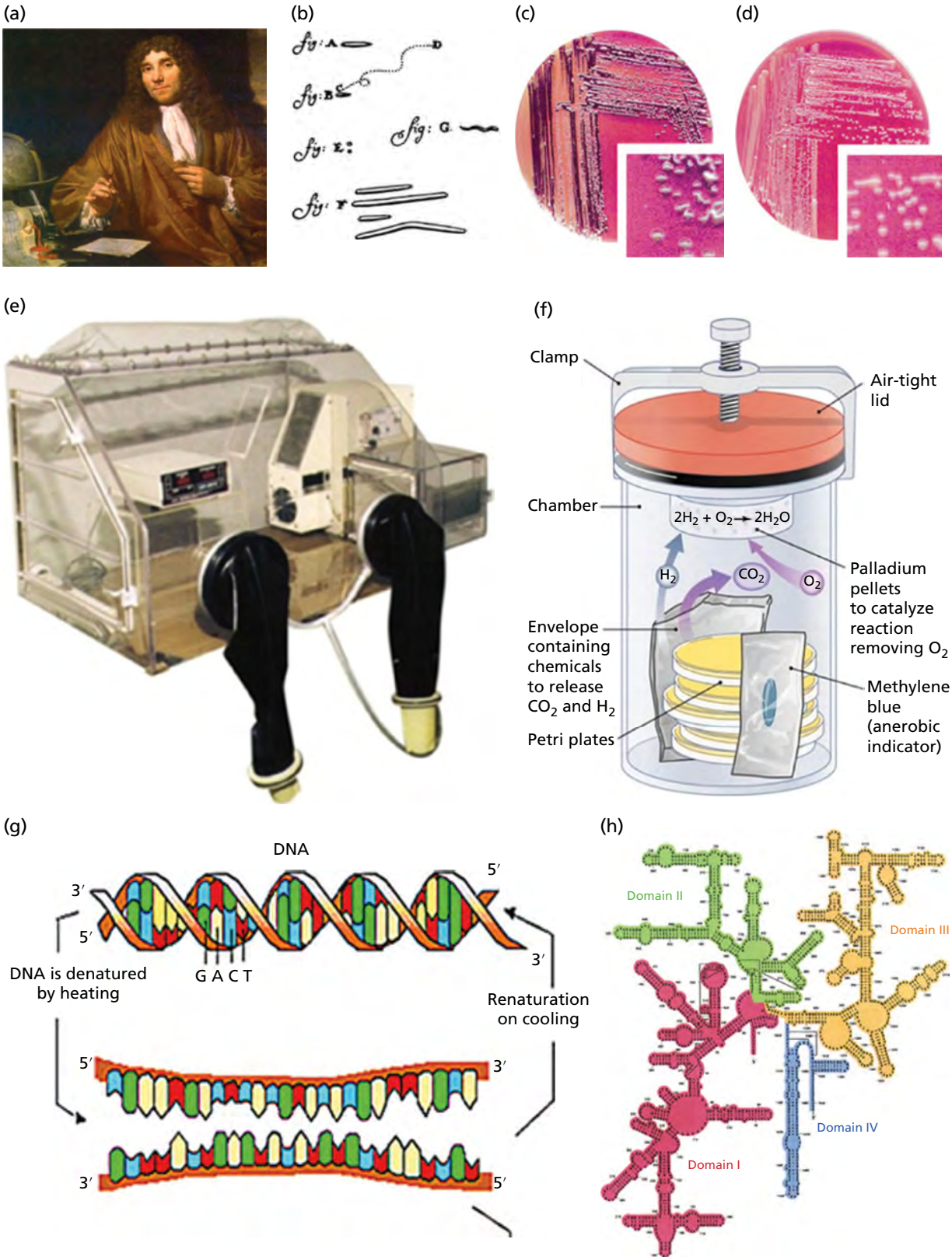


Fig. 9-2 Technological advances linked to increased understanding of the oral microbiota. Appreciation of the complexity of the oral microbiota has increased with the development of technology. Microscopy: (a) Antonie van Leeuwenhoek who used the first microscopes to characterize dental plaque bacteria (b). Bacterial culture on solid media: (c) *Porphyromonas gingivalis* grown on blood agar; (d) a non-pigmenting mutant of *P. gingvalis*. Anaerobic microbiology: (e) anaerobic chambers and (f) anaerobic jars enabled the culture of bacteria whose growth is inhibited by oxygen. Molecular techniques for bacterial identification: (g) DNA: DNA hybridization and (h) sequence analysis of the variable regions of the *16S rRNA* gene allow for the identification and quantitation of bacteria in the absence of culture.

to convincingly reveal the sheer complexity of the microbiota in periodontal disease to a level that had hitherto been unseen and began to develop a reference catalogue of bacterial taxa which would prove invaluable for later investigations. Furthermore, those bacteria which were significant components of the subgingival plaque from diseased sites were also frequently present, albeit at reduced levels in supragingival samples, and vice versa. Indeed, several studies demonstrated that many of the bacteria positively associated with the microbiota at a diseased subgingival site were also present in healthy subgingival sites. These investigations indicated that a specific etiology for the periodontal disease process could only be explained on the basis of a quantitative rather than solely qualitative perspective. To gain sufficient power to address the nature of the etiology it would be necessary to perform studies involving significantly more samples/subjects than was feasible by this total microbiological analysis approach which was typically restricted to investigations on relatively small numbers of individuals. However, these large scale anaerobic microbiological analyses on a relatively few samples had provided several valuable, potential "specific periodontal pathogens" for future studies.

Targeted analysis of periodontal microbiota

Having developed a candidate list of putative periodontal pathogens, it became possible to perform rather more targeted investigations which aimed to focus on detection of this group of bacteria in larger numbers of clinical samples than it was feasible to process when the entire cultivatable microbiota was examined. These investigations relied upon the application of a combination of identification approaches: novel selective media for the enrichment or selective culture of specific bacteria; immunological techniques using newly developed monoclonal antibodies or polyvalent sera to individual species; or microscopy for the identification of spirochaetes. For example, Bragd *et al*. (1987) used a selective media approach to evaluate the association of *Actinobacillus* (now *Aggregatibacter*) *actinomycetemcomitans, Bacteroides* (now *Porphyromonas*) *gingivalis*, and *Bacteroides (Prevotella) intermedia* in over 200 samples from progressing and non-progressing periodontal sites. Similarly Slots *et al*. (1990) employed a cultural approach to examine the influence of subject age on the prevalence and recovery of *A. actinomycetemcomitans* and *B. intermedius* in 1624 patients aged between 15 and 89 years. Grossi *et al*. (1995) used an immunochemical approach to assess the presence of eight candidate periodontal pathogens in a study involving 1361 subjects to identify risk markers for periodontal bone loss. Suda *et al*. (2002) used an indirect immunofluorescence approach to enumerate the levels of *Eikenella corrodens* in samples from over 250 periodontal and control samples and Riviere *et al*. (1997) used a similar antibody and microscopy-based investigation to determine the levels of different spirochaetes in an analysis of the development of periodontal disease using over 1000 samples from 65 subjects.

By focusing on a small group of candidate organisms using relatively high throughput approaches it became possible to design appropriately statistically powered investigations to address a number of key issues relevant to the etiology and treatment of periodontal disease. These included the presence of these candidate periodontal pathogens in different global populations (van Winkelhoff *et al*. 1999) studies of the association between different organisms such as *Bacteroides forsythus* and *Bacteroides gingivalis* (Gmur *et al*. 1989), their spatial distribution in plaque (Kigure *et al*. 1995), the association with disease of different morphotypes of the same species, such as the smooth and rough colony types *Peptostreptococcus micros* (van Dalen *et al*. 1998; Kremer *et al*. 2000) and the effect of treatment on persistence/eradication of these key organisms (Mandell *et al*. 1986; Rodenburg *et al*. 1990; Mombelli *et al*. 2000). Furthermore, when isolation and identification of a specific organism was coupled to more detailed characterization of the individual strain (by for example restriction digestion of the isolates' DNA followed by separation by agarose electrophoresis) it became feasible to perform transmission studies. Notably, Petit *et al*. (1993a, b) and Van Steenbergen *et al*. (1993) used this approach to demonstrate that *P. gingivalis* was transmitted between spouses and that intrafamilial transmission of individual strains of *P. intermedia* and *P. nigrescens* also occurred.

Other investigations utilized these selective methodologies to examine the association of alternative bacterial species with periodontal disease in addition to the, by now well-established periodontal bacteria mentioned above. In so doing the list of bacterial species positively associated with periodontal disease, in particular adult disease, was extended to include for example, *Wolinella* (now *Campylobacter*) *recta* (Lai *et al*. 1992; Rams *et al*. 1993), Enterococci (Rams *et al*. 1992), *P. micros* (van Dalen *et al*. 1998), eubacterial species (Grossi *et al*. 1995), *E. corrodens* (Suda *et al*. 2002), *Fusobacterium nucleatum* (van Winkelhoff *et al*. 2002), and other species. Hence, although a specific microbial etiology for periodontal disease was still considered by many to be the most reasonable interpretation of the accumulated data, there was an acceptance that the nature of the microbial challenge, particularly in the case of chronic adult periodontitis, was highly complex and likely to vary significantly between individuals and potentially within an individual at different sites and at different times (Maiden *et al*. 1990).

In contrast to adult-type chronic periodontitis, in one particular instance of aggressive periodontitis affecting adolescents of African descent, there is evidence to suggest that a single specific

microbial etiology may be responsible for the development of disease. *A. actinomycetemcomitans* is a Gram-negative rod that produces a leucotoxin that specifically lyses human neutrophils. The organism displays significant genetic diversity, but one particular clone, referred to as JP2, has a number of genetic variations that distinguish it from other clonal types, including a 530 base pair deletion in the promoter region of the leucotoxin gene operon. As a result, the JP2 clone produces significantly enhanced levels of leucotoxin compared to the other lineages of this bacterium which could theoretically lead to an enhanced potential to disrupt the immune defenses of the periodontium. Population genetic analysis by multilocus sequencing of *A. actinomycetemcomitans* strains from geographically dispersed individuals suggest that the JP2 clone originally emerged as a distinct genotype in the Mediterranean part of Africa over 2000 years ago and subsequently spread to West Africa, from where it was transferred to North and South America by the trans-Atlantic slave trade in the sixteenth to eighteenth centuries. Remarkably, despite its now global dissemination, the JP2 clone still remains exclusively associated with individuals of West African descent, indicating a strong host tropism effect (Haubek *et al*. 2008). Although the prevalence of aggressive periodontitis in adolescents is normally <1%, it is far higher in individuals of North and West African descent. In a longitudinal study of the disease in Moroccan adolescents, 61 of 428 (14.3%) individuals who were periodontally healthy at baseline had developed disease after 2 years. Moreover, in this population, individuals who carried the JP2 clone at baseline were far more at risk of developing disease than those who carried non-JP2 clones of this bacterium (relative risk 18.0 versus 3.0) (Haubek *et al*. 2008). Hence, the JP2 clone of *A. actinomycetemcomitans* has the characteristics of a traditional bacterial pathogen, albeit in a host-restricted background.

Introduction of nucleic acid-based techniques for bacterial identification

With the development of a catalogue of the major cultivatable species in the periodontal microbiota came the need to develop more rapid, less time-consuming and laborious methods for larger scale epidemiological analyses of the association of these organisms with health and disease. This was accomplished through the introduction of techniques that were not reliant on culture immediately following sample collection. The most commonly used of these were analyses based on nucleic acid approaches – PCR amplification of specific regions of the chromosome of the target organism, usually the *16S rRNA* gene, followed by quantitation of the product and DNA:DNA hybridization techniques.

Use of the DNA:DNA checkerboard methodology

A step change in the potential throughput of microbiological analyses of periodontal plaque samples arrived with the introduction and application of DNA:DNA hybridization technology. The development of the checkerboard assay allowed the simultaneous hybridization of 45 individual DNA samples extracted from periodontal plaque against 30 different DNA probes on a single membrane. The DNA probes can either be prepared from whole genomic DNA extracted from the relevant target bacterium or alternatively PCR amplicons of bacterial species-specific regions of the *16S rRNA* gene. Hybridization of the sample DNA with the probe DNA is then visualized via a chemifluorescent signal, the intensity of which is proportionate to the amount of the target organism DNA present in each sample.

Although there are some limitations to the accuracy of identification of individual bacterial species because of potential cross-hybridization of DNA from closely related bacterial species in the same clinical samples, application of this technology revolutionized the analysis of clinical samples and the ability to make definitive bacterial associations with periodontal health and disease. Now it was possible to perform qualitative and quantitative analysis of the bacterial composition of far, far greater numbers of clinical samples than the previous culture-based methodologies. For example, in a landmark investigation, Socransky *et al*. (1998) analyzed approximately 13 000 plaque samples from 185 subjects using whole genomic DNA probes to 40 bacterial species (Fig. 9-3). Associations were sought among species using cluster analysis and community ordination techniques. One of the key and fundamentally important findings of this study, which has shaped our understanding of periodontal infections, was the definition of bacterial complexes, as opposed to individual bacterial species, which were associated with either periodontal health or periodontal disease (Fig. 9-4).

This finding led to the concept that there may be a co-dependency or synergy between different bacterial species acting in concert as a specific complex. The complex most strongly associated with periodontal disease, the "red complex", was composed of three bacterial species which subsequently became the focus of intense investigation: *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia*. Other complexes, for example the yellow complex which comprised predominantly different streptococcal species, and the green complex which contained a preponderance of *capnocytophaga* species, represented early colonizers of dental plaque which were more closely associated with health. The orange complex contained those organisms generally considered to colonize dental plaque later: fusobacteria species, members

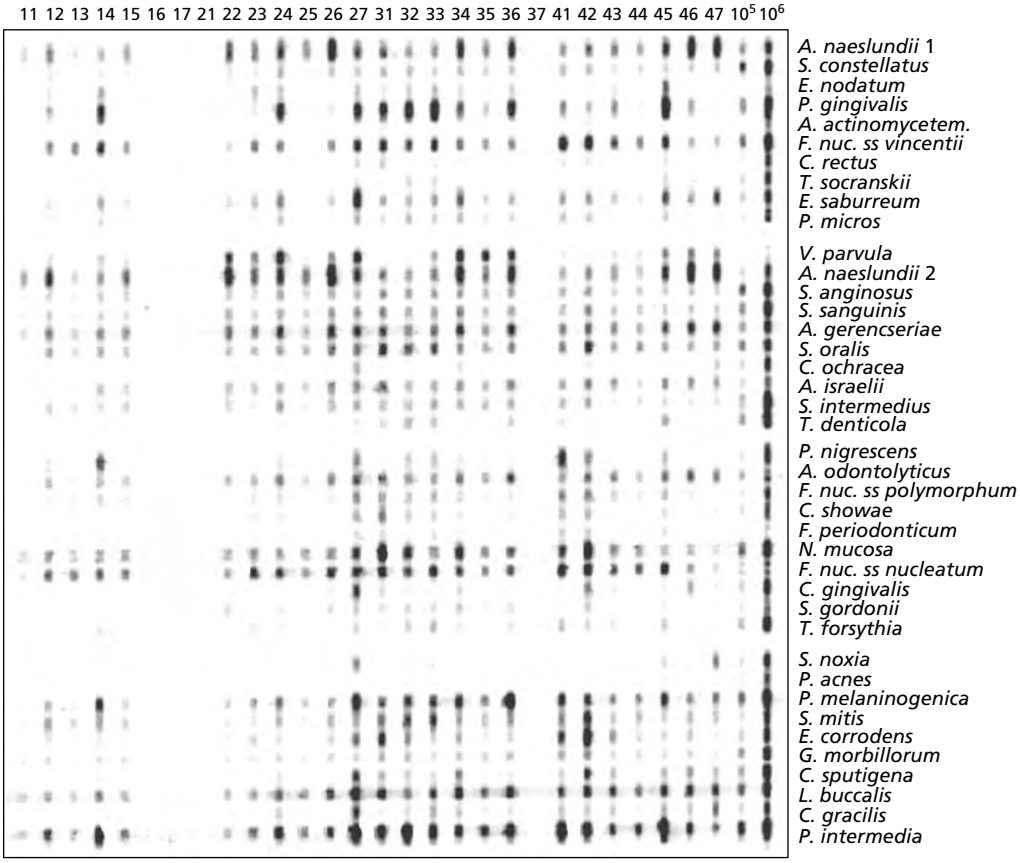


Fig. 9-3 The vertical lanes are the plaque samples numbered 11–47 and two lanes of standards on the far right contain either 105 or 106 cells of each test bacterial species. The horizontal lanes contain whole genomic DNA probes labelled with digoxygenin to each represented bacterium. A signal at the intersection of the vertical and horizontal lanes indicates the presence of a bacterial species and the intensity of the signal is related to the number of bacterial cells present. The methodology enables the simultaneous and rapid analysis of 40 different bacterial species in 28 different plaque samples. (Source: Reprinted from Socransky & Haffajee 2008, with permission of Wiley-Blackwell.)

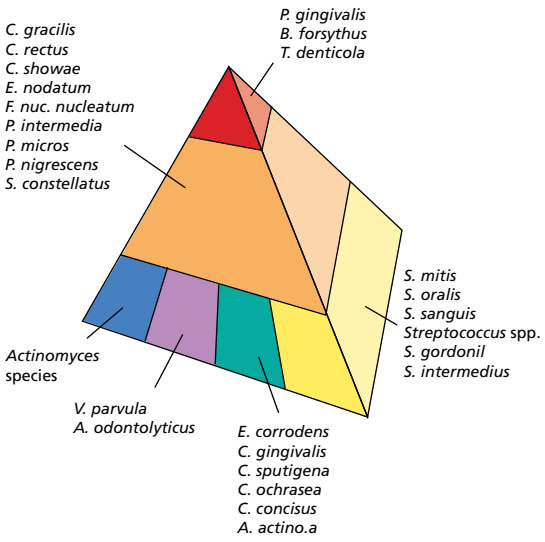


Fig. 9-4 The association among subgingival species. The different colors in the pyramid represent different bacterial complexes which are frequently detected in association with one another. The base of the pyramid represents the early stage of plaque development whereas the apex contains those organisms thought to be the last species to become established in the microbiota. The red complex of bacteria are those organisms frequently associated with sites of periodontal disease. (Source: Reprinted from Socransky & Haffajee 2002, with permission.)

of the *Prevotella* and the *Campylobacter* genera. The presence of these organisms is now thought to facilitate colonization of mature dental plaque by the red complex organisms either through the presentation of appropriate binding sites or by the creation of a suitable environment for the growth of these more fastidious species.

It is noteworthy that *A. actinomycetemcomitans*, the bacterium associated with rapidly progressive disease in individuals of West African descent, does not cluster with the most disease-associated red complex organisms. This probably reflects the very large effect of the host genetic background on the disease associated with this bacterium as described previously. Use of the checkerboard technology enabled a range of questions to be addressed concerning, for example, the sequential changes that occur in the composition of supragingival and subgingival plaque during development and the qualitative and quantitative influence of tooth cleaning on the microbiology of supra- and subgingival plaque. An example of this kind of study is shown in Fig. 9-5 which demonstrates the significant qualitative and quantitative differences associated with disease not only in subgingival but also supragingival plaque.

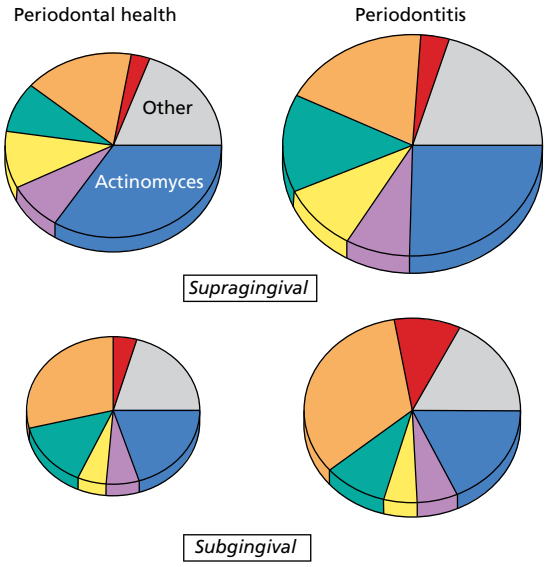


Fig. 9-5 The mean percentage DNA probe count of microbial groups in supragingival and subgingival plaque. Plaque samples from periodontally healthy (58) and periodontitis (136) subjects and subgingival plaque samples from periodontally healthy (189) and periodontitis subjects (635). The species were grouped into seven microbial groups based on the description of Socransky *et al.* (1998) and described in more detail in Fig. 9.4. The "other" category represents probes to species that did fall into a complex as well as probes to new species whose relationships with other species has not yet been ascertained. The areas of the pies were adjusted to reflect the mean total DNA probe counts at each of the sample locations. The significance of differences in mean percentages of the supra- and subgingival complexes in health and disease was tested using the Kruskal Wallis test. All complexes differed significantly among groups at $P < 0.001$ after adjusting for seven comparisons. (Source: Reprinted from Socransky & Haffajee, 2008, with permission of Wiley-Blackwell.)

PCR amplification of *16S rRNA* gene of periodontal bacteria

16S ribosomal RNA (or *16S rRNA*) is a component of the 30S small subunit of all bacterial ribosomes. The genes coding for it are referred to as 16S rDNA. Although the sequences of 16S rDNA are highly conserved between different bacteria, they also contain hypervariable regions that can provide species-specific signature sequences useful for bacterial identification. Therefore, once the sequence of a 16S rDNA gene from a bacterium has been determined, it is possible to design a PCR, using primers which will anneal to sequences within the hyper-variable regions, which will specifically amplify only the 16S rDNA from the target bacterium. The great advantages of the application of this methodology to the detection of periodontal bacteria in clinical samples is the high sensitivity of detection, the high throughput which can be attained, the speed of assay, and that multiple bacterial species can be detected in the same reaction – multiplex PCR. As a result, this technology has been used extensively for the detection of putative periodontal pathogens. Typically, these studies focused on the detection of only a few bacterial species including the well-established periodontal bacteria *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *A. actinomycetemcomitans* (Leys *et al*. 2002; de Lillo *et al*. 2004; Sanz *et al*. 2004; Tanner *et al*. 2006). However, studies involving PCR amplification of the 16S rDNA gene have also been used to confirm the presence of novel and, in some instances non-culturable, bacterial species whose presence was originally identified by cloning and sequence analysis of the 16S rDNA in periodontal samples. These investigations confirmed that several additional species, including those that have not yet been grown *in vitro*, were associated with oral health or periodontitis. These molecular studies have significantly extended the number of potential periodontal pathogens. For example, based on their 16S rDNA analysis of subgingival plaque samples from healthy subjects and subjects with refractory periodontitis, adult periodontitis, human immunodeficiency virus periodontitis, and acute necrotizing ulcerative gingivitis, Paster *et al*. (2001) described several new candidates. Species or phylotypes commonly detected in disease but rarely in health included *Eubacterium saphenum*, *Filifactor alocis* (previously *Fusobacterium alocis*), *Catonella morbi*, *Megasphaera* sp., *Dialister* sp., and *Selenomonas sputigena*, and several of these organisms, in particular *Filifactor alocis* have subsequently been confirmed to be positively associated with disease in other studies.

The initial studies in this area were largely qualitative in nature in that they only determined whether an organism was present or absent (or more correctly below the limits of detection of the assay – typically 100 bacterial cells). Subsequently, real-time PCR, also referred to as qPCR or qRT-PCR, has been introduced which quantifies the numbers of copies of the gene of interest in a given sample. Real-time PCR has been used to detect and quantify several periodontal pathogens including *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, and total bacteria, in clinical samples (Lyons *et al*. 2000; Maeda *et al*. 2003; Boutaga *et al*. 2007; Atieh 2008). Studies of this nature are now being superseded by the application of high throughput, next generation sequencing methodologies described in a following section.

The human oral microbe identification microarray

Recognition of the increased and substantial microbial diversity of dental plaque led to the development of new diagnostic methodologies capable of the rapid identification of greater numbers of bacterial phylotypes in periodontal infections (Paster & Dewhirst 2009). The Human Oral Microbe Identification Microarray (HOMIM) was developed in order to examine the complex oral microbial diversity in a single hybridization on glass slides (Paster *et al*. 2006; Preza *et al*. 2008, 2009b). This high sample-throughput, *16S rRNA*-based technology allows the simultaneous detection of approximately 300 key and predominant bacterial species,

including species that have not yet been cultivated *16S rRNA*-based, oligonucleotide probes are printed onto glass slides. The *16S rRNA* genes in clinical samples are PCR amplified using *16S rRNA* universal forward and reverse primers, fluorescently labeled and then hybridized to the probes on the slides. In order to analyze the large datasets from HOMIM arrays, individual signals are translated into a "bar code" format in which the bands correspond to the presence or absence of a particular organism and band intensities reflect the organism's abundance. The bar code format of HOMIMs comparing the microbial profiles of approximately 300 bacterial species from subjects with periodontal health and periodontitis is illustrated in Fig. 9-6. These data can be analyzed further to determine specific bacterial associations (Colombo *et al*. 2009; Preza *et al*. 2009a, b) or the relationships of *entire* microbial populations with respect to health and disease using correspondence analysis, as shown in Fig. 9-7. The dramatic difference in the overall bacterial population structure of these two sets of data vividly reinforces the findings of the total cultural microbiology studies performed some 30 years ago and is consistent with dysbiosis of the microbiota as a defining characteristic of periodontal disease.

Use of this array-type technology for relatively rapid semiquantitative analysis of the microbial community composition in periodontal research investigations is still widely used (Paes Batista da Silva A *et al*. 2016; Cui *et al*. 2019). However, there is now a growing consensus that next generation sequencing technologies, based on *16S rRNA*, provide significantly expanded oral bacterial species identification and hence a more comprehensive representation of oral bacterial community structure (Mougeot *et al*. 2016).

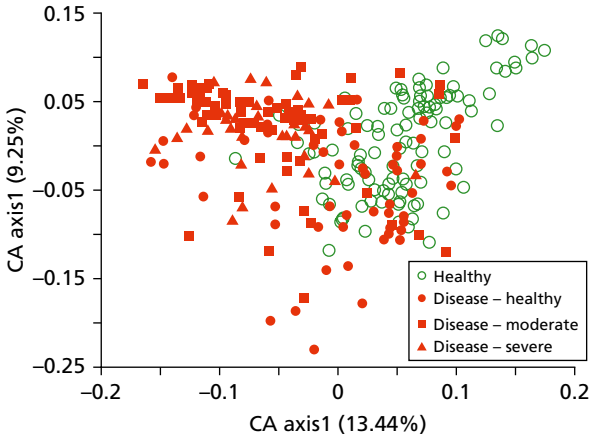


Fig. 9-7 Correspondence analysis of subgingival plaque bacterial communities in health and disease. Each symbol represents one community from one site. Communities that are closer together have more similar HOMIM profiles. In this plot, the healthy sites from healthy subjects (green circles) are distinct from healthy and diseased sites in diseased subjects (red symbols). (Source: Courtesy of Dr. Vanja Klepac-Ceraj: Forsyth Dental.)

Unculturable bacteria in the periodontal microbiome

The introduction of non-culture-based methods for description of the total microbial population of oral samples led to a recognition that a significant proportion of oral bacteria are unculturable and can only be detected using molecular techniques. This phenomenon is also recognized in other sites of the human body and environmental samples such as the soil and the river water. Particular interest in the periodontal research field has focused recently on the TM7 phylum (now renamed Saccharibacteri*a*) (Bor *et al*. 2019).

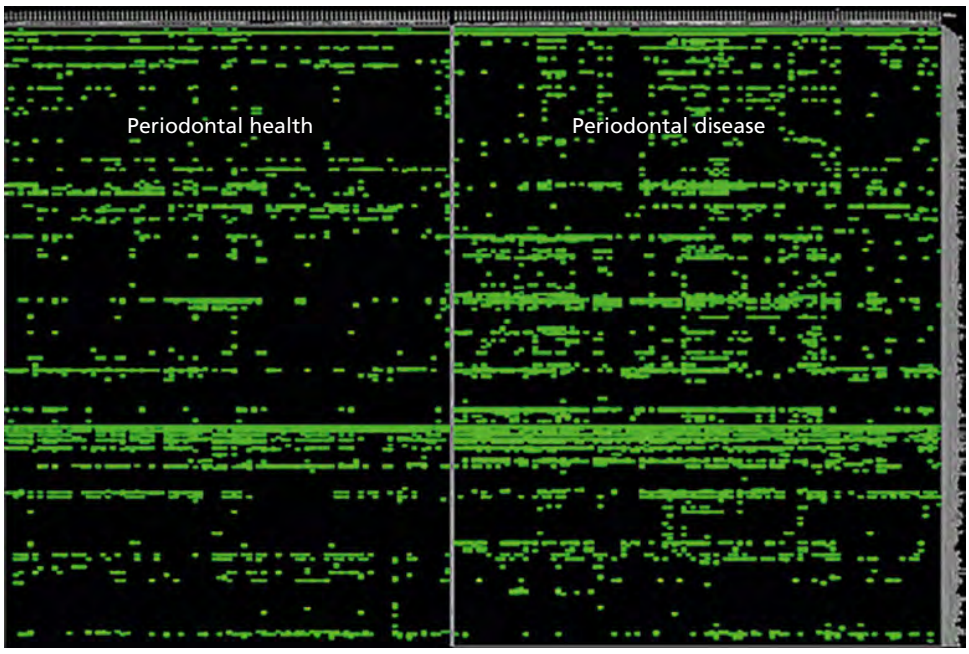


Fig. 9-6 Bacterial profiles of 461 bacterial taxa (representing approximately 300 species) comparing subgingival plaque from 105 healthy sites in periodontally healthy subjects ($n = 20$) with 154 diseased sites from periodontally diseased subjects (n = 47). (Source: Reprinted from Paster & Dewhirst 2009, with permission, figure courtesy of A.P. Colombo.)

This phylum belongs to a newly described bacterial major lineage or superphylum called Candidate Phylum Radiation (CPR) potentially containing over 70 phyla. Remarkably, the CPR may account for more than 25% of all bacterial diversity. TM7 bacteria are present in the microbiome at a variety of sites in the human body including the gastrointestinal tract, skin, and female genital tract (Brinig *et al*. 2003; Eckburg *et al*. 2005; Fredricks *et al*. 2005; Gao *et al*. 2007). Furthermore, the detection of TM7 using *16S rRNA* gene sequencing of the calcified dental plaque (calculus) from Neanderthal specimens suggests that these organisms have been constituents of the oral microbiome throughout human evolution (Brinig *et al*. 2003; Weyrich *et al*. 2017).

Until recently, there was little information on the biology of this group of organisms. However, insights into the TM7 lifestyle and genomics have begun to emerge following the first successful cultivation of a member of this phylum – TM7x (HMT_952) from the oral cavity (He *et al*. 2015) (Fig. 9-8). The isolation procedure involved targeted antibiotic enrichment with a culture medium that supports the growth of TM7 bacteria in an *in vitro* multispecies oral microbial community (Tian *et al*. 2010; Edlund *et al*. 2013). These studies have demonstrated that the TM7 are very small bacteria of approximately 200–300 nm, with a reduced genome size of 20–25% of most other oral bacteria. Furthermore, they are highly specialized obligate parasites of other bacteria. Although, there are many examples of parasitism of eukaryotic organisms by prokaryotes, the *in vitro* co-culture studies of the oral TM7x (HMT 952) with its host bacterium, *Actinomyces odontolyticus*, was the first ever demonstration of one bacterium able to parasitize another. As obligate parasites, TM7 organisms will represent a burden to their host bacteria and a number of negative consequences have been reported including reduced cellular growth rate and division, increased stress responses (Bor *et al*. 2019), and cell lysis under certain circumstances (He *et al*. 2015). Paradoxically, however, there may also be positive outcomes for the host bacterium including an increased tendency to form biofilms in the presence of TM7 and a subversion of the usual host response to the parasitized bacterium (Bedree *et al*. 2018).

Emerging evidence indicates that these obligately parasitic bacteria may have a role to play in the development of disease based on an increase abundance of TM7 in the microbiota associated

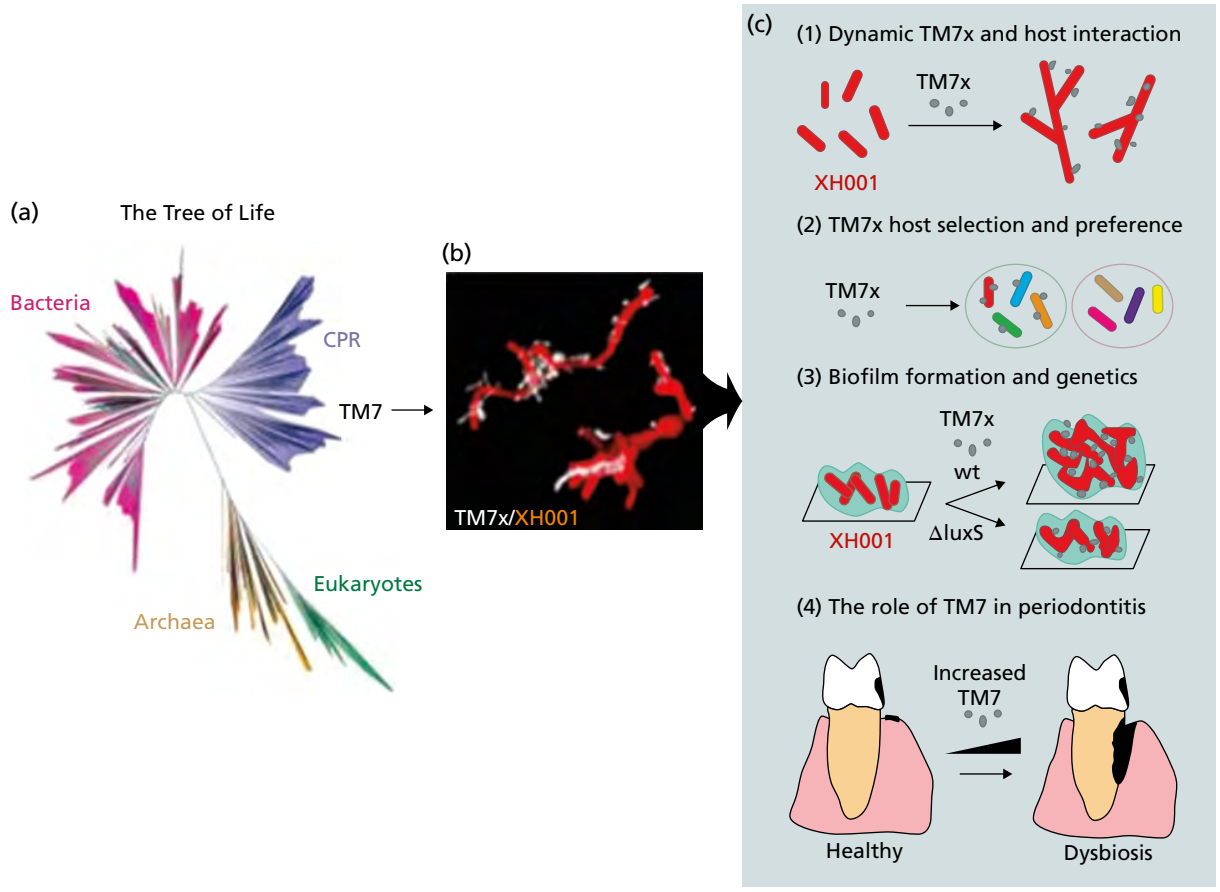


Fig. 9-8 TM7x represents the first Candidate Phylum Radiation (CPR) bacteria co-cultivated with its host. (a) Current view of the tree of life highlights TM7 and CPR. (b) Fluorescence *in situ* hybridization image shows the parasitic relationship between TM7x and its bacterial host XH001. (c) TM7x/XH001 provides a better understanding of bacterial epiparasitic interaction: (1) a detailed mechanistic understanding of the dynamic parasitic interaction between TM7x and its host bacterium XH001; (2) the host selection and host range of TM7x; (3) the impact of interaction on bacterial physiology; and (4) pathogenic potential. XH001, *Actinomyces odontolyticus* strain XH00; TM7x, *Nanosynbacter lyticus* type strain TM7x. (Source: Reproduced from Bor *et al*. 2019.)

with inflammatory disease including gingivitis and periodontitis (Brinig *et al*. 2003; Fredricks *et al*. 2005; Kuehbacher *et al*. 2008). In health, TM7 is normally present in low amounts of the order of 1% of the total microbiota (Brinig *et al*. 2003; Podar *et al*. 2007). However, significantly greater levels of TM7 were associated with gingivitis severity and periodontal disease (Paster *et al*. 2002; Brinig *et al*. 2003; Rylev *et al*. 2011; Liu *et al*. 2012; Kistler *et al*. 2013; Camelo-Castillo *et al*. 2015). Furthermore, the elevated levels in gingivitis appear to reduce after successful treatment (Huang *et al*. 2016). As a result of these studies, TM7 bacteria are now considered to be members of the core microbiota associated with periodontal disease (Abusleme *et al*. 2013).

The mechanism through which members of the TM7 may actively contribute to the pathogenesis of disease has not been established. However, given that these parasitic organisms interact with key members of the overall microbial community – *Actinomyces* spp. are now well-established hosts but it is likely that there will be many other examples – TM7 bacteria may play a significant role in modeling the composition of the periodontal microbial community structure, its activity, and its interaction with the immune and inflammatory response.

The next generation sequencing revolution

Sequence analysis of *16S rRNA* has become the method of choice for detection of culturable and non-culturable bacteria because of its universal presence in all organisms and because, through PCR primer design, it is possible to describe either all the species present in a given sample or target specific genera. Application of this approach led to the description of 13 phyla in the domain Bacteria in the human oral microbiome: Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, SR1, Synergistetes, Tenericutes, and TM7 in addition to methanogenic species of the *Methanobrevibacter* genus from the domain Archaea. Several hundred distinct species are contained within these divisions, representing the highly diverse microbial communities of the mouth (Dewhirst *et al*. 2010).

Application of next generation DNA sequencing (NGS) of 16s rRNA to the oral and periodontal microbiota is the newest technological advance in our study of the complex communities of bacteria which colonize the subgingival area in health and disease. The procedures build upon advances in both high throughput DNA sequencing technologies and bioinformatic tools to aid data analysis. Following extraction, the total DNA in a clinical sample is subjected to PCR amplification using a PCR primer set that targets a taxonomically informative region of the 16s rRNA: small fragments usually covering one or two hypervariable regions (such as V1–V3, V4, or V4–V5 regions) of the *16S rRNA* gene. After amplification, the resultant amplicons are sequenced and then mapped to a reference 16S sequence database for taxonomic identification and abundance estimation. Advances in NGS technology including extensive multiplexing of samples, now permits rapid analysis of hundreds of samples and the analysis of millions of PCR amplicons in a single NGS run.

Although the high-throughput sequencing of *16S rRNA* genes can usually profile taxonomic composition at the genus or species level, whole genome sequencing (metagenomics) can potentially provide species- or even strain-level taxonomic resolution in microbial population analysis. This may be particularly important where genetic variability within a given bacterial species leads to the appearance of potentially more virulent strains or clonal types which would not be detected by the analysis of *16S rRNA* sequencing. Furthermore, metagenomics provides more information regarding metabolic characteristics and enables an understanding of the functional capacities of microbial communities. Metagenomics based on NGS identifies the sequence of entire genomes by producing random fragments of DNA (25–500 bp) and comparing these to reference genome databases.

Over the last decade these approaches have been applied to the community composition of the periodontal microbiome in health and disease (Griffen *et al*. 2012; Abusleme *et al*. 2013; Kirst *et al*. 2015; Hong *et al*. 2015). The results have largely agreed with earlier cultivation-based and low throughput molecular analyses but at a far greater taxonomic resolution of the overall community. It is now broadly recognized that the diversity of the microbiota and hence its complexity increases in periodontitis compared with health. The increased diversity appears to be a consequence of the outgrowth of organisms present at only low abundance in health, rather than the exogenous acquisition of new organisms. Shifts in the microbiota which accompany gingivitis are different to those observed in periodontitis, with gingivitis potentially representing a transitional stage from health to disease. Similar to earlier studies, the community biomass increases significantly from health to gingivitis and then to periodontitis (Diaz *et al*. 2016).

An additional finding from these subgingival microbiome characterizations via *16S rRNA* gene sequencing is the identification of species whose proportions do not change from health to disease. These species are referred to as core species, as they are present in similar proportions regardless of health status. Core species represent bacteria capable of interacting with health-associated and periodontitis-associated community members. Two of the most consistently detected species in this group are *Campylobacter gracilis* and *F. nucleatum* ss. *vincentii*. The latter is also a very abundant component of both healthy and periodontitis-associated plaque and has been suggested as an important component of plaque structure because of its ability of coaggregation with many other species (Kolenbrander *et al*. 2010).

A summary of the key species most strongly associated with health or periodontitis, based on their repeated appearance in NGS analyses conducted by different groups in distinct patient cohorts is shown in Fig. 9-9 (Curtis *et al*. 2020). *Actinomyces* spp., *Rothia* spp., and *Streptococcus sanguinis* are the main health-associated taxa which are reduced in periodontitis and a diverse group of mostly Gram-negative species are enriched in periodontitis. The greater number of species associated with periodontitis than species associated with health is consistent with the higher diversity of periodontitis communities, in which species are more evenly distributed and therefore more species can be detected with a similar sequencing effort than in the less diverse healthy communities, which tend to be dominated by a few taxa. In summary, periodontitis is accompanied by profound shifts in the composition of subgingival communities, with the emergence of, for the most part, different Gram-negative species to those enriched during gingivitis, that outgrow health-associated taxa. Among enriched species are the previously described red complex triad composed of *Treponema denticola*, *P. gingivalis*, and *Tannerella forsythia* (Fig. 9-9). However, several other *Treponema* spp. also appear as abundant components of periodontitis communities, again in agreement with the early microscopy studies, which indicated the abundance of spirochaetes was associated with the severity of periodontal destruction (Armitage *et al*. 1982). *P. intermedia*, *Filifactor alocis*, *Desulfobulbus* sp. HOT 041 and *Fretibacterium* sp. HOT 360, among others, are also abundant components of periodontitis communities (Curtis *et al*. 2020). The shift in the microbial community structure of the periodontal microbiome is referred to as dysbiosis, meaning a deleterious change to a microbiota which is no longer in balance with the host, as opposed to symbiosis, the situation in health, where the host and its resident microbiota are in homeostatic equilibrium (Curtis *et al*. 2011).

Periodontal bacteria and virulence

In addition to dysbiosis, several other characteristics of this microbiota need to be considered to appreciate properly the role of bacteria in periodontal disease. First, the growth of these organisms in a subgingival biofilm leads to a number of characteristics which define the biology of these organisms and can present a unique challenge to the adjacent tissues. These include: interbacterial nutritional dependencies and communication; the development of specific

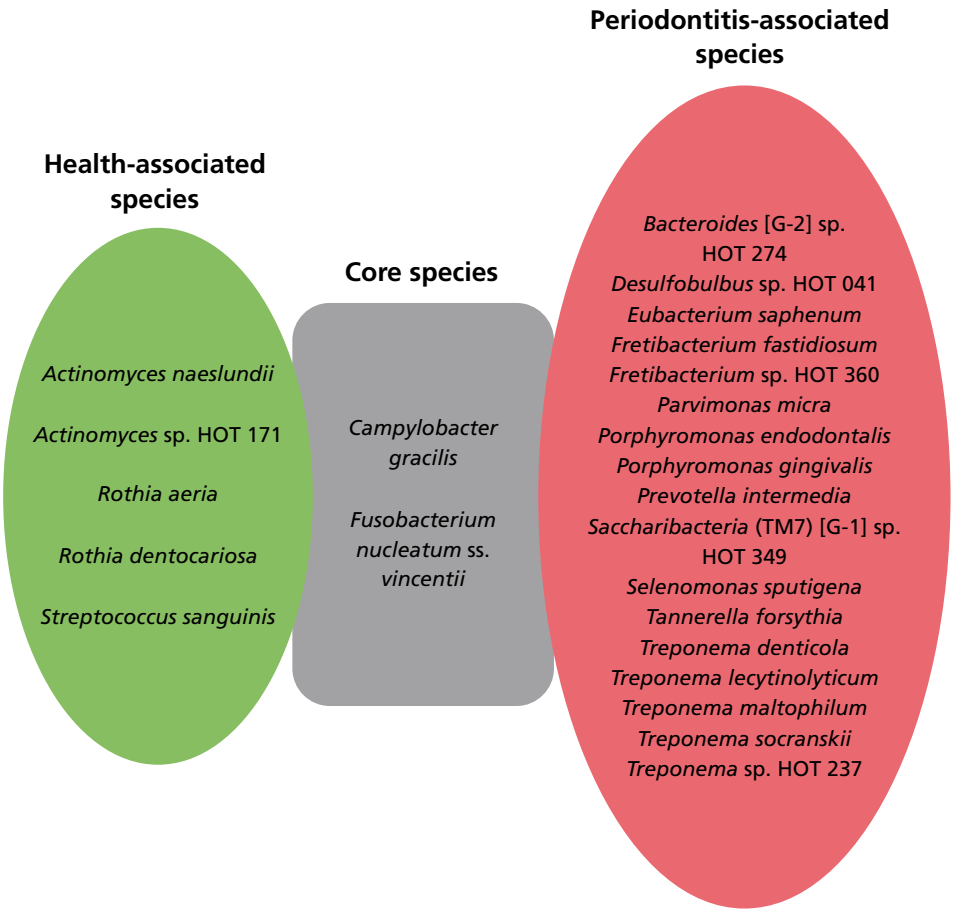


Fig. 9-9 Health-associated, periodontitis-associated, and core species of the subgingival microbiome. The green and red circles show species with significantly increased proportions in either health or periodontitis and therefore strongly associated with health or disease. The gray circle indicates core species, which are those with unchanged proportions in health and periodontitis. (Source: Adapted from Curtis *et al*. 2020.)

consortia of different bacterial species which may act cooperatively in the presentation of a microbial challenge; an optimal environment for genetic exchange between different species and, finally, resistance to the immune and inflammatory clearance mechanisms of the host and to chemical antimicrobial agents. A more detailed description of the consequences of the biofilm lifestyle adopted by dental plaque bacteria is given in Chapter 8. Secondly, analysis of the population structure of some of the bacterial species associated with periodontal disease reveals significant genetic differences which, in some instances, has a defining role in the pathogenic variation within an individual species. Third, analysis of the properties of bacterial species frequently present in a dysbiotic periodontal microbiota has demonstrated that the ability to successfully manipulate elements of the innate and inflammatory response is a common characteristic of these microorganisms and may indeed represent an overriding principle of periodontal virulence.

The virulence of a microbial pathogen is generally defined as the degree of pathogenicity or ability of the organism to cause disease measured by an experimental procedure. It represents a combination of highly complex parameters and depends upon both the relative infectivity of the organism and the severity of the disease produced. However, in all cases these two parameters of infectivity and disease severity are profoundly influenced by the nature and status of the host organism or the site of colonization in that host. Thus, a breach in the normal defensive barriers of the host, for example, trauma, immunosuppression/dysfunction, or coinfection by another organism, can dramatically increase the virulence of a given organism. Hence, any description of microbial virulence is fundamentally reliant on an understanding of the relative susceptibility of the colonized host.

The requisite stages in the life cycle and spread of one organism which parasitizes another are presented in Fig. 9-10. The key steps are: initial colonization and attachment; multiplication and nutrition; evasion of the host defenses; (in some cases) invasion and, lastly, exit in order to disseminate to a new host. Specific gene products (presumptive virulence factors) are required to facilitate each of these processes, and these products will vary from organism to organism dependent upon the particular strategy employed to satisfy each element of the life cycle. The

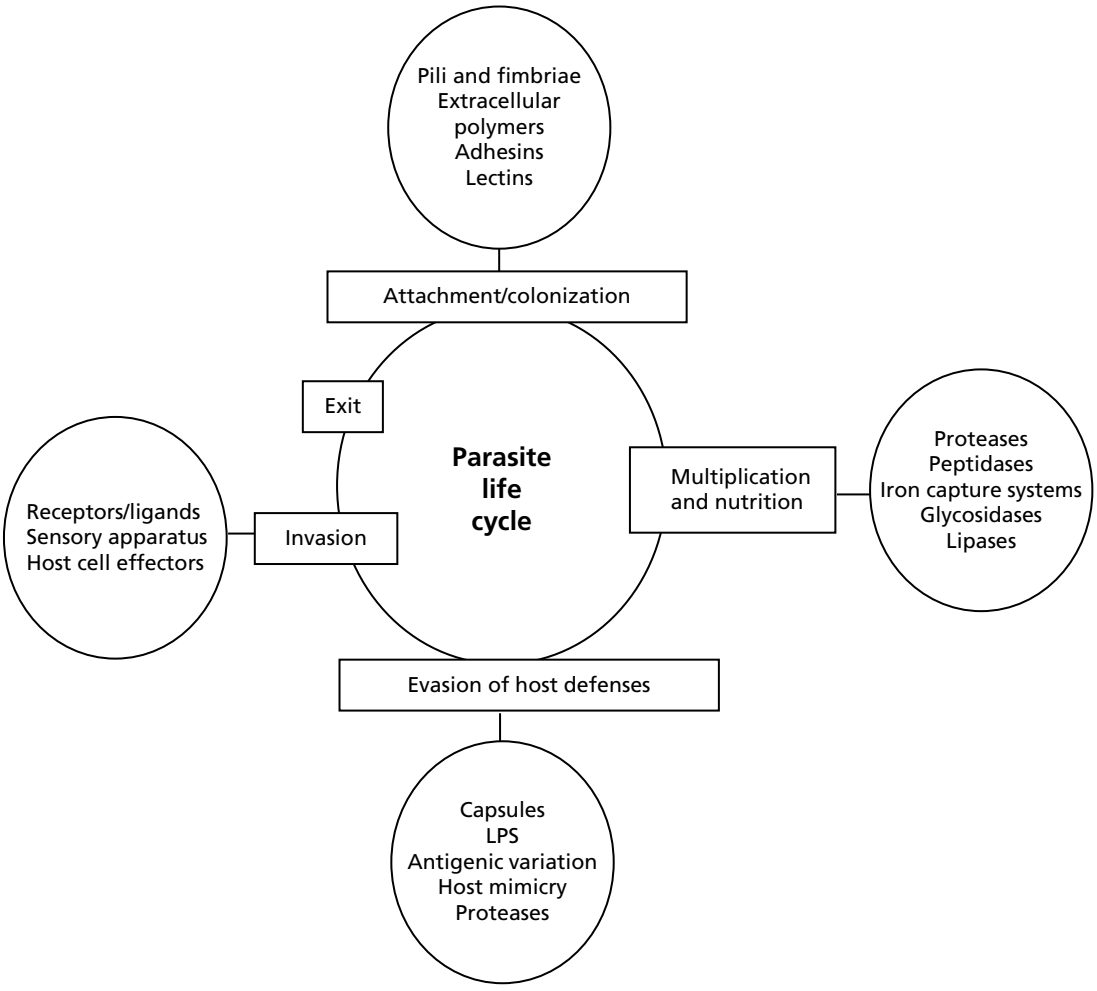


Fig. 9-10 Essential components of the parasite life cycle. Successful colonization and transmission of a parasite is dependent upon the ability to attach, multiply, evade host defenses, invade, and exit the host. These processes each require specialized gene products and processes. (Source: Adapted from Curtis *et al*. 2005.)

gene products or traits associated with each step in the life cycle presented in Fig. 9-10 represent examples drawn from multiple organisms. Disease can be defined as the unfavorable outcome to the host by the application of these life cycle stages of the pathogen *in a susceptible host background*.

The virulence determinants of a pathogen can simply be defined as those gene products which facilitate colonization, growth and survival within the diseased host organism, and spread to a new host In most cases, the rationale for considering these determinants to be important determinants of the virulence of these organisms is derived from a wealth of *in vitro* investigations and/or animal models employing isogenic mutants of the gene of interest. Further details of the properties of these organisms in relation to the pathogenesis of disease can be found in reviews on this subject (Hajishengalis 2009; Henderson *et al*. 2010; Sharma 2010; Dashper *et al*. 2011; Bostanci & Belibasakis 2012; Dahlen *et al*. 2019). However, an emerging key property of several of these organisms concerns the strategies they appear to employ in order to evade the host defenses operative in the periodontium.

It is becoming increasingly evident that microbial organisms, having co-evolved with the innate defense systems of their respective hosts, have developed strategies not only to overcome protective host barriers but also to manipulate these systems to their own advantage. One example of this phenomenon is the ability of cell surface proteins of both Gram-negative and Gram-positive bacteria, including *A. Actinomycetemcomitans* and *P. gingivalis*, to influence the pattern of cytokine expression by host cells (Darveau *et al*. 1998). The term "bacterial modulins" was introduced by Henderson, Poole, and Wilson to describe these bacterial cytokine-inducing molecules because of their ability to modulate eukaryotic cell behavior (Henderson *et al*. 1996). More recently, a sophisticated manipulation of the host response by *P. gingivalis* has been described as a consequence of the biological properties of different molecular species of the lipid A portion of the lipopolysaccharide of this bacterium (Darveau *et al*. 2004). Some of these lipid A species are able to act as agonists of the host response through Toll-like receptor signaling, and thus have similar biological properties to the hexa-acylated lipid A species of enteric organisms. Conversely, other lipid A moieties produced by *P. gingivalis* act as antagonists of this signaling pathway and are able to block the activity of the proinflammatory lipid A forms (Reife *et al*. 2006). This has led to the suggestion that by altering the proportions of the different lipid A components, *P. gingivalis* may be able to manipulate the innate response in order, for example, to downregulate the inflammatory response as a defensive measure.

An additional evasive measure practised by some of the more well characterized periodontal bacteria, a component of the so-called "stealth technology", involves entry into other host cells, primarily epithelial cells, to gain access to an immune privileged site (Lamont & Jenkinson 1998; Fives-Taylor *et al*. 1999; Meyer *et al*. 1999). Verification of this process *in vivo* is now emerging by the detection of these and other species using fluorescent labelling within buccal epithelial cells taken directly from the mouth (Fig. 9-11) (Rudney *et al*. 2005). In the case of *P. gingivalis*, the organism has been shown to rapidly invade epithelial cells derived from the human gingiva and accumulate and persist in high numbers with a perinuclear localization (Lamont & Jenkinson 2000). This positioning is similar to the localization observed for purified preparations of RgpA which is able to translocate the plasma membrane of epithelial cells (Scragg *et al*. 2002). Although the precise mechanism is still under investigation, FimA, a major fimbria, and the gingipain proteinases are required for the attachment and internalization of the bacterial cells. In the case of *A. actinomycetemcomitans*, although the precise details of the mechanism are unknown, there is a suggestion that the invasion process may be augmented by soluble CD14 derived from saliva (Takayama *et al*. 2003).

The recognition that the virulence properties of some of the key organisms involved in periodontal disease may be more directed towards an anti-inflammatory or subversive phenotype is leading to a new appreciation of the etiopathogenesis of the disease process and this is presented in the next section of this chapter.

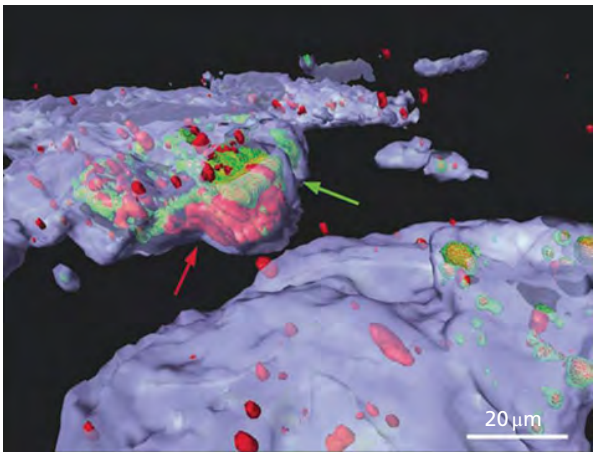


Fig. 9-11 Intracellular bacteria in buccal epithelial cells. A three-dimensional reconstruction of buccal epithelial cells stained using a specific probe for *A. actinomycetemcomitans* (green) and a universal probe for all bacteria (red). Bacteria recognized only by the universal probe are shown in solid red, whereas co-localization of the *A. actinomycetemcomitans* and universal probes is depicted by a green wireframe over a red interior. Reconstructed buccal epithelial cell surfaces are presented in blue. The red and green colors are muted when bacterial masses are intracellular, and brighter when bacteria appear to project out of the surface. The large mass which appeared to have a lobular structure was seen to be a cohesive unit containing *A. actinomycetemcomitans* in direct proximity to other species (red and green arrows). (Source: Adapted from Rudney *et al*. 2005.)

Microbial pathogenesis of periodontal disease

The underlying principles of infectious disease first enunciated by Louis Pasteur and subsequently proven by Robert Koch provided the essential framework for the identification of microorganisms responsible for diseases of a monospecific etiology. Koch's postulates provide four criteria which should be met in order to identify an infectious agent as a disease-causing agent: the microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms; the microorganism must be isolated from a diseased organism and grown in pure culture; the cultured microorganism should cause disease when introduced into a healthy organism; finally the microorganism must be re-isolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent. Although these principles have undergone significant revisions since their introduction and have been updated into a molecular interpretation by Falkow (1988), they underpinned the discovery of the causative agents of very many medically important infections throughout the mid-nineteenth and early twentieth centuries. Koch himself applied these criteria to the discovery of *Mycobacterium tuberculosis* and *Bacillus anthracis* – the causative agents of tuberculosis and anthrax respectively.

The extensive microbiological analyses of periodontal infections which have been undertaken over the last 100 years have led to the formulation of a number of hypotheses on the fundamental nature of the pathogenesis of the disease. In each case, bacteria in dental plaque are acknowledged to be the critically important agent in driving an inflammatory response in the periodontal tissues which can ultimately lead to destructive disease. Hence, although the processes of irreversible destruction of the soft tissues of the periodontium and the bony support structures of the teeth occur through host-mediated mechanisms, these are dependent upon stimulation by a bacterial challenge. However, the underlying principles of each of these hypotheses differ significantly. From the initial stages of the last century it was believed that periodontal disease was the cumulative effect of all the bacterial species found in dental plaque. This non-specific plaque hypothesis held that the precise microbial composition of dental plaque was not the critical determinant of disease, rather it was the magnitude of the total bacterial challenge, or the amount of dental plaque, in juxtaposition to the periodontal tissues, that was the overriding factor which determined the balance between health and disease. The origins of this hypothesis extend as far back as the end of the nineteenth century when bacterial isolation and identification techniques were still in their infancy. Gradually, this non-specific view of the etiology came under increasing scrutiny. First, it was clear that the presence of large accumulations of dental plaque in some individuals did not lead to destructive disease or, in some instances, even mild symptoms of inflammation. Furthermore, the increased sophistication of clinical microbiology was beginning to demonstrate that there were very marked differences in the microbial composition of dental plaque taken from sites in patients with disease in comparison to healthy sites in the same patient or indeed from healthy individuals. Hence, the prevailing view altered to one in which the presence and potential overgrowth of specific bacteria, or periodontal pathogens, was decisive.

The specific plaque hypothesis (Loesche 1979) has provided the conceptual framework for much of the investigation of the microbial etiology of periodontal disease for the last 40 years. More detailed investigations of the microbiota have led to the identification of increasing numbers of bacterial species which appear to be more associated with disease than health. Patterns in the association between different bacterial species in different clinical conditions were observed which encouraged the view that there may be specific combinations or complexes of species which were the most critical in the development of disease. Importantly, laboratory investigations of the pathogenic potential of some of these candidate species, either singly or in combination, came under investigation in both animal models and using *in vitro* systems. This led to the development of plausible biological mechanisms by which these specific organisms could contribute to the promotion or deregulation of an inflammatory response and/or impaired immune defense of the periodontal tissues.

The diagnostic and treatment implications of the specific plaque hypothesis are self-evident. If specific bacterial species are the driving force of the disease, then identification of the presence of these organisms in an individual ought to be helpful in predicting clinical outcome. Furthermore, targeted treatment strategies which aim to eliminate or at least control these particular organisms rather than necessarily attempting to eliminate the entire microbial population should be clinically beneficial. The specific plaque hypothesis also raises the issue of where and how these organisms are acquired. If they are acquired exogenously, that is transmitted from another individual rather than being component members of the oral microbiota acquired early in life, then strategies which prevent or limit transmission in the human population could be considered beneficial in the same way as prevention of transmission of more well known medically important human pathogens is an accepted and successful public health measure. This latter issue has been subsequently addressed by an alternative hypothesis – the ecological plaque hypothesis (Marsh 2003). In this thesis, the contribution of the environment in which the bacteria of dental plaque reside is paramount. The varying abilities of different bacteria to grow and proliferate

under different environmental conditions will dictate the balance of microbial communities at any given site on the tooth surface. For example, in a periodontal pocket where the pH can rise to well over pH 7, those bacteria most well suited to grow at alkaline pH will be able to out compete those bacteria most suited to more acid conditions. Similarly, organisms able to withstand the antimicrobial properties of the host's inflammatory response will be more predominant at inflamed sites in the periodontium than those bacteria ill equipped for this injurious environment. Hence, the composition of microbial communities in disease will be intimately linked to the environmental conditions prevalent at a diseased site.

Shifts in the environmental conditions caused by, for example, the introduction of different nutrients because of the arrival of a plasma exudate in the form of gingival crevicular fluid, will lead to concomitant shifts in the microbial community. Organisms previously limited in their growth because of, for example, only very low concentrations of the iron source, hemin, will have the nutritional capacity to increase in number and potentially out compete those bacteria most frequently found in health where low or no gingival crevicular fluid is present. Those bacteria able to withstand the killing effects of migratory phagocytic cells will be able to increase in number at the expense of those organisms susceptible to these killing mechanisms. In so doing the newly selected microbial community will present a different and potentially more injurious challenge to the periodontal tissues and hence the escalation of increasing inflammation coupled to frustrated bacterial clearance will continue. Importantly, the ecological plaque hypothesis allows for the fact that potential periodontal pathogens may be present in health, albeit in relatively low numbers, but with the capacity to become more dominant members of the community when the environmental conditions favor their competitiveness over the other, more health-associated, members of the microbiota. In so doing, this hypothesis can explain the microbial specificity of the disease without the requirement for the acquisition of these periodontal pathogens via an exogenous route of transmission in order to initiate the disease. This evolving view of the pathogenesis of periodontal disease now has a further modification which incorporates elements of all the preceding views, both specific and non-specific, and acknowledges the fundamental importance of dysbiosis of the normally benign microbial populations of the tooth surface in the development of disease (Darveau *et al*. 2012). The essence of this more recent concept of pathogenesis comes primarily from the recognition of the global population changes that occur to the microbiota in periodontal disease. As described above, there is now a broad consensus that during the progression of periodontal disease, the oral microbiota undergoes a major transition wherein the microbial community structure is shifted to an increase in total bacterial diversity accompanied by an outgrowth in the total number of disease-associated bacteria which start to predominate in the population, while otherwise being present in low numbers in a state of health (Diaz *et al*. 2016). This transition to dysbiosis of the oral microbiota during disease is completely contrary to the changes observed in microbially mediated diseases in other environments of the body such as the gut. During inflammatory disease conditions at this site, dysbiosis is accompanied by a decreased level of microbial diversity, particularly by a reduction in the anaerobic microbes, otherwise associated with conditions of health.

The drivers of the shift in microbial populations during periodontal disease are complex and multifactorial. They will include the composition of the microbial challenge and the efficacy of the immune and inflammatory systems of the host which themselves will be governed by both environmental and genetic factors. Two particular characteristics of the periodontal microbiota have acquired some significance. First, certain groups of organisms that subvert the inflammatory response are known to be responsible for influencing a community wide change on the overall bacterial population. For example, *P. gingivalis*, an organism long associated with the development of periodontal disease, has been suggested to exert a "keystone" effect in the oral microbial population during periodontal disease, by triggering a state of dysbiosis and inflammation (Hajishengallis *et al*. 2012). *P. gingivalis* is involved in both immune subversion and maintaining inflammation in the host tissues by facilitating communication between the C5aR arm of the complement system and toll-like receptor 2 molecules (TLR2) (Maekawa *et al*. 2014). Studies in mice have also shown that *P. gingivalis* is not just the sole orchestrator of this shift but is also greatly assisted by the involved activity of the commensal bacterial population (. This was particularly demonstrated in germ-free mice where the absence of the commensal microbiota failed to initiate periodontal disease and alveolar bone loss (Hajishengallis *et al*. 2011). More recently, the dysbiotic state induced by *P. gingivalis* has been shown to be a highly stable system in experimental animal models and, moreover, can be transmitted and cause periodontal bone loss in healthy recipient animals (Payne *et al*. 2019).

Further evidence to support a role for the normally benign, commensal microbiota in periodontal disease has come from a combination of metagenomic and metatranscriptomic approaches in human oral samples. For example, in a comparison of baseline versus progressing periodontal sites (Duran-Pinedo *et al*. 2014), those organisms with the largest number of upregulated putative virulence determinants were health-associated streptococcal species. Similar results were obtained when comparing baseline non-progressing with baseline progressing sites. These findings further emphasize that focusing solely on those organisms which become dominant in disease as the drivers of periodontitis may be an oversimplification: although the contribution of the disease-associated species, many of which have been shown

to have properties consistent with deregulation of the immune and inflammatory response, cannot be ignored, the overall virulence challenge in periodontitis may actually be a product of the entire microbial community (Siqueira & Rôças 2009; Berezow & Darveau 2012).

Another potential driver for the conversion to dysbiosis is the largely inflammophilic nature of the oral microbial population (Hajishengallis 2014). Disease-associated bacteria are present in subgingival plaque even in states of health at very low abundances, and these may be responsible for triggering persistent baseline levels of inflammation, albeit low, even during healthy conditions. It can be argued that provoking the inflammatory response has two benefits to an inflammophilic organism: first, through the initiation of tissue destruction, a protected site for colonization is produced which may allow the organism to out compete other less inflammophilic organisms; secondly, the accumulation of nutrients such as hemin-containing compounds and proteins from tissue exudates/plasma will facilitate the survival of specific types of anaerobic bacteria, thus generating a competitive survival advantage in the ecosystem. Thus, the inflammophilic nature of the oral microbiome drives a "self-feeding" cycle of tissue damage and bacterial survival and growth (Hajishengallis *et al.*, 2012) (Fig. 9-12). Hence the inflammatory response and the microbiome are in a bi-directional balance in oral health (homeostasis) and a bi-directional imbalance in periodontitis.

In summary, our understanding of the microbial pathogenesis of periodontal disease has undergone significant changes over the last century and continues to be refined to this day through more detailed analyses of clinical samples, improved understanding of the biology of the component organisms of this microbiota, and application of experimental model systems. The central role of a dysbiotic microbiota has been highlighted, similar to our understanding of the etiology of diseases with a complex microbial etiology at other sites of the human body. In all of these cases, disease is a consequence of a breakdown in the normally homeostatic balance between the commensal microbiota and the immune and inflammatory systems of the tissues. In this regard, periodontal infections and the response to them represent an excellent, accessible, and tractable system to understand the underlying principles of a wide range of inflammatory diseases of humans characterized by a dysbiotic commensal microbiome.

Peri-implant infections

Introduction

With a large and increasing number of dental implants being placed worldwide, it is expected that there will be an increase in the number of patients diagnosed with peri-implant diseases. Peri-implant diseases are plaque-associated inflammatory conditions of the tissues surrounding an implant and are defined as either (1) peri-implant mucositis, where there are clinical signs of inflammation (bleeding on probing, BoP) of the peri-implant mucosa without loss of supporting bone, or (2) peri-implantitis, where there is progressive bone loss in addition to

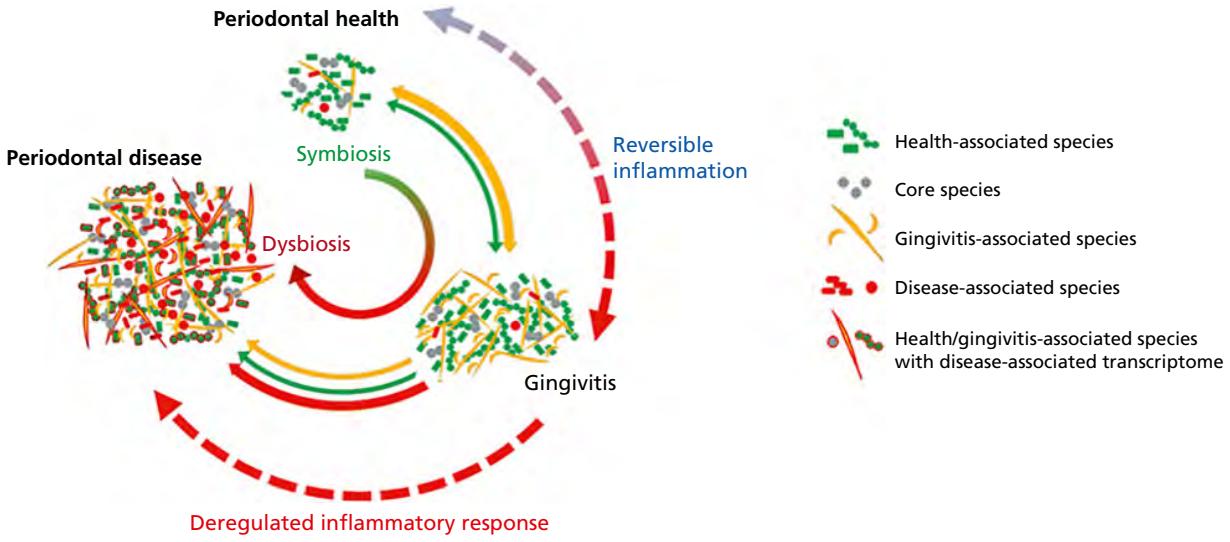
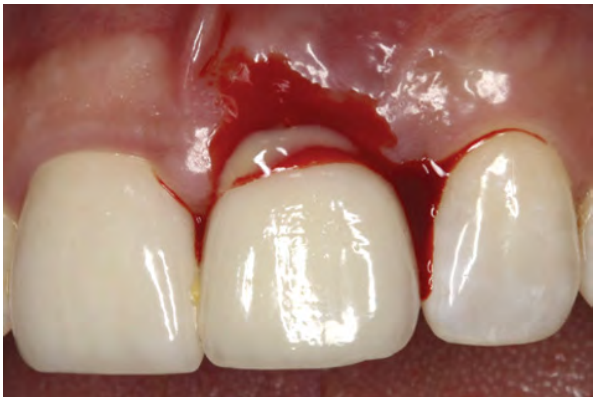


Fig. 9-12 The bidirectional relationship between the subgingival microbiome and the inflammatory and immune response. The symbiotic microbiota in health is dominated by health-associated species (green) and low abundances of species associated with gingivitis (orange) and periodontitis (red). Gingivitis is characterized by an increased biomass (green and orange arrows) comprising both green and particularly orange species and an associated increase in inflammation. In periodontitis, biomass increases further (green, orange, and red arrows) and the red species become increasingly dominant in the dysbiotic microbiota. Furthermore, the repertoire of gene expression in the green and orange species is altered with increased expression of virulence determinants. This is accompanied by the development of a deregulated inflammatory response and tissue destruction. Interventions which are able to resolve the inflammatory response may also be important in the reversal of the dysbiotic microbiota. (Source: Adapted from Curtis *et al*. 2020.)

(a)



(b)

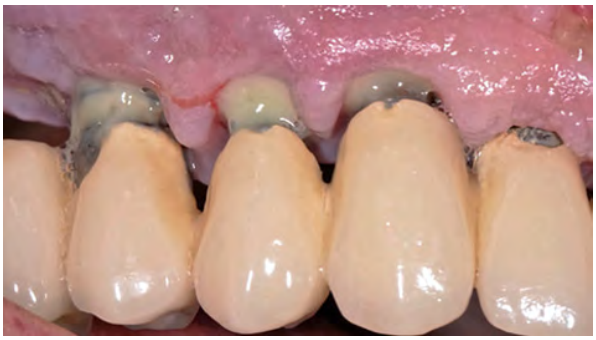


Fig. 9-13 Clinical appearance of a peri-implant infection.
(a) Bleeding and suppuration after gentle probing.
(b) Spontaneous suppuration of a deep (>6 mm) peri-implant pocket.

inflammation (BoP) of the surrounding soft tissues (Berglundh *et al*. 2018). In peri-implantitis, probing depths ≥6 mm and suppuration are frequently present (Fig. 9-13).

These infections represent an imbalance between the peri-implant biofilm and the host response to the biofilm, resulting in dysbiosis and tissue destruction. Recent advances in molecular techniques, already described in this chapter, have generated a significant body of data enabling characterization of the microbial diversity of peri-implant biofilms in health and disease.

This section addresses the etiology of peri-implant diseases, describing the nature of supra- and submucosal biofilms associated with healthy and diseased peri-implant tissues in both partially dentate and edentulous subjects. Factors influencing peri-implant biofilm formation including material surface characteristics, local environment, and implant-supported-prosthesis design are discussed. Similarities and differences in the microbiota associated with periodontal and peri-implant infections are outlined, and the clinical implications discussed.

Peri-implant biofilm formation

When a dental implant is placed, the endosseous part of the implant should ideally be surrounded by bone and is, therefore, usually not exposed to biofilm formation. In contrast, the transmucosal part of the implant/abutment, once exposed to the oral cavity, becomes rapidly colonized by microorganisms (Fürst *et al*. 2007), which attach to salivary proteins and peptides constituting the pellicle. The pellicle provides receptors for adhesins present on the cell surface of all oral bacterial species. Enamel pellicles and titanium pellicles are not identical. Salivary pellicles formed on titanium surfaces *in vitro* have been found to include molecules such as high molecular weight mucins, α- amylase, secretory IgA, and proline-rich proteins, whereas molecules commonly found on tooth enamel (cystatins and low molecular weight mucins) were not detected (Edgerton *et al*. 1996). Although the salivary pellicle that forms on titanium surfaces might differ from that forming on enamel surfaces, the differences do not seem to influence the bacterial composition of the biofilm formation (Leonhardt *et al*. 1995).

Because of a common ecologic environment, the principles and sequence of biofilm formation at teeth and implants are similar (Lang & Berglundh 2011). Biofilm formation is initiated by adhesion of early colonizers such as *Streptococcus sanguinis* and *Actinomyces naeslundii*, through interactions with the salivary pellicle. The early colonizers grow, modify the environment, and promote the adhesion of secondary colonizers via co-aggregation (Fig. 9-14).

The biofilm with its diverse community of interacting organisms, glycocalyx matrix, and complex structure becomes stable over time, affording a protective environment from host defenses and antimicrobial agents (Marsh 2005; Socransky & Haffajee 2005; Kolenbrander *et al*. 2006). Figure 9-15 shows a scanning electron micrograph illustrating the characteristic biofilm formation on a titanium implant surface. Factors which may influence microbial colonization include the surface characteristics of the implant/abutment, local environment, resident oral microbiota, and implant prosthesis design and its accessibility for oral hygiene.

Surface characteristics of the implant/abutment

Surface characteristics of the implant/abutment and restorative components, including chemical composition, surface free energy (SFE; wettability), and surface roughness, may impact biofilm formation. Both *in vitro* and *in vivo* studies have indicated that increasing the surface roughness of titanium results in greater bacterial adhesion and biofilm accumulation (Teughels *et al*. 2007, 2006; Subramani *et al*. 2009; Burgers *et al*. 2010; Fröjd *et al*. 2011). An *in vitro* scanning electron microscope study investigating attachment of oral species to titanium disks with various surface characteristics, demonstrated an increased bacterial attachment to rough surfaces (Wu-Yuan *et al*. 1995). In a series of split-mouth studies, it was demonstrated that an increase in the surface

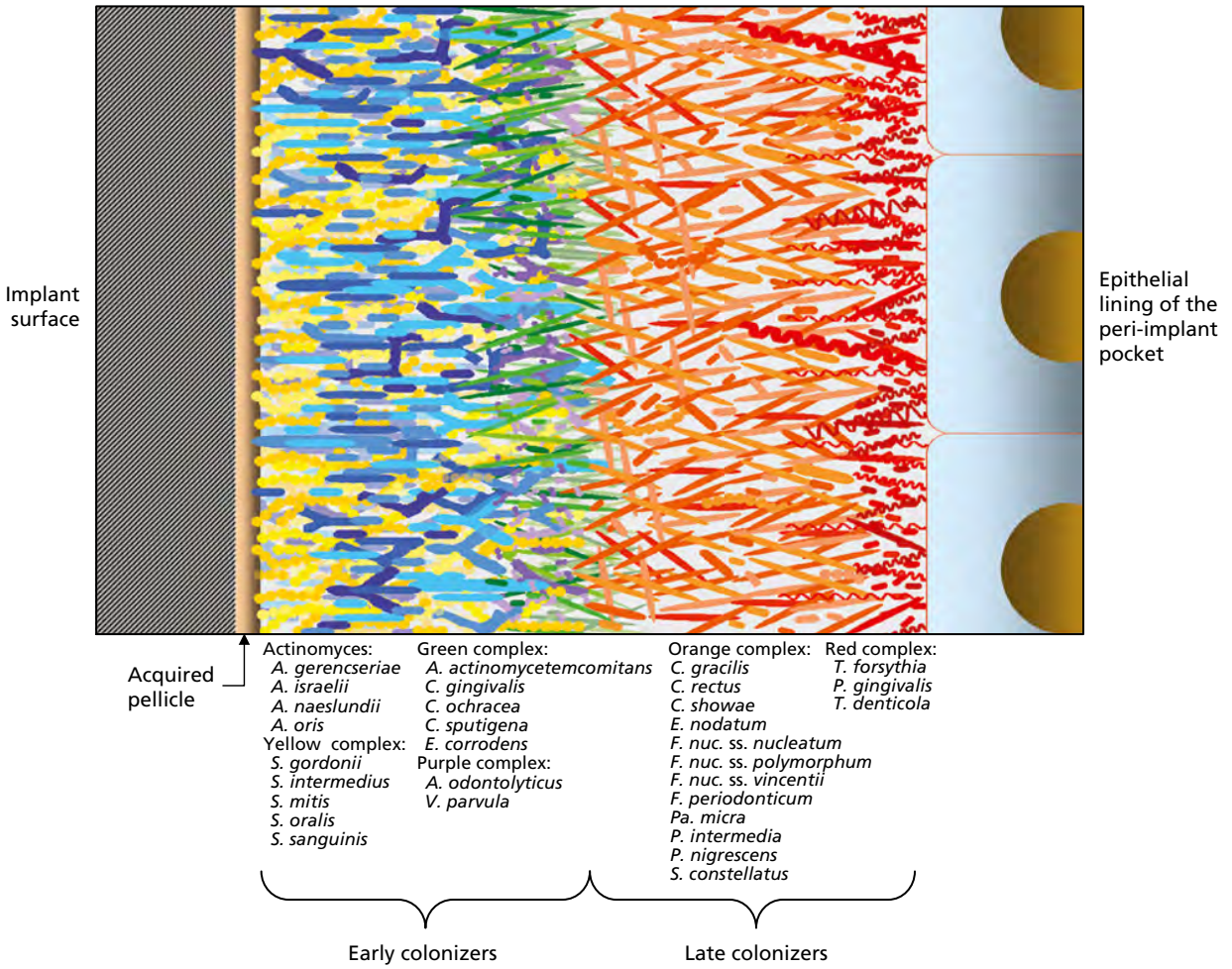


Fig. 9-14 Simplified schematic representation of the microbial succession that may take place on an implant surface exposed to the oral environment. Microbial species are colored according to the microbial complexes described by Socransky *et al*. (1998).

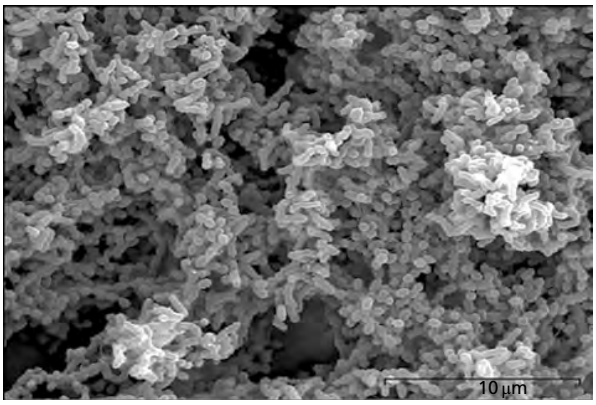


Fig. 9-15 Scanning electron micrograph depicting the characteristic biofilm structure on a titanium implant surface. The bacterial cell mass within the extracellular matrix covers the surface of the implant with the typical morphology of stacks containing bacterial communities interspersed among broad circulation channels.

roughness (Ra) above a threshold of 0.2 µm and/or an increase in the SFE facilitated biofilm formation on restorative materials (Teughels *et al*. 2006). The effect of SFE on supra- and submucosal plaque maturation around implants was investigated by comparing plaque from abutments with either a high (titanium) or a low (teflon coating) SFE (Quirynen *et al*. 1993). The teflon-coated titanium abutments harbored a less mature biofilm characterized by a higher proportion of cocci and a lower proportion of motile organisms and spirochetes than the uncoated titanium abutments (Quirynen *et al*. 1993). When both surface characteristics interact with each other, surface roughness was found to be predominant (Teughels *et al*. 2006). The impact of surface roughness on biofilm formation can be explained by several factors, including the protection from shear forces, increased area for adhesion, and difficulty in cleaning rough surfaces which enables rapid regrowth of the biofilm by multiplication of resident bacterial species (Quirynen & Bollen 1995). Quantitative analysis of 14-day supra- and submucosal biofilm formation on titanium healing abutments in 10 subjects, showed that biofilm formation was significantly increased by higher surface roughness in supramucosal areas, with no influence of increased surface roughness in the submucosal environment (Elter *et al*. 2008).

The recent development of *in vitro* multispecies biofilm models and the use of microscopic techniques such as scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM) has enabled investigators to study the dynamics and

structure of biofilms forming on implant surfaces. When comparing the biofilm formation between hydroxyapatite, titanium, and zirconia surfaces, the dynamics were similar irrespective of the surface. However, significant differences were reported on the three-dimensional organization of the biofilms and on the number of bacteria within the biofilms. Although hydroxyapatite and titanium surfaces showed similar biofilm dynamics and structure, biofilms on zirconium surfaces were significantly thinner than on titanium and hydroxyapatite surfaces and with the percentage of area coverage by biofilm on zirconium material significantly lower than over titanium surfaces (Sanchez *et al*. 2014). In a subsequent study, using the same *in vitro* biofilm model but on whole implant surfaces, studying implants with different micro surface topography CLSM demonstrated a significantly greater biomass in moderate-roughness surface implants when compared with minimal-roughness surface implants. SEM showed a higher number of bacteria within the characteristic surface micropores in the moderate-roughness surface implants and qPCR analysis also reported significantly higher number of total bacteria and concentrations in the moderate-roughness surface implant (Bermejo *et al*. 2019b) (Fig. 9-16).

Biofilm formation on implant surfaces may not only be influenced by the micro surface topography but also by the implant macro design. Analysis of biofilm formation on implant surfaces has shown that the

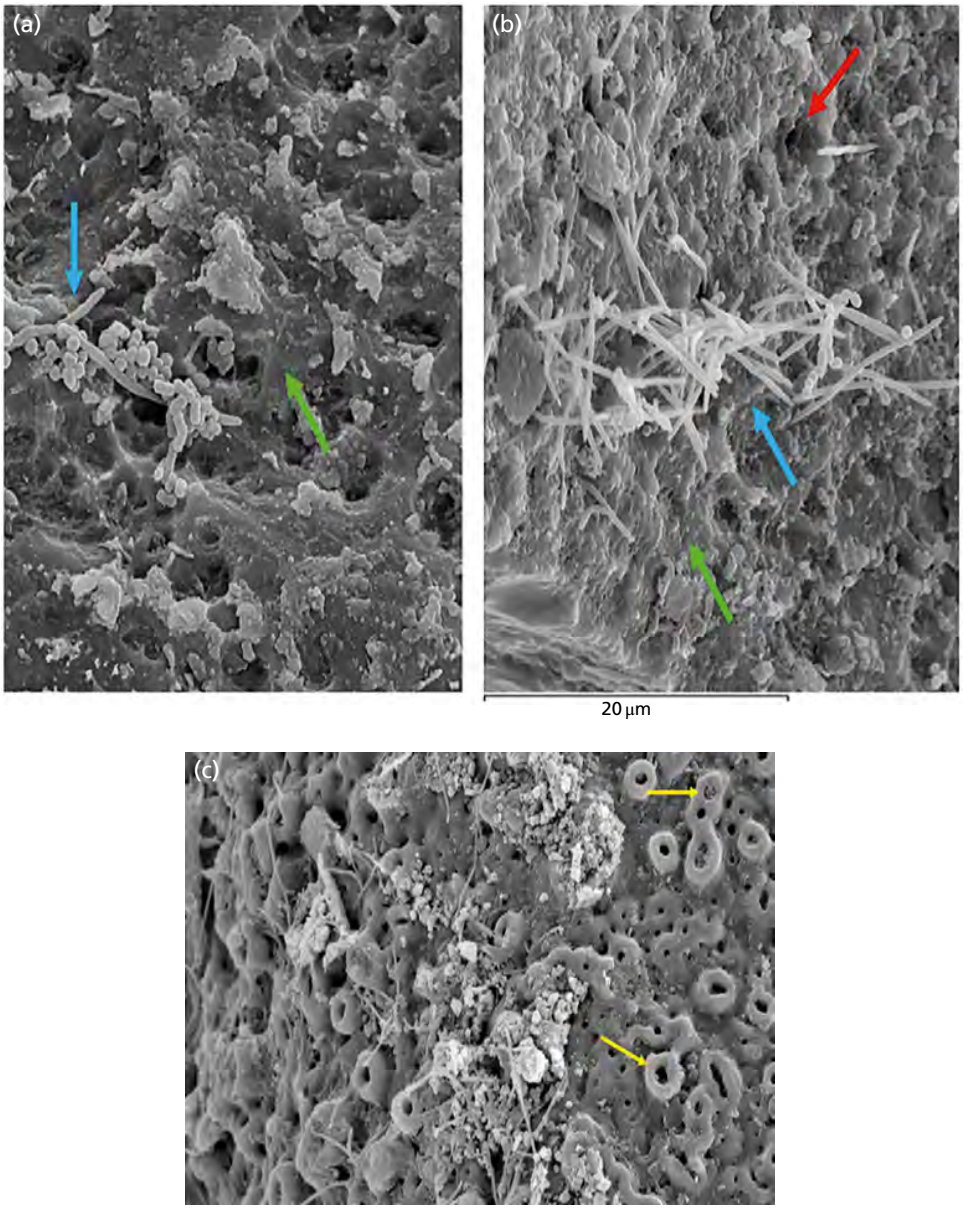


Fig. 9-16 (a, b) Biofilms on a minimal-roughness implant surface. Spindle-shaped rods forming 3-D structures and adherent short streptococcal chains (*Fusobacterium nucleatum* and *Streptococcus oralis*) (blue arrows). See titanium surface covered by a thick extracellular matrix covering the implant surface (green and red arrows). (c) Biofilms on a moderate-roughness implant surface with similar structural characteristics to those found on minimal-roughness surfaces. Bacteria are disposed in larger masses of bacterial communities covering the implant surface and within the larger pores of the moderate-roughness surface (yellow arrows).

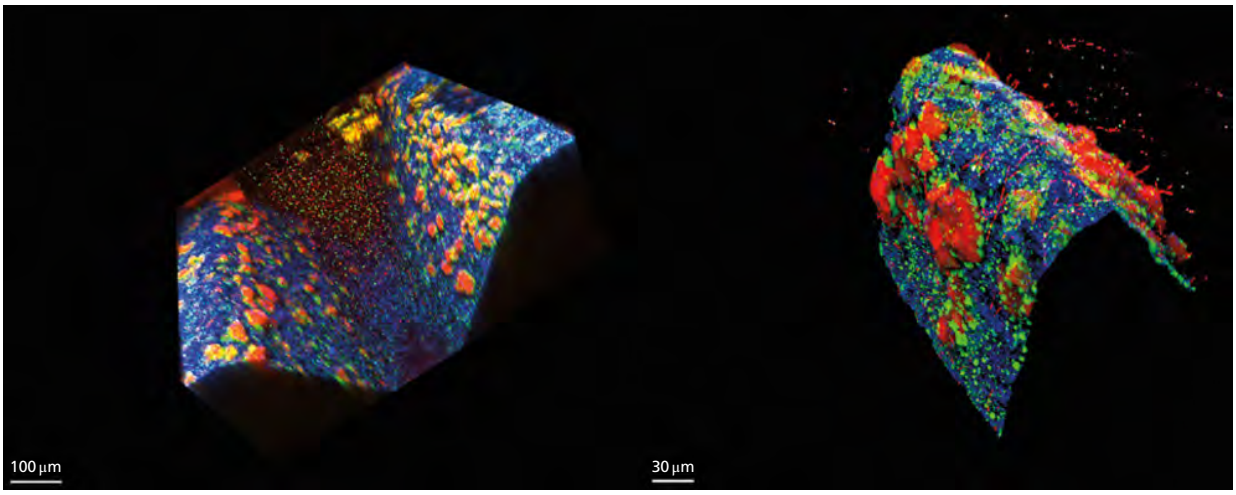


Fig. 9-17 Confocal laser scanning microscopy images depicting biofilm formation at both the peaks and the valleys of dental implants. BacLight Live/Dead stain assessing the vitality of cells within the biofilm clearly shows a higher proportion of dead cells in the valleys between the cells. Blue, implant material; green, live cells; red, dead cells.

entire implant surface will be colonized by bacteria in a short period of time evolving to a mature, well-structured biofilm. However, depending on the location, the biofilm will exhibit different ratios of cell viability, with the peaks of the threads harboring more live bacteria and the valleys between the threads accumulating greater amounts of dead bacteria, which possibly reflects the reduced availability of nutrients in the least accessible areas (Bermejo et al. 2019a) (Fig. 9-17).

Similar results have also been reported using *in vitro* two and three-species biofilm models, 16S ribosomal RNA (rRNA) fluorescence, and confocal scanning laser microscopy (CSLM) (Fröjd *et al*. 2011). After 2 hours, surfaces with increased surface roughness had higher bacterial adhesion, most likely the result of protection of bacteria from shear forces. However, after 14 hours the volume of biofilm was similar on all surfaces, indicating that the influence of surface characteristics on adhesion was surpassed by biofilm development (Fröjd *et al*. 2011).

A range of restorative materials is available for fabrication of implant components, including titanium, gold, ceramics, and zirconia. Because of an increased demand for tooth-colored restorations, zirconium oxide ceramics (zirconia) have become more widely used as materials for implant abutments and transmucosal components of implant prostheses. In an *in vivo* study using CSLM to investigate the formation of oral biofilm on various dental ceramics, zirconia was shown to exhibit low biofilm accumulation when used intraorally (Bremer *et al*. 2011). Several randomized controlled studies have compared the early bacterial colonization of periodontal pathogens at zirconium oxide abutments to titanium alloy abutments. Although zirconium oxide abutments showed lower SFE than titanium abutments, there was no difference in the adhesion of *A. actinomycetemcomitans* and *P. gingivalis*, 5 weeks after abutment connection (Salihoglu *et al*. 2011). This lack of difference between zirconia and titanium was confirmed in a similar study evaluating bacterial counts of seven bacterial species 2 weeks and 3 months following abutment connection (van Brakel *et al*. 2011).

Recent studies employing molecular methods of detection have found that titanium and zirconia abutment surfaces are rapidly colonized by a bacterial community similar to those found in adjacent teeth (de Freitas *et al*. 2018; Raffaini *et al*. 2018). De Freitas *et al*. (2018) examined the biofilm at implant sites after 1, 3, and 6 months of loading in 20 participants and found titanium or zirconia abutments as well as teeth showed similar total numbers of operational taxonomic units (OTUs) colonizing surfaces over time. The most prevalent phyla identified were Firmicutes, Proteobacteria, Fusobacteria, Bacteroidetes, and Actinobacteria with significant differences between abutment surfaces and time point. The results suggested that there may be a selective adhesion of different bacterial genotypes for either titanium or zirconia surfaces (de Freitas *et al*. 2018).

A study using DNA-checkerboard and 16S-rDNA-pyrosequencing identified 161 bacterial taxa representing 12 different phylotypes associated with either titanium or zirconia implant-abutments in 20 healthy participants (Nascimento *et al*. 2016). Species belonging to the genera *Fusobacterium*, *Prevotella*, *Actinomyces*, *Porphyromonas*, *Veillonella*, and *Streptococcus* were common in all sites. Some differences were observed at sites with titanium abutments compared with zirconia abutments and titanium abutments presented the highest total microbial count and higher counts of pathogenic species (Nascimento *et al*. 2016).

A cross-sectional study evaluated early biofilm formation, using checkerboard DNA-DNA hybridization, at titanium and zirconia implant abutments in 20 individuals over a period of 30 days. Genome counts were found to be low at the time of implant loading for both abutment materials and increased over time with similar microbial counts and diversity over time (Raffaini *et al*. 2018).

Based on the surface roughness value Sa (average 3D height deviation), a proposal to categorize the surfaces of titanium implants as smooth (Sa <0.5 µm), minimally rough (Sa 0.5–1.0 µm), moderately rough (Sa 1.1–2.0 µm), and rough (Sa >2.0 µm) was made (Albrektsson & Wennerberg 2004). The original Brånemark turned machined surface was a minimally rough surface. More recently, the surfaces of commercially available titanium implants have been modified to promote osseointegration and are moderately rough or rough. If these implant surfaces become exposed to the oral environment, because of loss of supporting peri-implant marginal bone, the roughened surface may enhance biofilm formation and contamination of the implant surface. Although there is no evidence that surface roughness of a properly placed and integrated implant influences the development of peri-implant infection, it has been documented that rough surface implants (titanium plasma sprayed [TPS]) are more likely to develop peri-implantitis than minimally rough implant surfaces if the implant surface becomes exposed to the oral environment (Lang & Berglundh 2011).

Local oral environment

Peri-implant colonization has been studied in both edentulous and partially dentate patients. A cause-and-effect relationship between biofilm formation on implants and peri-implant mucositis has been demonstrated in humans (Pontoriero *et al*. 1994; Zitzmann *et al*. 2001; Heitz-Mayfield *et al*. 2012; Salvi *et al*. 2012). In these studies, when oral hygiene was discontinued in order to allow undisturbed plaque accumulation, clinical signs of peri-implant inflammation appeared after a few days and resolved when oral hygiene was reinstated. Not surprisingly, the composition of peri-implant biofilms associated with this inflammation, which may lead to further peri-implant infection in a susceptible host, is influenced by the local environment and the microbiota on the remaining teeth in partially dentate subjects. Cross-sectional studies have shown that the microbiota identified in the peri-implant sulci are nearly identical to those found at neighboring teeth (Quirynen & Listgarten 1990; Leonhardt *et al*. 1993; Mombelli *et al*. 1995a; Lee *et al*. 1999b; Hultin *et al*. 2000, Agerbaek *et al*. 2006). It has been shown that deeper periodontal pockets harbor a greater number and proportion of periodontal pathogens (Socransky *et al*. 1991), serving as a potential reservoir for recolonization.

Transmission of bacteria from periodontal pockets to the peri-implant region of newly placed implants has been suggested in longitudinal studies (Mombelli *et al*. 1995a). A number of studies have used techniques to identify individual strains of bacteria in order to determine if transmission from a periodontal site to an implant site can occur in a patient (Sumida *et al*. 2002; Takanashi *et al*. 2004). Using pulsed field gel electrophoresis (PFGE), chromosomal DNA segmentation patterns of isolates of *P. gingivalis* and *P. intermedia* obtained from implants and natural teeth in the same subjects were found to be identical, whereas PFGE patterns differed among samples from different subjects (Sumida *et al*. 2002). Similarly, it was found that 75% of the *P. gingivalis* isolates in samples from teeth and implants were the same in one subject, whereas 100% of the *P. intermedia* strains within a subject were a perfect match, clearly demonstrating transmission from the natural teeth to the implant sites (Takanashi *et al*. 2004). Although the remaining dentition seems to be the primary source of bacteria for the colonization of implant surfaces in partially dentate subjects, the potential role of soft tissue surfaces, crypts of the tongue or tonsils, and saliva as reservoirs for implant colonization should also be considered. A comprehensive assessment of the microbiota associated with oral mucosal surfaces in edentulous subjects wearing complete dentures outlined the numerous habitats colonized by biofilms of differing complexities, unique to each individual (Sachdeo *et al*. 2008). Biofilm samples were taken from the dentures, the dorsal, lateral, and ventral surfaces of the tongue, the floor of the mouth, buccal mucosa, hard palate, vestibule/lip, and saliva. Checkerboard DNA–DNA hybridization was used to analyse the levels and proportions of 41 different species. Distinct patterns of microbial colonization were seen on different soft tissue surfaces and in saliva. One of the more important findings of this investigation was the detection of the periodontal pathogens *A. actinomycetemcomitans* and *P. gingivalis* in these edentulous subjects, as it was previously thought that these species would not be present following removal of all teeth (Sachdeo *et al*. 2008). Other studies have also reported the presence of periodontal pathogens in edentulous subjects (Danser *et al*. 1998; Cortelli *et al*. 2008) and in edentulous subjects in an elderly population who had never worn dentures but had a history of periodontitis (Fernandes *et al*. 2010).

In contrast, a recent study in 26 edentulous patients evaluated the levels of *P. gingivalis*, *T. forsythia*, and *S. aureus* prior to and 6 months after placement of one-piece zirconia and titanium implants (Siddiqi *et al*. 2016). A qRT-PCR assay using SYBR green/ROX chemistry was used for the detection and quantification of the three bacteria. Samples were collected from both the tongue and from around the implants once placed. The results showed that prior to implant placement all three bacterial species were below the limit of quantification and that they were not identified at either zirconia or titanium implants 6 months after placement (Siddiqi *et al*. 2016).

Taken together, the above findings have clinical implications for the prevention of peri-implant infections. Pathologic conditions in the oral environment, such as the persistence of untreated periodontal disease, could induce changes in the ecosystem that may favor the colonization of pathogenic microorganisms at implant sites (Lang & Berglundh 2011). Treatment

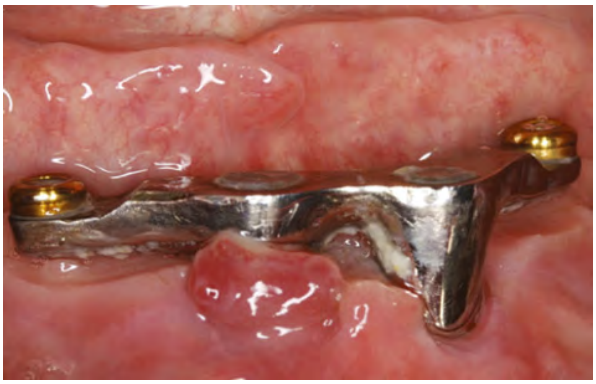
of periodontal disease prior to implant placement, and provision of adequate supportive periodontal/peri-implant maintenance care in order to reduce the reservoir of potential periodontal pathogens, may reduce the risk of peri-implant infections.

Oral hygiene and accessibility

The importance of maintenance care in the prevention of peri-implant infections has been demonstrated in several studies where subjects who did not follow a structured maintenance care program had a greater incidence of peri-implant infections than those who followed a maintenance care program (Roccuzzo *et al*. 2010, Costa *et al*. 2012). The importance of good compliance following treatment [adhering to the recommended prophylaxis/supportive periodontal therapy (SPT) interval, and maintaining a full-mouth plaque score of <20% (O'Leary *et al*. 1972)] was also highlighted in a cross-sectional study where the prevalence of peri-implantitis was associated with poor compliance (Rinke *et al*. 2011).

Peri-implant infection has been linked with poor oral hygiene (Lindquist *et al*. 1997; Ferreira *et al*. 2006) (Fig. 9-18). Higher plaque scores, assessed using the modified Plaque Index (mPI) (Mombelli *et al*. 1987), were significantly associated with peri-implant infection in a cross-sectional study evaluating 212 partially dentate subjects with implant-supported prostheses (Ferreira *et al*. 2006). One pertinent study underlined the importance of designing implant prostheses with adequate access for cleaning (Serino and Ström 2009). Subjects who were referred for treatment of peri-implantitis at one or more of their implants were found to have no access for appropriate oral hygiene measures in a high proportion of the implants diagnosed with peri-implantitis, whereas good access for oral hygiene was rarely associated with peri-implantitis (Serino & Ström 2009). Implant reconstructions should be designed to enable access for regular self-performed biofilm removal, and for early detection of clinical signs of peri-implant infection (Fig. 9-19).

(a)



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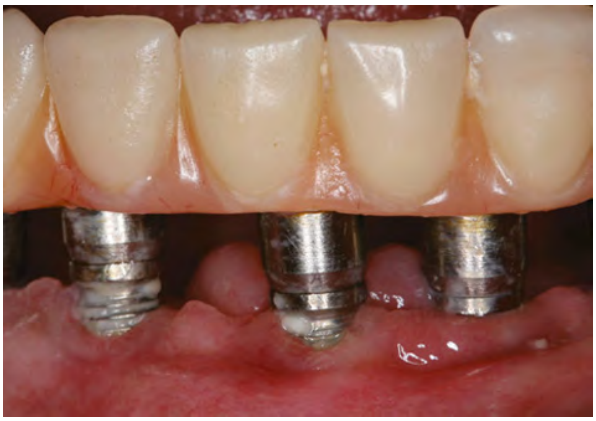
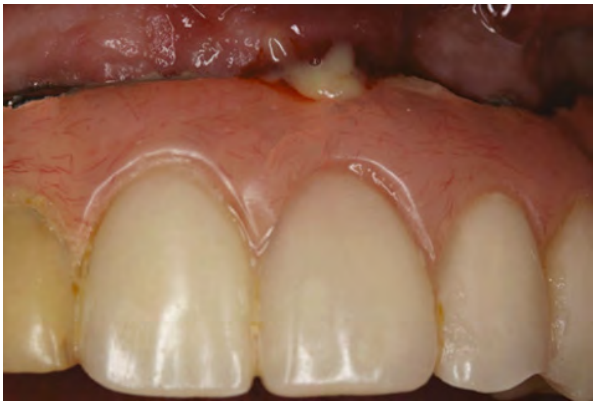


Fig. 9-18 Supramucosal peri-implant biofilm accumulation and associated peri-implant infections. (a) Biofilm present on the implant supported bar and implant abutments. (b) Biofilm present on the titanium abutment surfaces and exposed implant threads caused by poor oral hygiene.

(a)



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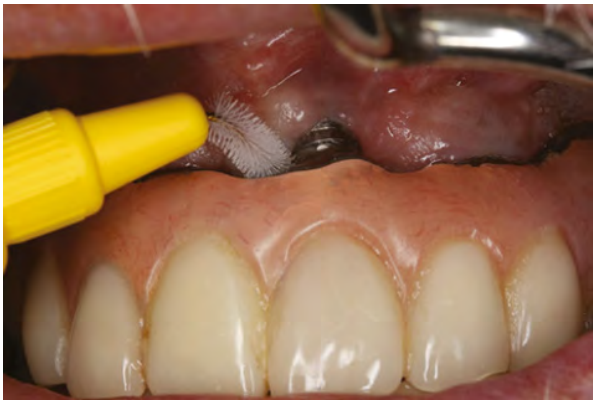


Fig. 9-19 (a) An implant-supported prosthesis where there is inadequate access for plaque removal and an associated peri-implant infection (suppuration and bleeding). (b) After remodeling of the implant-supported prosthesis to enable access for plaque removal.

Microbiota associated with peri-implant mucosal health

An understanding of the nature and composition of biofilms associated with peri-implant health and disease is important in order to develop targeted and effective preventive and treatment strategies for the management of peri-implant infections.

A peri-implant biofilm is formed within minutes of exposure to the oral cavity, and a multispecies supra- and submucosal complex community develops within weeks to months of exposure to the oral cavity (Quirynen *et al*. 2005; Fürst *et al*. 2007). This is similar to the dynamics of biofilm formation at teeth (Socransky & Haffajee 1997; Li *et al*. 2004; Kolenbrander *et al*. 2006), although it has been suggested that it may take longer for a mature biofilm to develop at implant sites (Papaioannou *et al*. 1995; Sbordone *et al*. 1999). Figures 9-20 and 9-21 illustrate the similarity of the microbiota colonizing tooth and implant sites within the same subject (Quirynen *et al*. 2006). Figure 9-22 illustrates the increase in detection frequency of *P. gingivalis* and *Tannerella forsythia* over time after non-submerged implant placement in 22 partially dentate subjects with a history of treated aggressive periodontitis (De Boever & De Boever 2006).

Early investigations characterized the peri-implant microbiota using darkfield microscopy and culture analyses to examine samples taken from the peri-implant sulci of newly placed implants in edentulous subjects (Mombelli *et al*. 1987, 1988; Mombelli & Mericske-Stern 1990). The microbiota associated with peri-implant health was described as predominantly Gram-positive facultative cocci, with high levels of *Actinomyces* and *Veillonella* spp., low total anaerobic counts, low levels of Gram-negative anaerobic rods, and low proportions of *Fusobacterium* spp., spirochetes, fusiforms, motile and curved rods. Thus, the microbiota appeared similar to that associated with healthy periodontal sites in healthy periodontal subjects (Socransky & Haffajee 2005).

As previously discussed, the lack of detection of species such as *P. gingivalis* in edentulous patients (Mombelli *et al*. 1987; Danser *et al*. 1994, 1995, 1997) and edentulous patients with implants (Mombelli *et al*. 1987; Ong *et al*. 1992) led to the suggestion that periodontal pathogens do not colonize dental implants placed in edentulous individuals. However, subsequent investigations incorporating more sensitive molecular techniques for analyses (including polymerase chain reaction [PCR], DNA– DNA checkerboard hybridization) have shown this not to be the case. Using molecular techniques, the presence of periodontal pathogens (including *P. gingivalis*, *T. forsythia*, *A. actinomycetemcomitans*, *Treponema denticola*, *Parvimonas micra*, *Streptococcus intermedius*) in low proportions and levels was demonstrated in healthy peri-implant sulci in fully edentulous subjects (Lee *et al*. 1999b; Hultin *et al*. 2002; Quirynen *et al*. 2005;

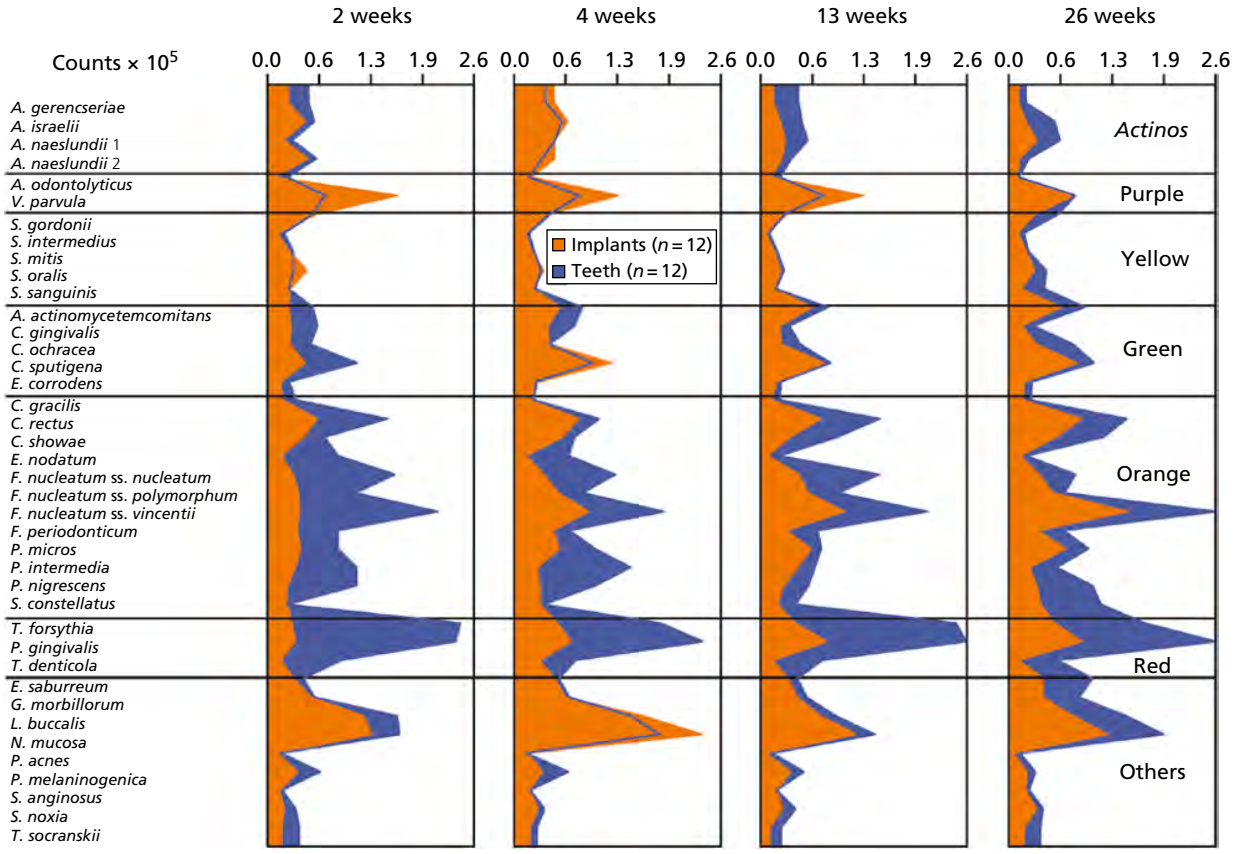


Fig. 9-20 Mean counts (×10^5) of 40 species in samples from 48 implants and 48 teeth in 12 subjects at 2, 4, 13, and 26 weeks after exposure of the implant to the oral environment. Mean counts of each species were computed by averaging the data for each site category separately in each subject, and then averaging across subjects at each time point separately. Significance of differences between site categories was sought using the Mann–Whitney test. No significant differences were found after adjusting for multiple comparisons (Socransky *et al*. 1991). The species were ordered and grouped according to the complexes described by Socransky *et al*. (1998). (Source: Data adapted from Quirynen *et al*. 2006.)

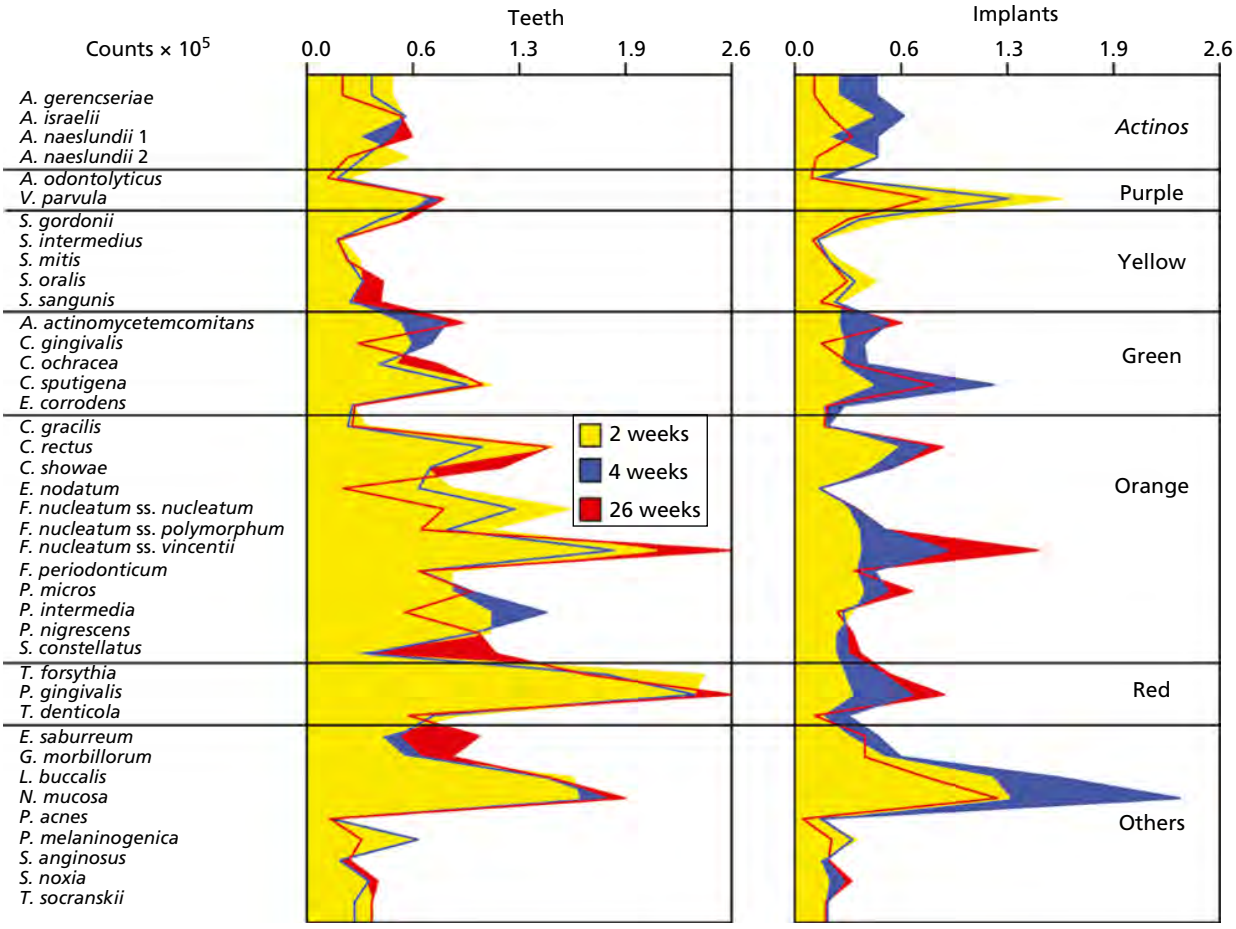


Fig. 9-21 Mean counts (×10^5) of 40 species at 2, 4, and 26 weeks after implant exposure in samples from 48 teeth (left panel) and 48 implants (right panel) from 12 subjects. Mean counts of each species were computed by averaging the data for each site category separately in each subject, and then averaging across subjects at each time point separately. Significance of differences over time was sought using the Friedman test. No significant differences were detected after adjusting for multiple comparisons (Socransky *et al*. 1991). The species were ordered and grouped according to the complexes described by Socransky *et al*. (1998). (Source: Data adapted from Quirynen *et al*. 2006.)

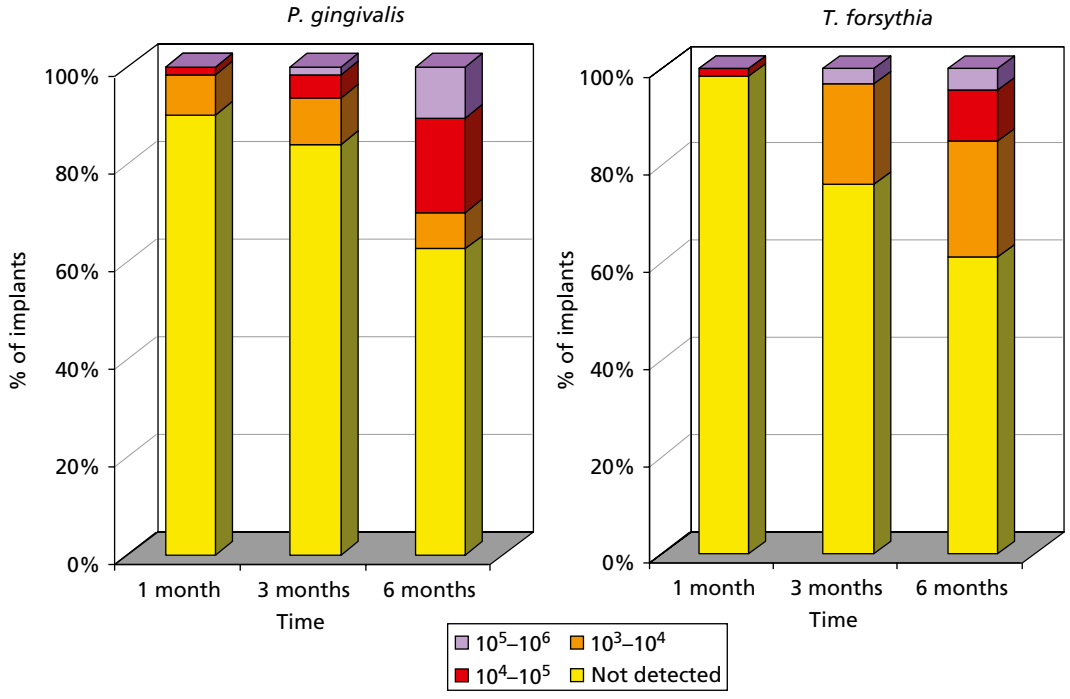


Fig. 9-22 Stacked bar charts of the frequency of detection of *Porphyromonas gingivalis* (left panel) and *Tannerella forsythia* (right panel) at different levels on 68 implants inserted in 22 subjects with a history of treated aggressive periodontitis at different time points. The bar colors indicate the different levels of detection of *P. gingivalis* and *T. forsythia* using DNA probes. (Source: Data adapted from De Boever & De Boever 2006.)

Devides & Franco 2006; Van Assche *et al*. 2009; Fernandes *et al*. 2010; Quirynen & Van Assche 2011) and partially dentate subjects (Lee *et al*. 1999b; Casado *et al*. 2011; Van Assche *et al*. 2011) (Figs. 9-20, 9-21, 9-22). It should be emphasized that in patients with good oral hygiene and a stable periodontal condition, implants can maintain a successful treatment outcome without peri-implant infection despite the presence of periodontal pathogens (Van Assche *et al*. 2011).

Microbiota associated with peri-implant infections

The characteristics of biofilms associated with peri-implant disease (peri-implant mucositis and peri-implantitis) have been studied using various microbiologic techniques and sampling methods, most of which disrupt the three-dimensional structure of the biofilm. Although the majority of studies have found the composition of the submucosal microbiota to be similar to that in periodontitis, with a mixed anaerobic infection dominated by Gram-negative bacteria, some studies have found high numbers of other microorganisms not commonly associated with periodontal diseases, including enteric rods and yeasts, or microorganisms associated with extraoral infections such as staphylococci (i.e. *Staphylococcus aureus* and *Staphylococcus epidermidis*) or peptostreptococci (Leonhardt *et al*. 2003; Fürst *et al*. 2007; Persson *et al*. 2010).

Numerous studies have documented the presence of periodontal pathogens at peri-implantitis sites (Rams and Link, 1983; Rams *et al*. 1984, 1991; Mombelli *et al*. 1987, 1988, 2001; Becker *et al*. 1990; Sanz *et al*. 1990; Alcoforado *et al*. 1991; Rosenberg *et al*. 1991; Mombelli & Lang 1992; Augthun & Conrads 1997; Danser *et al*. 1997; Salcetti *et al*. 1997; Kalykakis *et al*. 1998; Muller *et al*. 1999; Hultin *et al*. 2000; Rutar *et al*. 2001; Leonhardt *et al*. 2003; Botero *et al*. 2005; Covani *et al*. 2006; Persson *et al*. 2006, 2010; Shibli *et al*. 2008; Emrani *et al*. 2009; Maximo *et al*. 2009; Tabanella *et al*. 2009). Figure 9-23 illustrates the microbial complexity of a submucosal biofilm associated with a peri-implantitis lesion. Some studies have examined the microbiota of healthy peri-implant sites, comparing that found in the context of an otherwise healthy mouth versus that found when peri-implantitis was present at some implants, noting an increased level of pathogens even in healthy sites in patients with peri-implantitis (Fig. 9-24). The findings of the mentioned studies outline the similarities in microbiota found at sites with peri-implant infection and periodontitis.

The microbiota associated with peri-implant mucositis appears to be similar to that associated with peri-implantitis (Maximo *et al*. 2009; Casado *et al*. 2011), suggesting that supramucosal plaque formation and development of peri-implant mucositis is the precursor to peri-implantitis. Plaque samples, analyzed using checkerboard DNA–DNA hybridization for 40 bacterial species, from 13 subjects with peri-implantitis and 12 subjects with peri-implant mucositis found similar levels of all species with the exception of three species (*T. forsythia*: higher levels in peri-implantitis; *Actinomyces gerencseriae* and *Campylobacter ochracea*: lower levels in peri-implantitis) (Maximo *et al*. 2009) (Fig. 9-25). In another study evaluating the presence and levels of 36 species by DNA–DNA hybridization, there were no significant differences observed in supra- and submucosal microbial profiles from the same implant site, in 22 subjects with peri-implantitis (Shibli *et al*. 2008) (Fig. 9-26). Deeper peri-implant pockets harbor greater total anaerobic counts and presence of *P. gingivalis* compared to shallower peri-implant pockets (Rutar *et al*. 2001). Human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) have also been associated with peri-implant infection, suggesting a possible etiologic role via local immune suppression allowing overgrowth of periodontal pathogens (Jankovic *et al*. 2011). HCMV was detected in 65% and EBV in 45% of the 20 peri-implantitis sites evaluated, whereas co-infection was reported in 33% of peri-implantitis sites. In healthy and peri-implant mucositis sites, no co-infection was detected (Jankovic *et al*. 2011).

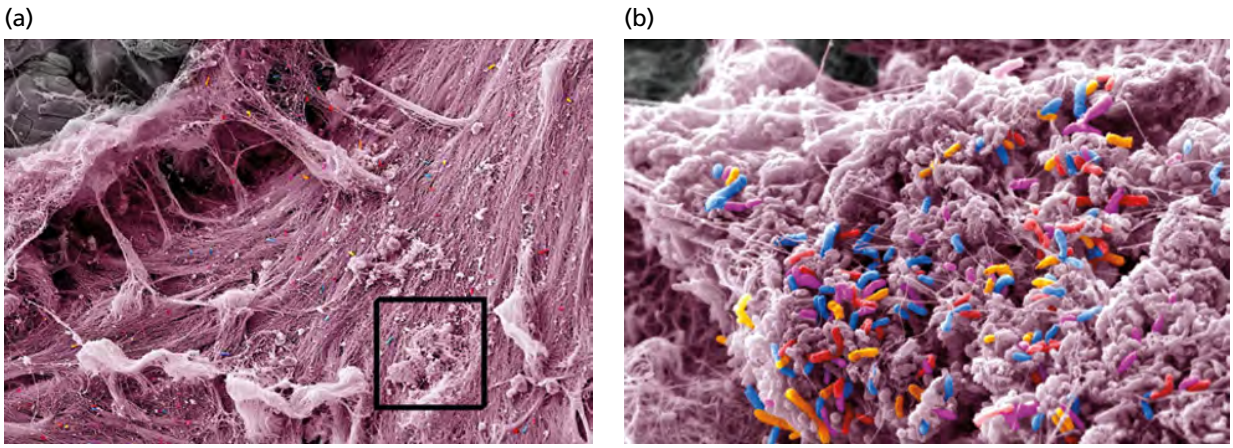


Fig. 9-23 (a) Scanning electron micrograph showing biofilm on an implant surface (black square) from a biopsy specimen retrieved from a peri-implantitis patient. (b) Higher magnification of the biofilm surface demonstrating its microbial complexity (subgingival bacteria marked with different colors).

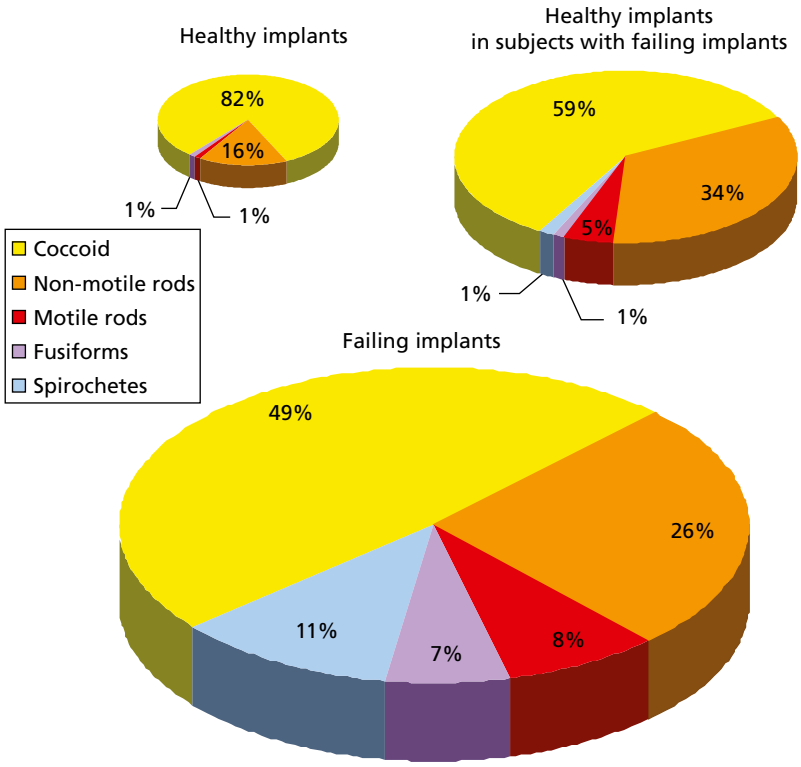


Fig. 9-24 The mean percentage of different morphotypes in the microbiota of samples from 10 healthy implant sites in subjects with only successful implants, samples from six healthy implant sites, and from eight peri-implantitis sites in subjects with peri-implantitis. The numbers correspond to the mean percentage of each morphotype within the microbiota. The areas of the pie charts have been adjusted to reflect mean total counts of each site category. (Source: Data adapted from Mombelli *et al*. 1987.)

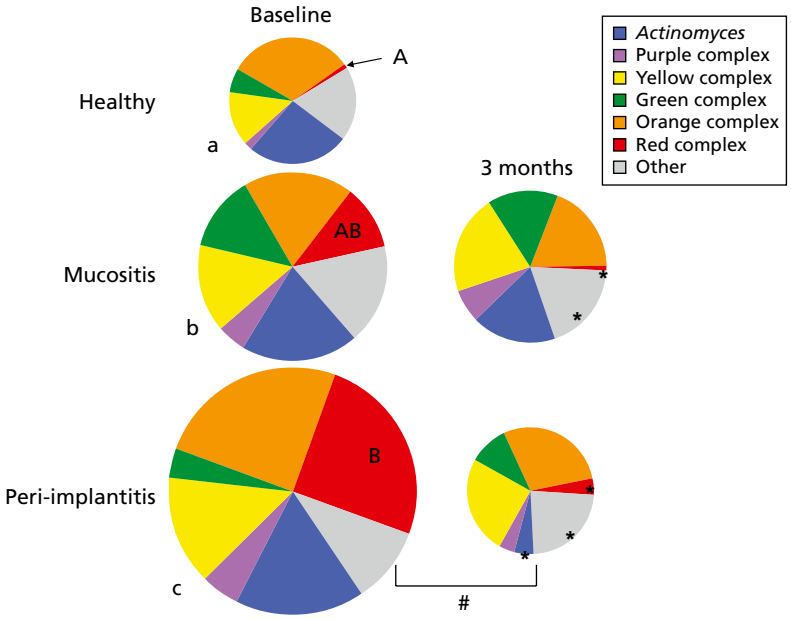


Fig. 9-25 The mean percentage DNA probe count of subgingival microbial complexes (Socransky *et al*. 1998) from samples of submucosal biofilms obtained from healthy implants ($n = 10$), implants with mucositis (n = 12), and implants with peri-implantitis (n = 13) at baseline and 3 months after mechanical therapy (diseased implants only). The areas of the pie charts were adjusted to reflect the mean total counts of each clinical group. Significance of differences between the two time points for the total DNA probe counts ($^{\#}P < 0.05$) and the proportions of each complex ($^{*}P < 0.05$) was tested using the Wilcoxon signed-rank test. Different uppercase letters indicate differences in proportions of microbial complexes among groups at baseline using the Kruskal–Wallis and Dunn *post-hoc* tests. Different lowercase letters indicate differences in the mean total DNA probe counts at baseline using the Kruskal–Wallis and Dunn *post-hoc* tests. (Source: Data adapted from Maximo *et al*. 2009.)

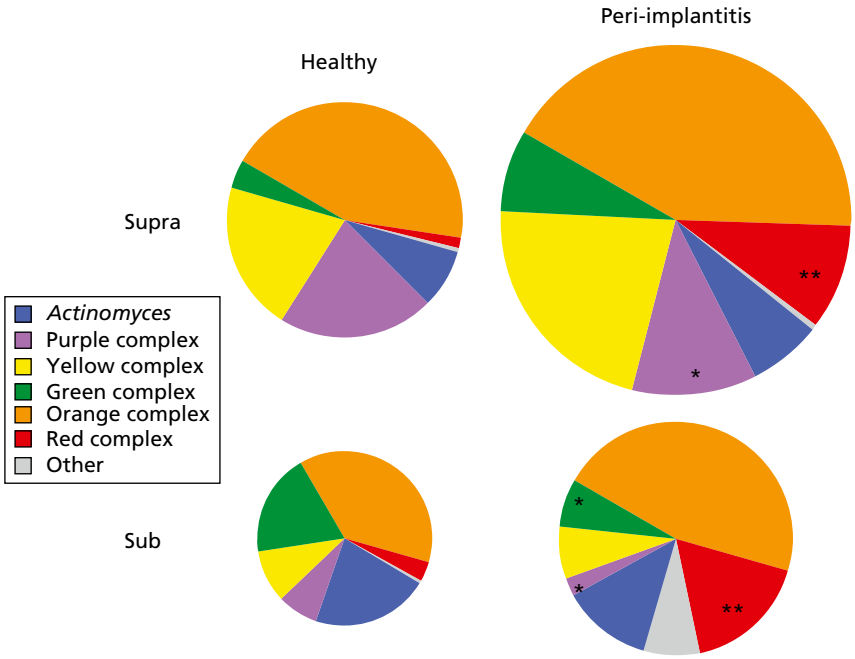


Fig. 9-26 The mean percentage DNA probe count of microbial complexes (Socransky *et al*. 1998) in samples of supra- and submucosal biofilms obtained from healthy implants (n = 22) and implants with peri-implantitis (n = 22). Areas of the pie charts were adjusted to reflect the mean total DNA probe counts of each sample type. Significance of differences between the two clinical groups for the proportions of each complex was tested for supra-and submucosal samples separately using the Mann–Whitney U-test ($^{*}P$ <0.05; $^{**}P$ <0.01). (Source: Data adapted from Shibli *et al*. 2008.)

There is no histologic documentation of bacterial invasion of the peri-implant tissues, although it has been suggested that this may occur because of the epithelial ulceration and disruption of connective tissue adhesion observed in experimental peri-implantitis studies (Lang & Berglundh 2011).

Molecular techniques, including *16S rRNA* gene sequencing, have led to the identification and discovery of previously unrecognized microorganisms in the oral cavity (Faveri *et al*. 2008; Ahn *et al*. 2011; Wade 2011). Because of these advances, researchers are now recognizing the diversity of both the periodontal and peri-implant microbiota. Phyla including Chloroflexi, Tenericutis, and Synergistes, and species including *P. micra*, *Peptostreptococcus stomatis*, *Pseudoramibacter alactolyticus*, and *Solobacterium moorei*, have been identified from peri-implantitis sites (Koyanagi *et al*. 2010) (Fig. 9-27). Furthermore, Archaea, a distinct group of single-cell microorganisms that produce methane gas and have been associated with periodontal disease severity (Lepp *et al*. 2004) have also been identified using *16S rRNA* clonal analyses at peri-implantitis sites, suggesting a role in the etiology of peri-implant infection (Faveri *et al*. 2011). Subgingival/submucosal samples were obtained from 50 periodontally healthy sites, 50 healthy peri-implant sites, and 25 peri-implantitis sites. The prevalence of Archaea (*Methanobrevibacter oralis*) was significantly higher at peri-implantitis sites compared with healthy sites at implants and teeth (Faveri *et al*. 2011).

The true nature, role, and diversity of the microbiota associated with peri-implant infections may only be realized as future investigations focus on the study of non-cultivable organisms, using techniques which do not disrupt the three-dimensional structure of the biofilm.

Periodontal and peri-implant microbiomes in health and disease

Recent studies using molecular techniques have evaluated patient-specific periodontal and peri-implant microbiomes indicating that peri-implant and periodontal microbiomes are both complex, diverse, and may differ from one another (Heuer *et al*. 2012; Dabdoub *et al*. 2013; Zhuang *et al*. 2016; Yu *et al*. 2019).

Dabdoub *et al*. (2013) used a deep-sequencing approach to analyze subgingival and peri-implant biofilm samples in 81 partially dentate individuals with periodontal and peri-implant health and disease. They found that 60% of individuals shared less than 50% of all species between their periodontal and peri-implant biofilms. The periodontal microbiome demonstrated significantly higher diversity than the peri-implant microbiome, and distinct bacterial lineages were associated with health and disease at teeth and implants (Dabdoub *et al*. 2013). The above study suggests that the concept of simple proximity is likely insufficient to determine colonization of topographically distinct habitats. The peri-implant and periodontal microbiomes appear to represent microbiologically distinct ecosystems.

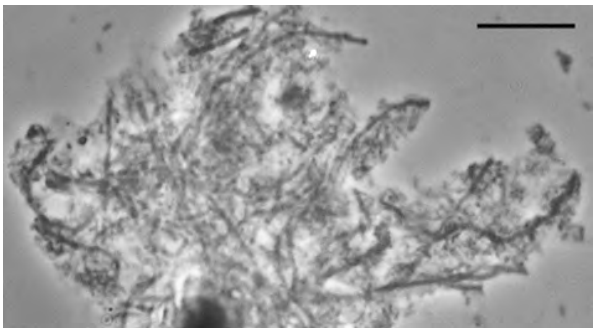
Zhuang *et al*. (2016) evaluated 22, partially dentate Chinese subjects with periodontal/peri-implant healthy sites and periodontitis/peri-implantitis sites.

Quantitative real-time polymerase chain reaction (q-PCR) was used to quantify six bacterial species including *P. gingivalis*, *T. denticola*, *A. actinomycetemcomitans*, *F. nucleatum*, *P. intermedia*, and *S. aureus*. Within the same subjects the six species evaluated were common to both periodontal and peri-implant sites irrespective of health status. The prevalence and levels of *P. gingivalis* and *F. nucleatum* were significantly associated with periodontitis but not with peri-implantitis. *A. actinomycetemcomitans* was only associated with periodontitis and peri-implantitis (Zhuang *et al*. 2016).

Yu *et al*. (2019) characterized single-site subgingival and submucosal microbiomes of 18 partially dentate Chinese subjects treated with dental implants. Each subject contributed samples from a site with periodontal health, periodontitis, peri-implant health, and peri-implantitis. Microbial analyses using Illumina MiSeq sequencing revealed 26 phyla and 5726 OTUs. Species (OTU) composition of the periodontal and peri-implant microbiota varied widely between subjects. Firmicutes, Proteobacteria, Fusobacteria, Bacteroidetes, Actinobacteria, Synergistetes, TM7, and Spirochaetes comprised 99.6% of the total detection. Bacterial communities shared high levels of taxonomic similarity. Putative "periodonto-pathogens" such as *Prevotella*, *Porphyromonas*, *Tannerella*, *Bacteroidetes* (G-5), and *Treponema* spp. were associated with periodontitis and peri-implantitis sites. However, the variation between subjects in subgingival/submucosal microbiome composition was greater than the differences observed between implant vs. tooth sites, or between diseased vs. healthy peri-implant/periodontal sites (Yu *et al*. 2019).

The diversity of the peri-implantitis microbiome was also highlighted in a cross-sectional study evaluating 45 submucosal samples from peri-implantitis sites with varying degrees of severity assessed by probing depth (Kroger *et al*. 2018). Analyses by 16s sequencing identified 337 different taxa in the submucosal microbiome. There was a significant correlation of 12 taxa with increasing severity of disease indicating an increased level of dysbiosis in deep peri-implant pockets (Kroger *et al*. 2018).

(a)



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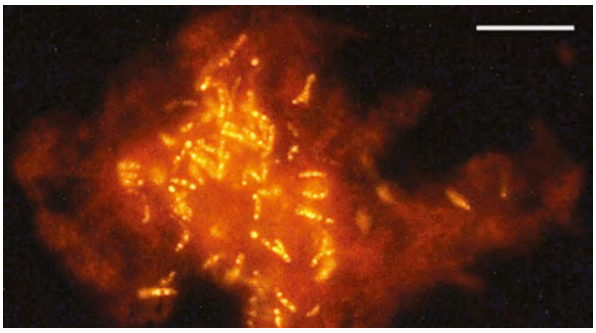

Fig. 9-27 (a) Inverted light microscopy of a subgingival biofilm obtained from a peri-implantitis site. (b) Fluorescent image of the same field stained specifically by fluorescence *in situ* hybridization (FISH) for Synergistes group A2. Bars correspond to 10 µm. (Source: Courtesy of G.N. Belimpasakis and Helga Lüthi-Schaller, University of Zürich, Switzerland.)

Patients at risk for peri-implant infections

There is strong evidence that patients who have a history of treated periodontitis have an increased risk for peri-implant infections (Hardt *et al*. 2002; Karoussis *et al*. 2003, 2004; Heitz-Mayfield 2008; Ong *et al*. 2008; Roccuzzo *et al*. 2010; Schwarz *et al*. 2018a, b). This is perhaps not surprising considering the two diseases share common risk factors, and patients with a host susceptibility to periodontitis will still be susceptible to biofilm infections at implant sites if periodontal pathogens colonize these sites.

This consideration is supported by findings that in patients diagnosed with advanced periodontitis, the persistence of periodontal pathogens was observed following full-mouth extraction and implant placement (Quirynen & Van Assche 2011). Ten patients with advanced periodontitis had all their teeth extracted and 6 months after tooth extraction, implants were placed. Abutment connection was completed 3–6 months later. Plaque samples were collected from the tongue dorsum, saliva, and subgingival/mucosal area (teeth/implants) before extraction and up to 1 year after abutment connection, and analyzed by culture, quantitative PCR, and checkerboard technology. A reduction in the total number of aerobic and anaerobic colony-forming units (CFU)/mL was observed, and there was a reduction in the detection of *P. gingivalis* and *T. forsythia* in the saliva and on the dorsum of the tongue. However, the submucosal areas of the peri-implant sulci were rapidly colonized by these key pathogens, and no changes could be detected for *A. actinomycetemcomitans*. Thus, whereas the extraction of the remaining periodontally involved teeth resulted in a significant reduction of bacteria related to periodontitis and peri-implantitis, they were not eliminated. The pathogens could then colonize the peri-implant regions and detection frequencies remained high (Quirynen & Van Assche 2011). Although it may take many years, peri-implant infections may develop if periodontal pathogens become established in the peri-implant biofilm in a susceptible host.

Furthermore, periodontal patients with residual probing depths of ≥6 mm at remaining teeth were found to have a greater prevalence of peri-implantitis (bone loss and peri-implant probing depth ≥5 mm with BoP) compared with periodontal patients with no residual pockets, or periodontally healthy subjects (Cho-Yan Lee *et al*. 2012). Moreover, a study including patients in maintenance care, with an average follow-up of 8 years, reported that periodontitis-susceptible patients with implants who developed peri-implantitis had significantly more residual periodontal pockets (≥5 mm) at the end of active periodontal therapy than patients who did not develop peri-implantitis (Pjetursson *et al*. 2012). This highlights the maintenance of periodontal health as a critical factor in reducing risk for peri-implant infection. Clinicians should inform patients with a history of periodontitis of their increased risk for peri-implant infections, and of the importance of optimal oral hygiene and regular supportive periodontal/peri-implant care.

Few studies have investigated the presence of specific bacterial species as a risk for the initiation or progression of peri-implantitis. One study found that the addition of a positive DNA test (which determined the presence of *A. actinomycetemcomitans*, *P. gingivalis*, *P. intermedia*, or *T. denticola*) enhanced the diagnostic power of the presence of bleeding on gentle probing (0.25 N) to predict progression of peri-implant disease (Luterbacher *et al*. 2000).

Acknowledgment

The authors would like to acknowledge the significant contribution of the late Professor Ricardo Teles in the previous edition of this chapter.

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Part 4: Host–Parasite Interactions

Chapter 10

Pathogenesis of Gingivitis and Periodontitis

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Introduction

The experimental gingivitis studies of the 1960s (Löe *et al*. 1965) elegantly demonstrated that there is a one-to-one relationship between the development of dental plaque and the development of gingivitis (Figs. 10-1, 10-2). These studies, together with those of more recent times (Trombelli *et al*. 2004, 2008), also show that there is variation in this response, with some individuals manifesting disease to a greater or lesser degree and at different time periods compared with others. So, while it has been known for many years that plaque is the etiologic agent, the factors contributing to individual patient susceptibility are still not fully understood. While all individuals with periodontitis will have had, at some stage, gingivitis, not all patients with gingivitis, nor all gingivitis lesions, will necessarily progress to periodontitis. The difficulty arises in identifying those lesions with gingivitis which will progress to periodontitis.

As with any disease, treatment planning in periodontics should be based on an understanding of the etiology and pathogenesis of the disease. In this context, it is clear that the bacteria in dental plaque are the cause of both gingivitis and periodontitis; however, it is the way in which an individual responds to these bacteria, rather than the bacteria per se, that determines disease expression and subsequent progression (Seymour 1991, Socransky & Haffajee 2005).

Over the past three decades it has become established that periodontitis results from the interaction

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

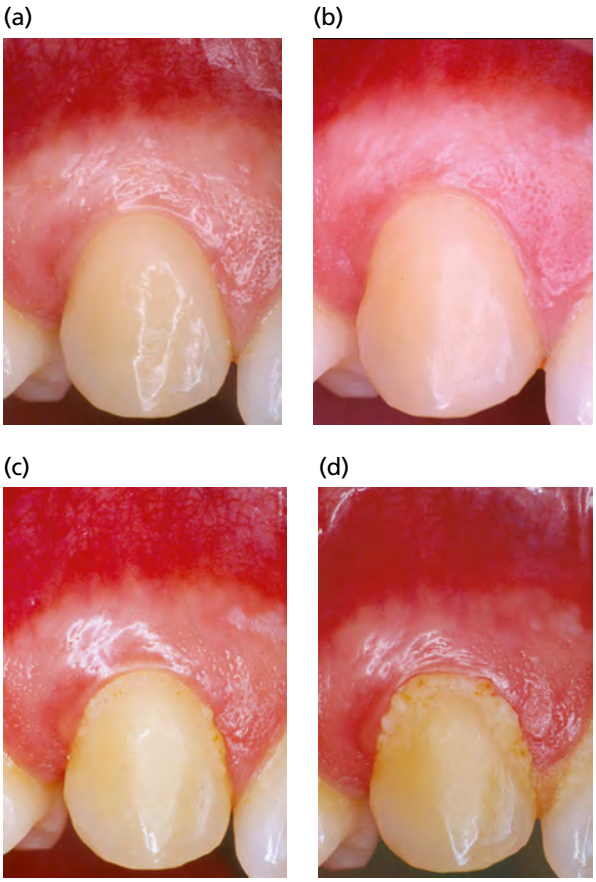

Fig. 10-1 Experimentally induced gingivitis lesion (Trombelli *et al*. 2004). (a) Clinically healthy state; (b) after 7 days of plaque accumulation, dental biofilm is visible and slight inflammation of the gingival margin is present; (c) at day 14, a substantial amount of plaque deposit is associated with an increasingly evident gingival inflammation; (d) at day 21, large deposits of plaque are present along the gingival margin (buccally and interproximally) in association with severe edema and erythema of the gingiva. (Source: Trombelli *et al*. 2004. Reproduced with permission from John Wiley & Sons.)

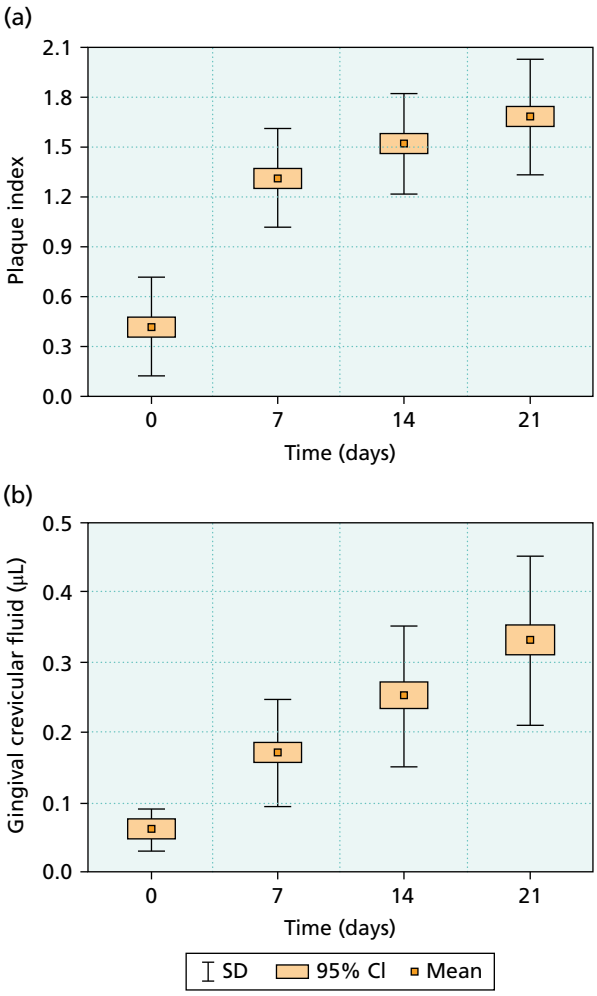

Fig. 10-2 Descriptive statistics (box and whisker plot) for (a) plaque index and (b) gingival crevicular fluid volume over experimental gingivitis period (0, 7, 14, and 21 days of undisturbed plaque accumulation). (Source: Modified from Trombelli *et al*. 2004. Reproduced with permission from John Wiley & Sons.)

of the host's defense mechanisms with biofilms containing complexes including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* (Socransky *et al*. 1998). Notwithstanding these observations, it has also been shown not only that they occur in a large proportion of the normal population (Cullinan *et al*. 2003), but that there is a high degree of volatility with respect to the presence and/or absence of these organisms over time, such that it would appear that they are more widespread in the community than previously thought. Indeed, it is now recognized that many people carry the organisms without manifesting disease progression (Cullinan *et al*. 2003). In this context, it is clear that most people are in balance with their biofilm for most of the time and it is only when this balance is disturbed that disease results. Such disturbances may occur as a result of environmental influences leading to an opportunistic increase in the numbers of organisms, or a depression of the host's defense mechanisms, or both. Indeed, it has been proposed that the development of inflammation in the gingival tissue itself can change the local ecology of the gingival sulcus thus leading to changes in the plaque microbiota with the ensuing dysbiosis or imbalance between the bacteria and host response resulting in disease progression (Bartold & Van Dyke 2019).

Not all individuals with gingivitis will progress to periodontitis, and not all individuals with periodontitis will progress to tooth loss. This individuality of disease expression is a reflection of individual susceptibility and is due to the interaction of the patient's specific individual pathogenic microbiota, the host's immune system and their own innate susceptibility, together with the impact of environmental and systemic factors (Fig. 10-3) (Cullinan *et al*. 2001; Seymour & Taylor 2004). Individuality of disease expression implies individuality of treatment which is the basis of so-called 'precision periodontal care' and which is reflected in the 2017 classification of periodontitis.

The development of gingivitis and periodontitis was loosely classified into the "initial", "early", "established", and "advanced" lesions by Page and

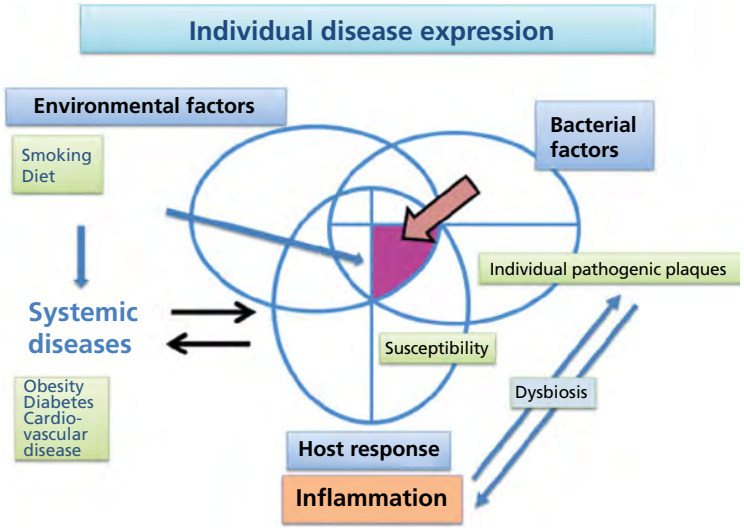

Fig. 10-3 Individuality of disease expression is due to the interaction of the patient's specific individual pathogenic microbiota, the immune system and innate susceptibility, together with the impact of environmental and systemic factors. (Source; Modified from Seymour & Taylor 2004. Reproduced with permission from John Wiley & Sons.)

Schroeder 44 years ago (Page & Schroeder 1976). However, today this is probably better viewed in the first instance as the development of a stable, homeostatic, gingivally confined lesion (gingivitis) in which the plaque microbiota is in balance with the host response. A subsequent dysbiosis or imbalance in this relationship, as a result of environmental, systemic or host factors, including the development of inflammation per se, then leads to the development of a progressive lesion (periodontitis) which is characterized by the loss of connective tissue attachment, destruction of alveolar bone, and apical migration of the junctional epithelium.

Gingivitis

Development of the homeostatic lesion

The development of gingivitis can be studied using the experimental gingivitis model. Two to four days following the beginning of plaque accumulation an "initial" lesion develops. This lesion is subclinical and can only be seen histologically. It is characterized by: (1) the formation of edema, manifesting as an increase in gingival crevicular fluid (GCF) flow; (2) an accumulation of polymorphonuclear neutrophils (PMNs); and (3) loss of connective tissue (Fig. 10-4). Streptococci are among the first organisms to colonize the acquired pellicle as plaque develops. While there is no evidence that these organisms actually invade the tissues they do produce a range of enzymes and metabolic end products which increase the permeability of the sulcular and junctional epithelia, allowing both the ingress of bacterial products and at the same time the outflow of GCF. At this early stage, the GCF is essentially the same as interstitial fluid, but nevertheless contains many serum proteins, including all the components necessary for the activation of complement.

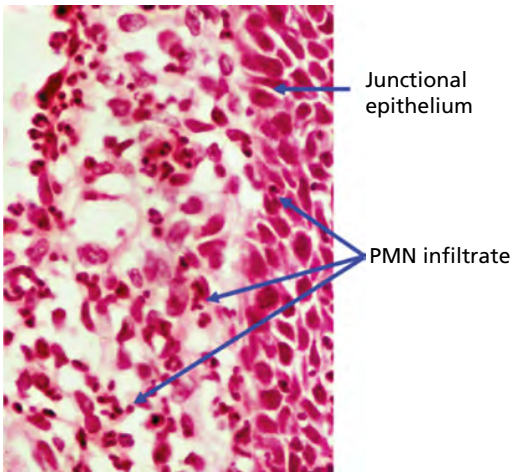

Fig. 10-4 Polymorphonuclear neutrophil (PMN) infiltration with destruction of the infiltrated connective tissue in the initial lesion.

Lipoteichoic acid and peptidoglycans, which are components of the cell wall of these early colonizers, are capable of activating complement via the "alternative pathway". This occurs in the gingival sulcus and results in the production of the "anaphylatoxins" C3a and C5a, which in turn flow back into the tissues, establishing a concentration gradient from the gingival sulcus into the tissues. Once in the tissue, these anaphylatoxins lead to the release of vasoactive amines from resident mast cells. In turn, these vasoactive amines lead to an increase in vascular permeability and the formation of edema, one of the hallmarks of inflammation. Mast cells also release preformed cytokines, including tumor necrosis factor-alpha (TNF-α), which results in the expression of adhesion molecules by endothelial cells and the subsequent sticking and migration of PMNs into the gingival tissues. While activation of the alternative complement pathway is essential for the vascular responses,

bacterially derived chemotactic substances together with C5a are responsible for the migration of PMNs into the gingival sulcus. Once in the gingival sulcus, however, the PMNs are unable to phagocytose the bacteria, which are beginning to form a biofilm and as such are firmly adherent to the tooth surface. In this situation, the PMNs disgorge their lysosomal contents into the gingival sulcus in what has been termed "abortive phagocytosis". These lysosomal enzymes can then return into the tissues and contribute to the local destruction of connective tissues. In addition, PMNs release structures called neutrophil extracellular traps (NETs) which can trap and kill microbial pathogens. These were first described by Brinkman *et al*. (2004) and consist of chromatin structures, nuclear histones, and many granular antimicrobial proteins. NETs are released during a form of pathogen-induced cell death, called NETosis, that differs from apoptosis and necrosis (Steinberg & Grinstein 2007) and represents one of the first lines of defense against pathogens. *In vivo* both dead and viable PMNs can release NETs, which in turn can be associated with severe tissue damage. In addition, a variety of proinflammatory stimuli, all of which can be found in the gingival sulcus, such as lipopolysaccharide (LPS), interleukin-8 (IL-8), TNF, as well as the streptococcal M protein, can all induce NET formation (for review, see Remijsen *et al*. 2011).

While NETs have been described in periodontitis, it is likely that they are also formed in this initial lesion stage of gingivitis and then persist through all stages of gingivitis and periodontitis. Evidence for this, however, is at present lacking.

Other cell types, such as eosinophils and mast cells, are also able to release extracellular traps (von Kockritz-Blickwede *et al*. 2008). These mast cell extracellular traps (MCETs) appear to be released in response to the same factors that lead to NET release from PMNs. MCETs are also composed of nuclear histones together with the antimicrobial cathelicidin LL37, as well as tryptase, a granular mast cell marker, and their formation in the tissues would not only limit the ingress of bacteria but also of bacterial vesicles. They may, however, contribute to localized tissue destruction. Again, while highly likely, evidence for the formation of both NETs and MCETs in the tissues is lacking. Indeed, the role of mast cells in periodontal disease is largely unknown.

Within the gingival sulcus, PMNs also produce and release a variety of cytokines including IL-1, the IL-1 receptor antagonist (IL-1RA), and high levels of IL-17. IL-17 in turn induces the production of IL-8 by sulcus epithelial cells. IL-8 is not only a very strong chemoattractant for PMNs, but as stated earlier, is also a strong stimulus for NET formation, thus establishing a positive feedback loop in an attempt to contain the developing bacterial infection. Indeed, it is highly likely that the role of IL-17 in periodontal disease is a protective one in that it maintains the PMN barrier in the gingival sulcus. It is well established that loss of this barrier, either due to an absence of PMNs (such as agranulocytosis or cyclic neutropenia) or a defect in their function (either chemotactic or phagocytic), leads to severe and rapid progression of periodontal destruction. At this initial stage, however, the lesion occupies no more than 5–10% of the connective tissues and is still not evident clinically.

After approximately 4–7 days of plaque accumulation, the nature of the developing lesion changes from one consisting primarily of PMNs to one with increased numbers of lymphocytes and macrophages (Fig. 10-5). Vascular changes become more pronounced with the opening of previously dormant capillary beds, the formation of postcapillary venules, increased vascular permeability, and the development of perivascular inflammatory infiltrates. As a result, there is a net increase in the flow of fluid into the affected gingival tissues, and a subsequent increase in the flow of GCF. The nature of the GCF at this stage changes from that of interstitial fluid to that of an inflammatory exudate, in other words edema. An increase in the permeability of the sulcular and junctional epithelia, as a result of widening of the intercellular spaces between the epithelial cells, allows increased ingress of bacterial products into the gingival tissues and escalation of the inflammatory response.

This lymphocyte/macrophage lesion develops as small perivascular infiltrates which progressively increase in size and coalesce such that at around day 12–21 following the beginning of plaque accumulation the lesion becomes clinically evident. By day 21, lymphocytes make up 70% of the infiltrate and although there is a four-fold increase in PMN numbers within the junctional epithelium (Lindhe & Rylander 1975),

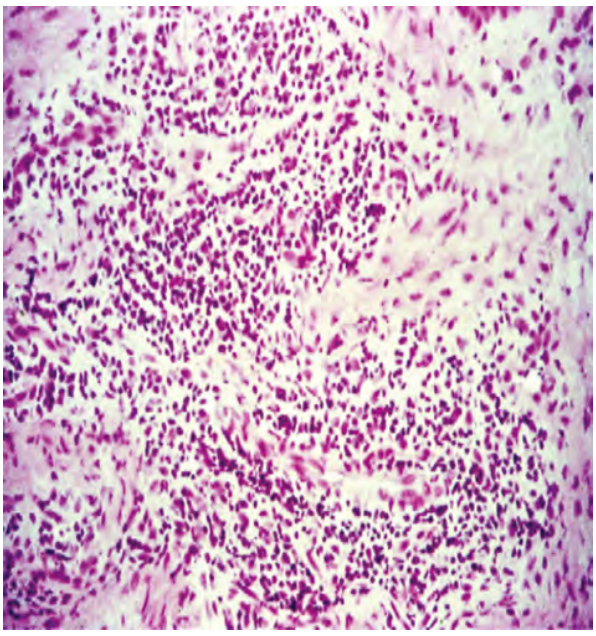

Fig. 10-5 Perivascular lymphocyte/macrophage infiltrate seen in a 21-day experimental gingivitis lesion. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

PMNs and plasma cells make up <10% of the total infiltrate (Seymour *et al*. 1983). As with the initial lesion, the release of cytokines such as TNF-α and IL-17 from mast cells and PMNs undergoing NETosis leads to an increase in cell adhesion molecules, such as endothelial cell leukocyte adhesion molecule-1 (ELAM-1) and intercellular adhesion molecule-1 (ICAM-1), which together with an increase in IL-8 production by the epithelial cells help to establish a fast flow of PMNs through the junctional epithelium and into the gingival sulcus (Moughal *et al*. 1992), where they form a barrier against plaque microorganisms (Attstrom 1971). Although the infiltrated area remains fairly localized at this stage, up to 60–70% of collagen within the infiltrated zone is degraded (Page & Schroeder 1976).

The immunologic events occurring during the development of gingivitis have been described (Seymour *et al*. 1988). These events are identical to the development of delayed-type hypersensitivity (DTH) and involve the formation of perivascular lymphocyte/macrophage infiltrates (Fig. 10-5) which, as they increase in size, coalesce and merge, eventually becoming clinically evident. The infiltrates consist predominantly of T cells (Fig. 10-6), with a CD4:CD8 ratio of around 2:1 (Fig. 10-7), together with both dendritic antigen-presenting cells (APCs) and infiltrating phagocytic macrophages. These activated T cells, along with the sulcular epithelial cells, express high levels of MHC class II antigens (HLA-DR and HLA-DQ) (Fig. 10-8). Langerhans cells are seen in increased numbers in both the oral as well as the oral sulcular epithelium (Fig. 10-9a). Fewer than 5% of the T cells express the IL-2 receptor CD25 (Fig. 10-9b), suggesting that these cells are not proliferating locally. As soluble antigen enters the tissues, it is taken up by the resident Langerhans cells and carried to the regional lymph nodes where antigen-specific T cells are sensitized. In chronic

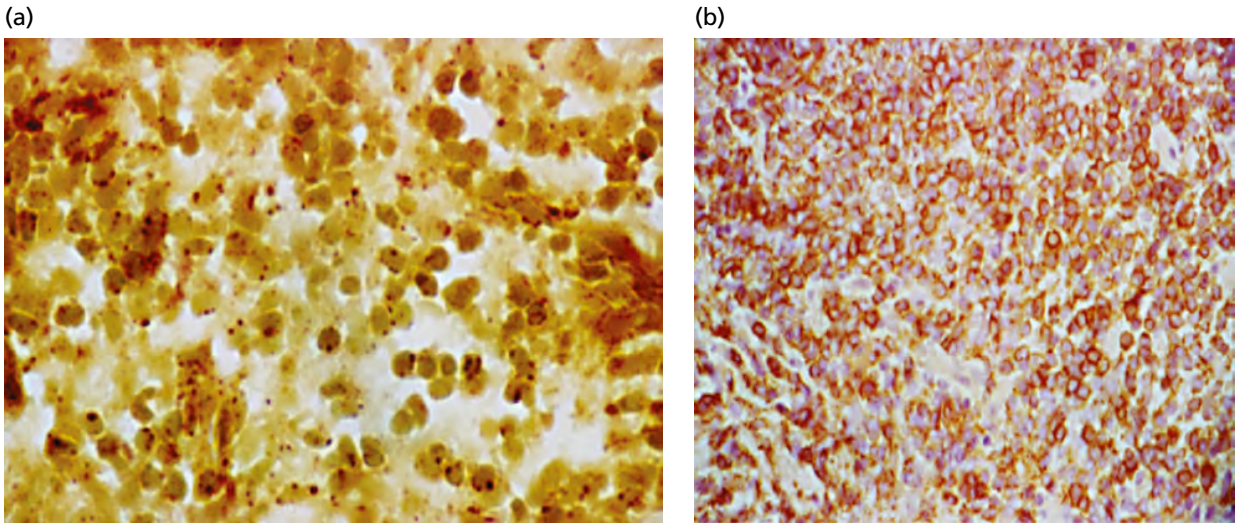

Fig. 10-6 21-Day experimental gingivitis lesion showing the predominance of (a) non-specific esterase-positive and (b) CD3-positive T cells. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

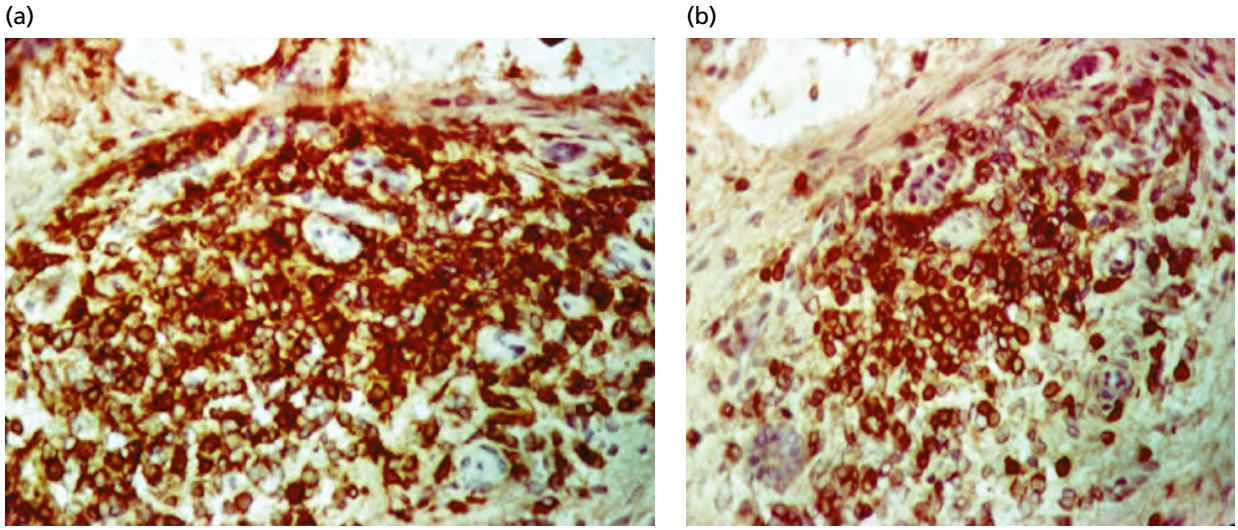

Fig. 10-7 21-Day experimental gingivitis lesion showing a (a) CD4 to (b) CD8 ratio of 2:1. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

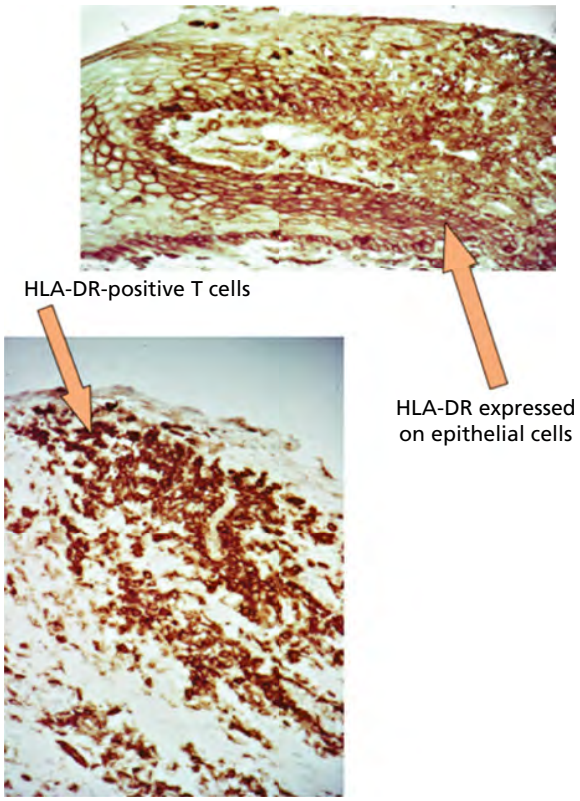

Fig. 10-8 21-Day experimental gingivitis lesion showing HLA-DR-positive activated T cells and HLA-DR-positive epithelial cells. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

gingivitis Langerhans cells can be seen migrating out of the epithelium and through the connective tissue (Fig. 10-10). The sensitized T cells then travel back to the site of original antigen challenge (i.e. the gingival tissues). Once there, following further antigen presentation by dendritic cells, they become activated and together with the infiltrating phagocytic macrophages, they control the ingress of antigen and achieve a balance with the plaque biofilm. While in the developing lesion the majority of macrophages are phagocytic cells, in chronic gingivitis the major APC is the CD14-positive/CD83-positive dendritic cell (Gemmell *et al*. 2002c), with fewer classical pro-inflammatory M1 macrophages compared with the alternative prohealing M2 macrophages (Garaicoa-Pazmino *et al*. 2019). Nevertheless, the production of interferon gamma (IFN-γ) by the activated CD4 T cells further activates the PMNs and macrophages. Although these cannot eliminate the bacterial challenge, they, via the production of NETs in the gingival sulcus and the production of cytokines within the tissues, are able to control the infection. As noted earlier, this sequence of events is identical to that seen in the development of DTH (Poulter *et al*. 1982). The development of DTH is a well-controlled immunologic response which develops in 12–24 hours, peaks within 48 hours, and is gone within a week. In this context, gingivitis can also be considered to be a

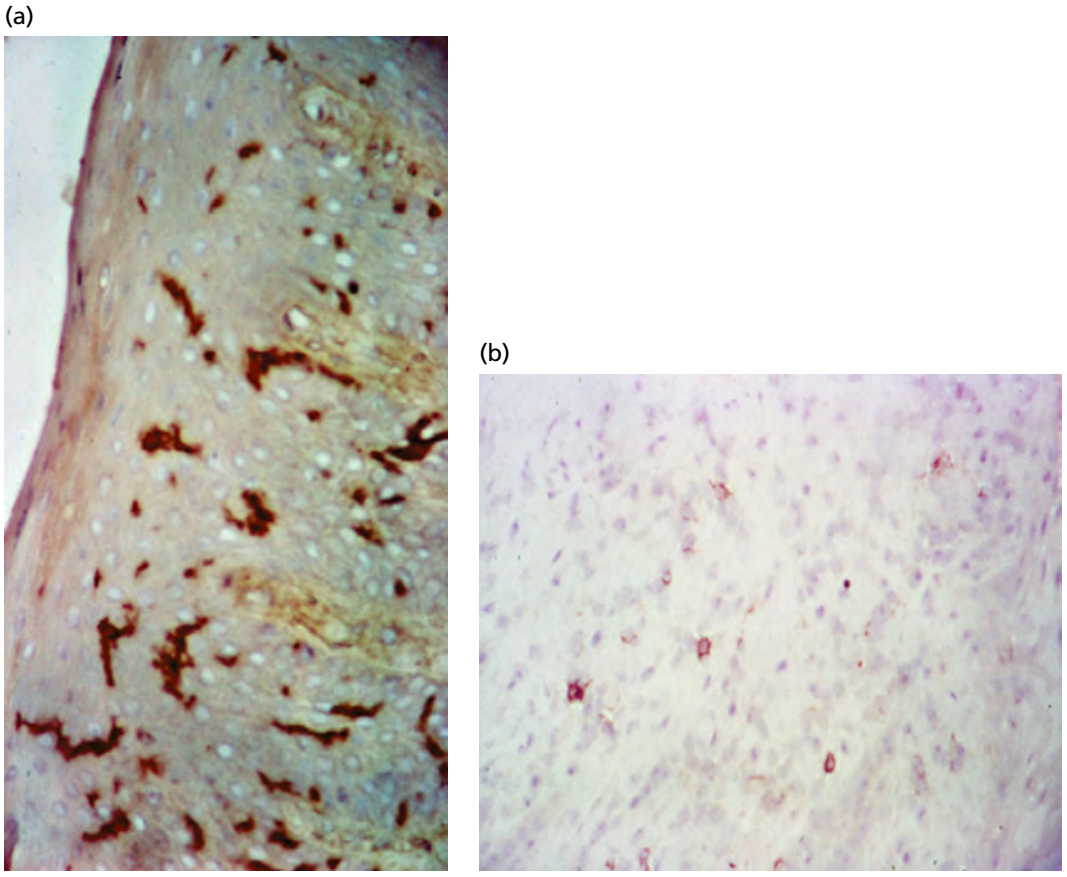

Fig. 10-9 21-Day experimental gingivitis lesion showing (a) increased CD1a-positive Langerhans cells in the oral epithelium and (b) relatively few CD25 (IL-2 receptor)-positive T cells in the infiltrate. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

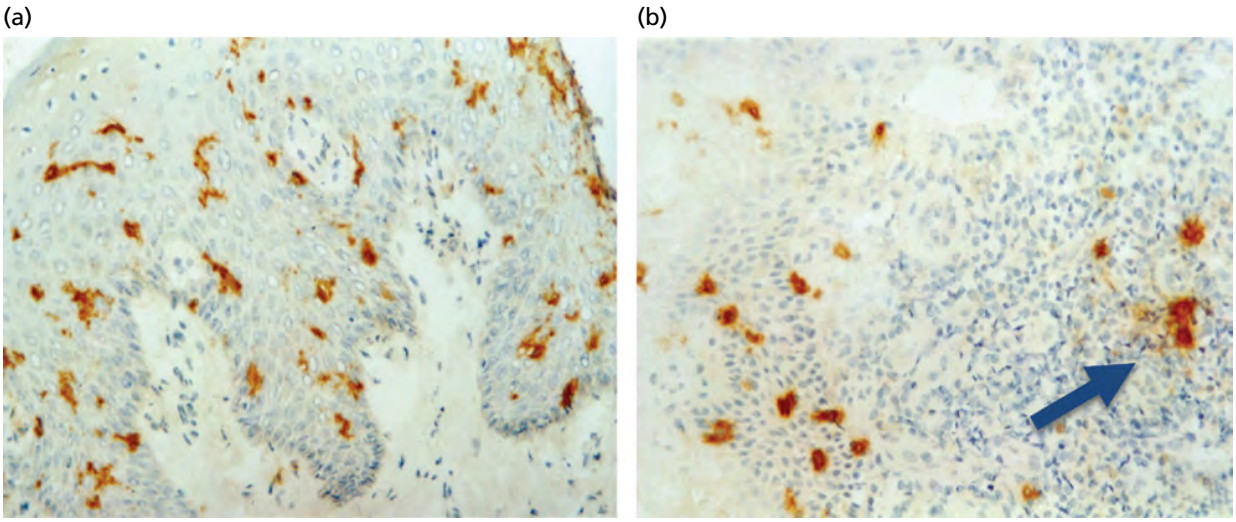

Fig. 10-10 Chronic gingivitis lesion showing (a) increased CD1a-positive Langerhans cells in the oral epithelium and (b) CD1a-positive cells within the inflammatory infiltrate (arrow). (Source: Gemmell *et al*. 2002c. Reproduced with permission from John Wiley & Sons.)

well-controlled immunologic response but, as noted earlier, because of the persistence of the plaque biofilm, the immunologic response persists rather than resolving. The subsequent, prolonged nature of the inflammatory response results in gingivitis becoming chronic in nature. While in most people the immune response is able to contain the microbial challenge, it is only with mechanical cleaning that the microbial challenge can be cleared. Collagen is degraded in the stable lesion but does not result in any loss of attachment. When the plaque is removed, gingival tissues repair and remodel, and there is no permanent damage to or alteration of tissue architecture.

The epithelial barrier

The gingival epithelium is not only a physical barrier to the ingress of microorganisms and their products, but it also plays an important role in in the innate immune system and in maintaining homeostasis. The discovery of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), has led to a far greater understanding of innate immunity and the induction of adaptive immunity. TLRs are found on a range of cells including gingival epithelial cells which express a number of TLRs including TLR2,3,4,5,6, and 9 (for review see Mahanonda & Pichyangkul 2007). These TLRs recognize structures known as pathogen-associated molecular patterns (PAMPs) that are highly conserved across a wide variety of pathogens. Such PAMPs include LPS, peptidoglycan, bacterial DNA, double-stranded RNA, and lipoprotein.

Activation of gingival epithelium via TLR-2 leads to the production of IL-8 which, as stated earlier, is a very powerful chemoattractant and stimulus for NET formation thus contributing to the formation of the PMN barrier (Attstrom 1971) and maintenance of the stable, homeostatic lesion. Deficiencies in PMN numbers or function result in rapid and advanced periodontal destruction.

TLR signaling also leads to the production of antimicrobial peptides (α- and β-defensins, the cathelicidin LL37, and calprotectin) which further limit bacteria within the gingival sulcus and are thus important in maintaining the symbiotic relationship between the host and the plaque microbiota. α-defensins are not only potent antimicrobial agents; they also activate the classical complement pathway and can upregulate the production of IL-8. The β-defensins hBD1, hBD2, and hBD3 have been demonstrated in both oral and sulcular epithelium (Dale 2002; Dunsche *et al*. 2002; Dommisch & Jepsen 2015). These too are not only antimicrobial but may also be involved in mediating inflammation (Ganz 2003). In a recent study, Dommisch *et al*. (2019) have shown the sequential expression of a number of antimicrobial peptides (including β-defensins, the CC-chemokine 20 ligand CCL20, S100A7/psoriasin, and calgranulin A/B) during the development of gingival inflammation. These authors showed that there was a significant increase in hBD2 and hBD3 mRNA expression by day 3 of an experimental gingivitis, reaching a peak at day 14 and then declining by day 21. In contrast, CCL20 mRNA peaked at day 3 but declined by days 14 and 21. The S100A7/psoriasin and S100A/B calgranulin A and the S100A9 calgranulin B also peaked at day 3 but the levels were maintained through day 14. These mRNA results were largely confirmed by protein analysis of GCF although the authors did note a large degree of interindividual variation. This study is the first to show the sequential and differential expression of these antimicrobial peptides in an experimental gingivitis model and, as the authors point out, again highlights the importance of these molecules in maintaining gingival homeostasis.

Factors influencing the pathogenesis of gingivitis

Predisposing factors are defined as those factors which retain or hinder the removal of plaque and therefore are associated with both the maintenance and severity of gingival inflammation. On the other hand, modifying factors are defined as those factors which alter the nature or course of the inflammatory response. As chronic inflammation involves a vascular response and a cellular response together with the simultaneous presence of destruction and repair, anything which alters the vascular response, the cellular response, or the repair potential of the tissues can be considered a modifying factor.

Vascular response

Sex hormones

Physiologic and pathologic endocrine changes have long been established as significant modifying factors in the expression of gingivitis (Sooriyamoorthy & Gower 1989; Mariotti 1999; Tatakis & Trombelli 2004). The variation in sex hormone levels during puberty (Mombelli *et al*. 1989; Bimstein & Matsson 1999), pregnancy (Hugoson 1971), and menstruation (Koreeda *et al*. 2005) has been shown to alter the plaque–gingivitis relationship, resulting in increased levels of inflammation. Gingival and periodontal tissues contain receptors for sex steroid hormones and their physiology is regulated, at least in part, by serum and salivary hormonal levels (Soory 2000). In particular, estrogen has a stimulatory effect on both the metabolism of collagen and on angiogenesis, and at the same time it leads to a decrease in keratinization of the gingival epithelium. However, it is progesterone which is thought to have the major effect in the gingival tissues, both in terms of its effect on the levels of proinflammatory mediators (Lapp *et al*. 1995; Markou *et al*. 2011) and on the gingival vasculature. It has been known for many years that progesterone not only increases vascularity of the gingival tissues but also increases their permeability, thus resulting in a highly vascular edematous inflammatory response (Hugoson 1970; Lundgren *et al*. 1973).

Pregnancy was one of the first conditions identified as having an impact on the expression of gingivitis (Ziskin *et al*. 1946; Löe & Silness 1963; Silness & Löe 1964). In particular, increases in both the prevalence and severity of gingivitis were reported during the second and third trimester of pregnancy (Löe & Silness 1963; Hugoson 1971; Arafat 1974). The generally accepted mechanisms leading to the exaggerated inflammatory response are related to the increased levels of progesterone, which lead to increased permeability and dilatation of gingival capillary vessels, resulting in increased vascular flow and exudation (Hugoson 1970; Lundgren *et al*. 1973). These effects are partly mediated by an increased synthesis of prostaglandin (Miyagi *et al*. 1993).

Variations in the severity of gingival inflammation have also been described with the onset of puberty in both males and females (Parfitt 1957; Sutcliffe 1972; Hefti *et al*. 1981; Mombelli *et al*. 1989) as well as during the menstrual cycle, particularly during the ovulation period (Koreeda *et al*. 2005). Fluctuation of sex steroid hormones, which may affect blood volume, flow rate, and vascular permeability, are thought to alter the host response, leading to the observed increase in the clinical signs of gingival inflammation (Baser *et al*. 2009; Becerik *et al*. 2010) and the observed increase in gingival exudate (Hugoson 1971). The evidence, however, suggests that hormonal variations do not affect clinically healthy gingiva, but do exacerbate existing chronic gingivitis (Holm-Pedersen & Löe 1967; Kovar *et al*. 1985; Niemi *et al*. 1986; Becerik *et al*. 2010).

Early clinical studies reported a higher incidence of gingival inflammation in women taking hormonal contraceptives compared with women not taking these agents (Lindhe & Bjorn 1967; El-Ashiry *et al*. 1970; Pankhurst *et al*. 1981). However, formulations of oral contraceptives have changed dramatically, resulting in substantially lower concentrations of hormones and more recent studies suggest that the effect of newer contraceptive pills on gingivitis is practically nil (Preshaw *et al*. 2001).

Diabetes

Diabetes is an endocrine condition with a well-characterized effect on gingivitis. Clinically, subjects with diabetes, whether insulin-dependent or non-insulin dependent, have significantly higher gingival inflammation compared with those who do not have diabetes with similar plaque levels (Bernick *et al*. 1975; Cutler *et al*. 1999; Salvi *et al*. 2005, 2010).

At the vascular level, the accumulation of advanced glycation end products (AGEs) alters the function of several intercellular matrix components, including vascular wall collagen, resulting in thickening of the capillary basement membrane and loss of vascular elasticity (Ulrich & Cerami 2001). Results from controlled histologic studies in animals showed that diabetes was associated with changes of the gingival vasculature, such as the formation of new vessels with variable wall thickness, hyperemia, localized moderate-to-severe vasculitis (Tesseromatis *et al*. 2009), increased vascular permeability accompanied by increased leukocyte adhesion molecule expression, and enhanced leukocyte rolling (Sima *et al*. 2010).

Smoking

The effect of smoking on the expression of plaque-induced gingival inflammation is controversial. A number of studies have shown that smokers, when compared with non-smokers, accumulate plaque at the same rate but exhibit significantly less gingival

inflammation in experimental gingivitis studies, albeit with similar plaque levels (Bergstrom & Preber 1986; Danielsen *et al*. 1990; Lie *et al*. 1998; Müller *et al*. 2002). In addition, significantly lower GCF volumes were detected at periodontally healthy or slightly inflamed sites in young regular smokers compared with non-smokers (Persson *et al*. 1999). At the same time, a single episode of smoking has been shown to produce a transient increase in GCF volume (McLaughlin *et al*. 1993).

The biologic mechanisms underlying the suppressive effect of smoking on clinical parameters of gingival inflammation are poorly understood. A structural and/or functional impairment of the gingival and periodontal microcirculatory system, however, has been put forward (Scott & Singer 2004). In one, albeit small, study, the periodontal vascular system in smokers was found to be composed of smaller numbers of large vessels, but larger numbers of small vessels, compared with non-smokers, with no differences in terms of mean vascular density between smokers and non-smokers (Mirbod *et al*. 2001). This, together with the well-established nicotine-induced peripheral vasoconstriction as well as the reduction in GCF, is consistent with the effect of smoking being mediated, at least in part, by modulation of the local vascular response.

Cellular response

Blood dyscrasias

The systemic conditions usually identified as affecting the cellular response in gingivitis are the blood dyscrasias, including neutropenias (Andrews *et al*. 1965; Rylander *et al*. 1975; Reichart & Dornow 1978), leukemias (Levin & Kennedy 1973; Bergmann *et al*. 1992), and human immunodeficiency virus/acquired immune deficiency syndrome (AIDS) (Glick *et al*. 1990). These conditions are characterized either by low numbers of functional PMNs (neutropenias) or large numbers of immature dysfunctional leukocytes (leukemias) infiltrating the gingival tissues or, as in the case of AIDS, by a very low CD4-positive T-cell count and the inability to mount an effective T-cell response. Other conditions which are characterized by defective PMN function, either phagocytic (Chédiak–Higashi syndrome) or chemotactic (Down's syndrome) (Izumi *et al*. 1989), also display severe gingival inflammation. These conditions highlight the fact that abnormalities in cell numbers or function can modify the inflammatory response to plaque and manifest as severe gingival inflammation.

Diabetes

As noted earlier, the development of gingivitis involves an initial innate immune response to the formation of plaque. In the presence of a poor innate response and the relative lack of PMNs in the gingival sulcus, a more severe inflammatory response occurs. In addition to the vascular response noted earlier, hyperglycemia also leads to an impairment of immune cell function (Gugliucci 2000). In this respect, individuals with uncontrolled diabetes show reduced PMN function (Marhoffer *et al*. 1992), defective chemotaxis (Ueta *et al*. 1993), and significantly more severe gingival inflammation compared with those without diabetes with similar plaque levels (Gislen *et al*. 1980; Cianciola *et al*. 1982; Rylander *et al*. 1987; Salvi *et al*. 2005).

Chronic hyperglycemia leads to the accumulation of AGEs, which bind to macrophages and monocytes (Brownlee 1994), resulting in an increased release of proinflammatory mediators (Iacopino 1995) and more severe gingival inflammation with higher levels of IL-1β and matrix metalloproteinase-8 (MMP-8) (Salvi *et al*. 2010).

Smoking

Smoking also has a profound effect on the immune system and the development of inflammation (Barbour *et al*. 1997; Palmer *et al*. 2005). Reduced migration (Eichel & Shahrik 1969) and phagocytic capacity of PMNs (Kenney *et al*. 1977) and increased numbers of circulating T and B lymphocytes (Sopori & Kozak 1998) has been demonstrated in smokers. However, the relevance of these mechanisms in altering the gingival inflammatory response to the dental biofilm needs to be determined.

Longitudinal studies using ante-dependence modeling, such as a Markov chain, enables the results of a sequence of exams to be analysed longitudinally, taking into account serial dependence, allowing for both progression and regression between disease categories. Using this approach Faddy *et al*. (2000), showed that smoking had no effect on disease progression but significantly reduced disease regression. Using a similar approach Shätzle *et al*. (2009) reanalysed the data from the 26-year longitudinal Norwegian academic study on the natural history of periodontitis and showed that smoking led to initiation of disease 3–4 years earlier, compared with that in the non-smokers. These studies were then confirmed by Ramseier *et al*. (2017) who reexamined the Sri Lankan tea laborers originally examined in 1970 (Löe *et al*. 1986) and showed that in this population smoking was associated with disease initiation but not with disease progression (Fig.10-11). While the mechanism underlying this association of smoking with the initiation of periodontitis remains speculative, it is likely that reduction in PMN migration and function, noted above, is involved.

Repair potential

The final feature of a chronic inflammatory response is the ability of the tissue to repair itself, such that anything which affects this ability will modify the gingival response to plaque and will either manifest

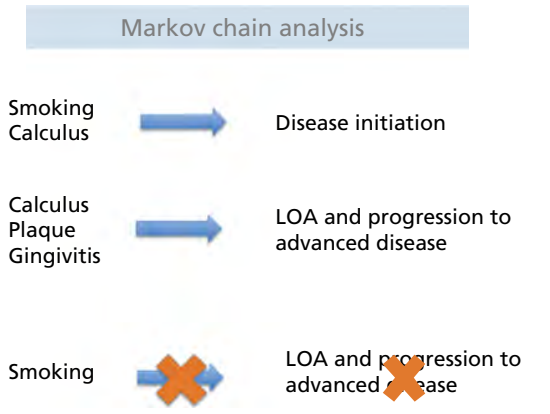

Fig. 10-11 Markov chain analysis of the effect of smoking on the initiation and progression of periodontitis (Ramseier *et al*. 2017) indicating that smoking and calculus are associated with the initiation of periodontitis, calculus plaque and gingivitis are associated with loss of attachment (LOA) and progression to advanced disease, while smoking was not associated with progression of periodontitis.

as an enlargement (over response) or loss of connective tissue (impaired response) and progression to periodontitis.

Over response

Several drugs (Seymour 1993), including anticonvulsants such as phenytoin (Angelopoulos 1975a, b), antihypertensive calcium channel blockers such as nifedipine (Nery *et al*. 1995; O'Valle *et al*. 1995), and the immunosuppressant cyclosporine (Seymour & Jacobs 1992; O'Valle *et al*. 1995) cause severe gingival enlargement, a reaction related to the plaque-induced gingival inflammation (Seymour *et al*. 1996). Although these drugs have different pharmacologic mechanisms, a common denominator appears to be their effect on calcium metabolism which has been hypothesized to result in gingival enlargement (Hassell & Hefti 1991). Consistent with this concept is the fact that the clinical and histologic features of gingival enlargement induced by phenytoin, cyclosporine, or nifedipine are all similar (Hassell & Hefti 1991; Seymour *et al*. 1996). Histologic studies have shown that accumulation of extracellular matrix within the gingival connective tissue is the main feature of the overgrown tissues (Rostock *et al*. 1986; Mariani *et al*. 1993).

It is well established that the severity of the gingival enlargement is related to the level of plaque control and the presence of gingivitis (Steinberg & Steinberg 1982; Addy *et al*. 1983; Hassell *et al*. 1984; Tyldesley & Rotter 1984; Daley *et al*. 1986; McGaw *et al*. 1987; Modeer & Dahllof 1987; Yahia *et al*. 1988; Barclay *et al*. 1992; Lin & Yang 2010), which supports the concept that the enlargement reflects an over response of the repair component of the inflammatory reaction. Further, a high concentration of tissue plasminogen activator (t-PA) (Buduneli *et al*. 2004) and plasminogen activator inhibitor type 2 (PAI-2) has been demonstrated in GCF from enlarged sites, which suggests that the enlargement itself may act as a predisposing factor and lead to the aggravation of gingival inflammation (Kinnby *et al*. 1996). However, whether and to what extent the drugs associated with gingival enlargement may intimately modulate the complex host–bacteria interaction leading to gingival inflammation remains to be determined.

Impaired response

An example of how an impaired repair potential can influence the expression of gingivitis can be seen in vitamin C deficiency where an impairment of collagen metabolism results in highly inflamed, friable gingivae in the presence of plaque. Indeed, in both humans (Leggott *et al*. 1986, 1991) and non-human primates (Alvares *et al*. 1981) a subclinical deficiency of ascorbic acid results in increased gingivitis relative to non-deficient controls with similar plaque levels and the same type of microbiota.

Other studies, although preliminary and limited in number, suggest that other nutritional factors, including vitamin E (Cohen & Meyer 1993; Offenbacher *et al*. 1990; Asman *et al*. 1994), riboflavin, calcium, and frequency of fiber intake (Petti *et al*. 2000) may influence the incidence and severity of plaque-induced gingivitis, but their mechanisms are unknown.

Ante-dependence modeling has shown that smoking significantly inhibits the healing capacity of the periodontal tissues. Indeed, Faddy *et al*. (2000) showed that the healing capacity of smokers was only 28% that of non-smokers and was equivalent to that of non-smokers 36 years older. In other words, the periodontal healing capacity of a 45-year-old smoker is that of an 81-year-old non-smoker. This inhibition of healing together with the earlier initiation of disease progression could account for the increased prevalence of periodontitis seen in smokers.

Periodontitis

Histopathology of periodontitis

In 1965, Brandtzaeg and Kraus (1965) demonstrated the presence of immunoglobulin-producing plasma cells in the gingival tissues of patients with periodontitis. This was the first direct evidence that adaptive immune mechanisms play a role in the pathogenesis of periodontal inflammation. It was not until 1970, however, that Ivanyi and Lehner (1970), using peripheral blood lymphocyte transformation assays, highlighted a role for cell-mediated immunity. It is now well established that the periodontitis lesion itself involves predominantly B cells and plasma cells (Fig. 10-12) (Mackler *et al*. 1977; Seymour *et al*. 1978; Seymour & Greenspan 1979; Berglundh *et al*. 2011). Although the majority of lymphocytes are immunoglobulin-bearing B cells, up to 30% of the lymphocytes may be T cells. Clinically it is not yet possible to

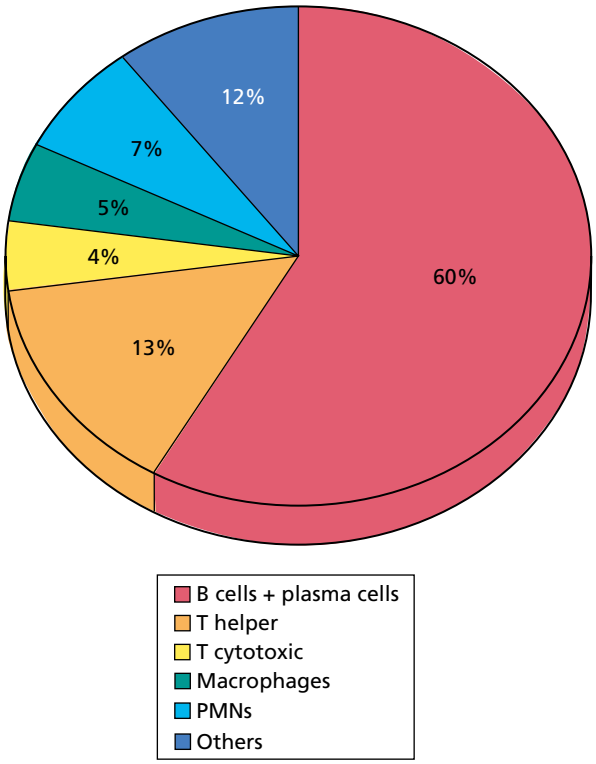

Fig. 10-12 Distribution of cells in periodontitis lesions. (Source: Adapted from Berglundh *et al*. 2011. Reproduced with permission from John Wiley & Sons.)

determine disease activity; hence, it is not possible to say if the increased proportions of B cells and plasma cells seen in some clinical gingivitis lesions represent a stable gingivitis lesion or indeed is the beginning of a progressive periodontitis lesion. In this context, and in terms of the development of periodontal disease (gingivitis and periodontitis), it is probably better to consider this end stage of gingivitis and the increasing numbers of plasma cells as a possible transitional lesion between gingivitis and periodontitis.

While the gingivally confined T-cell lesion remains relatively stable, this B-cell/plasma cell lesion progresses and leads to the development of a periodontal pocket. Connective tissue breakdown leads to loss of the connective tissue attachment to the tooth and as a result the junctional epithelium migrates in an apical direction, thus forming a periodontal pocket (Fig. 10-13). This in turn becomes lined by pocket epithelium with in-growth of rete pegs into the surrounding connective tissue (Fig. 10-14). Polymorphonuclear neutrophils continue to migrate through this pocket lining epithelium and into the periodontal pocket where they form a barrier between the tissues and plaque biofilm. Increased permeability and ulceration of the pocket epithelium allows further ingress of microbial products, leading to the continued production of inflammatory cytokines such as interleukin-1 (IL-1), TNF-α, and prostaglandin E_2 (PGE_2) (for review, see Gemmell *et al*. 2007), and perpetuation of the inflammatory process resulting in destruction of both connective tissue and bone (Reynolds & Meikle 1997).

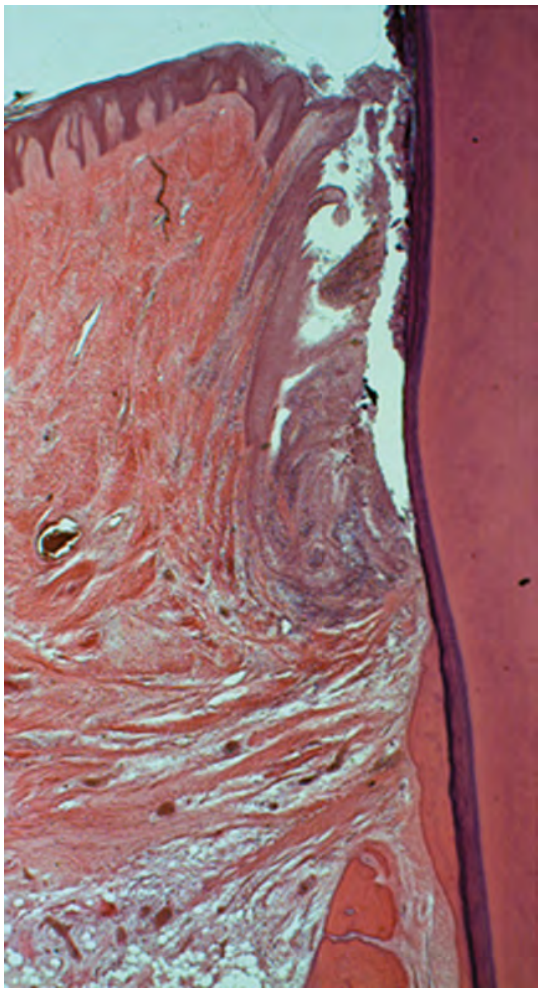

Fig. 10-13 Autopsy specimen showing a human periodontitis lesion. Calculus and biofilm in the pocket. Note the infiltrated connective tissue lateral and apical of the pocket epithelium.

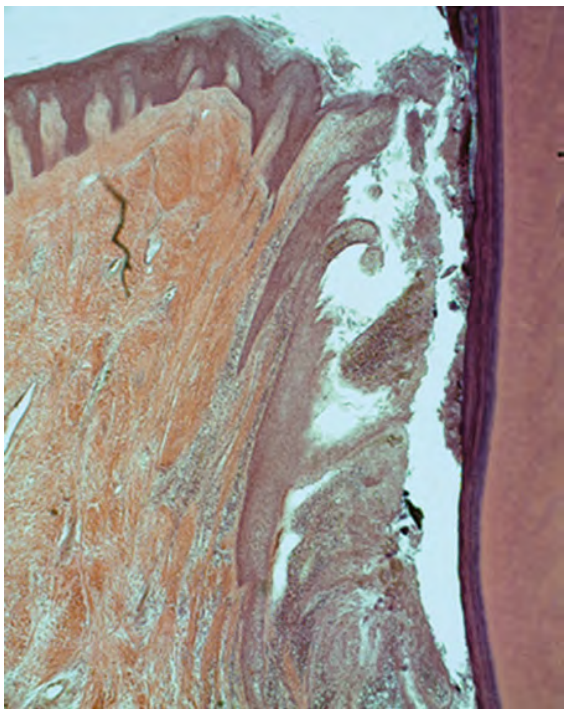

Fig. 10-14 Detail of Fig. 10.13. Note the ulcerated pocket epithelium with rete pegs into the connective tissue.

Surrounding the inflammatory infiltrate is a fibrous tissue band. This is common to all chronic inflammatory lesions and is an attempt by the lesion to wall off from the surrounding tissues. Indeed, in periodontitis, irrespective of the depth of the pocket, the underlying alveolar bone and periodontal ligament do not become inflamed (Fig. 10-15).

As the lesion progresses the same cellular make-up persists with the overt loss of attachment becoming evident clinically and histologically (Figs. 10-16, 10-17). It is now generally accepted that the mechanism of tissue destruction is via the effects of the immune response (Birkedal-Hansen 1993) and is not a direct consequence of the bacteria *per se*. Macrophages are not a dominant feature of the advanced lesion, comprising fewer than 5% of the cells. Fibroblasts, however, when stimulated by the inflammatory cytokines IL-1, IL-6, TNF-α, and PGE_2, produce matrix metalloproteinases (MMPs), which are a family of proteinases whose primary purpose is the degradation of the extracellular matrix. Collagen molecules are cleaved into smaller fragments, which then become denatured in the extracellular environment or are phagocytosed by surrounding fibroblasts. As the lesion advances, alveolar bone loss becomes apparent. However, the non-infiltrated fibrous band remains adjacent to the crestal bone, effectively encapsulating the progressing lesion and walling it off from the surrounding tissues. It should be noted again that the underlying bone and periodontal ligament remain non-inflamed (Fig. 10-18).

B cells in periodontitis

As noted above, the periodontitis lesion is characterized by large numbers of B cells and plasma cells. Immunoglobulin-bearing B cells in a periodontitis lesion are illustrated in Fig. 10-19. B cells can be activated either by specific antigens or by polyclonal activators. Indeed, a number of the putative periodontal pathogens, including *P. gingivalis, A. actinomycetemcomitans,* and *Fusobacterium nucleatum* have been shown to have profound polyclonal B-cell activation properties (Bick *et al*. 1981; Mangan *et al*. 1983; Carpenter *et al*. 1984; Ito *et al*. 1988). However, polyclonal activators do not activate all B cells.

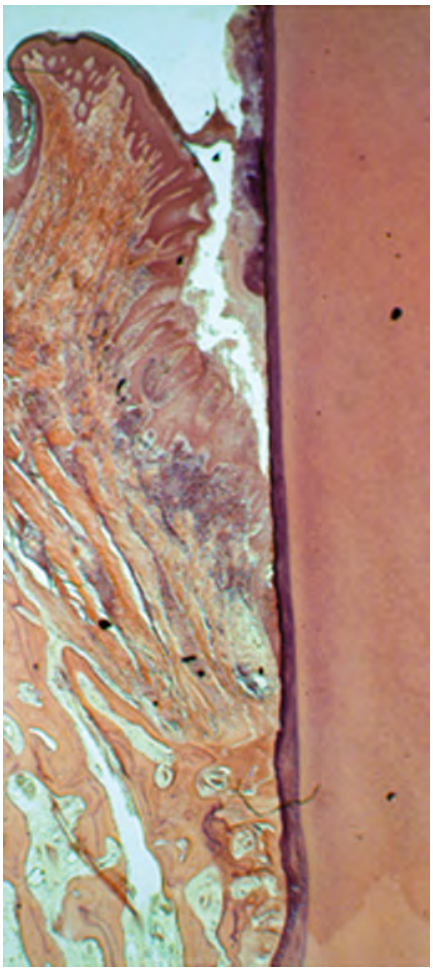

Fig. 10-16 Autopsy specimen showing a human periodontitis lesion. The overt loss of attachment and bone is characteristic for the advanced lesion.

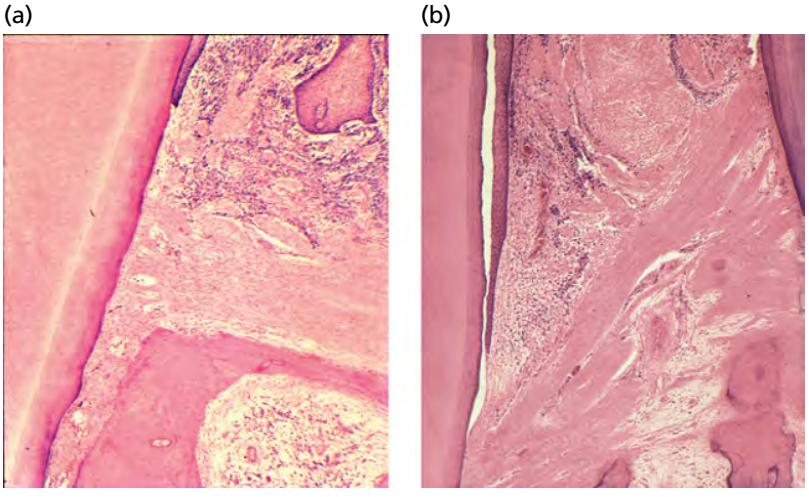

Fig. 10-15 A band of non-infiltrated connective tissue is interposed between the infiltrated connective tissue and the alveolar bone. (a) Suprabony pocket. (b) Infrabony pocket.

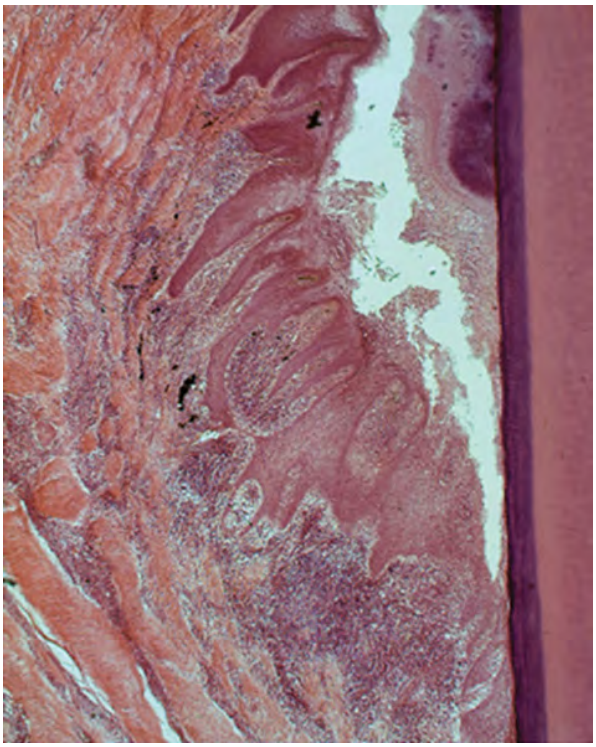

Fig. 10-17 Detail of Fig. 10.16. Pocket epithelium walling off calculus and biofilm in the pocket.

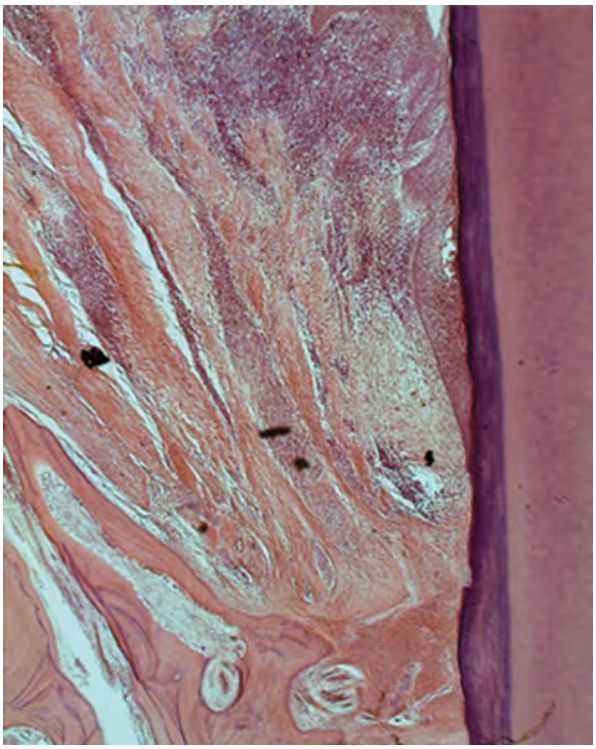

Fig. 10-18 Detail of Fig. 10.16. Note the non-infiltrated fibrous band between the infiltrated connective tissue and the bone.

Approximately 30% of B cells may be stimulated by a single polyclonal activator, with different activators acting on different B-cell subpopulations. Further, the antibodies produced as a result of this polyclonal activation are likely to be of low affinity and the memory component may not be induced (Tew *et al*. 1989). At the same time, a degree of antigen-specific induction of sensitized B cells is also likely to occur. The principal immunoglobulin class produced in the periodontal tissues is IgG, followed by IgM and some IgA.

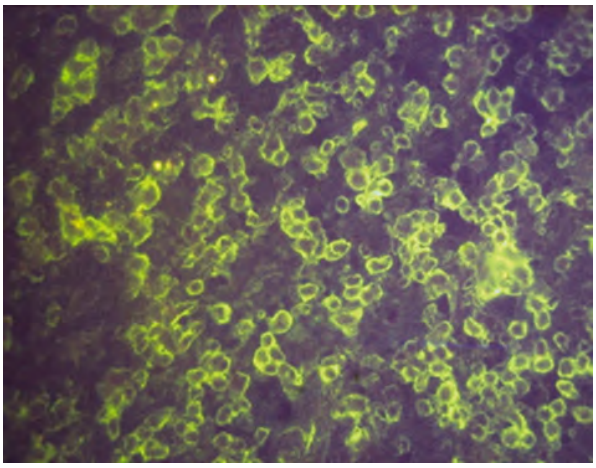

Fig. 10-19 Immunoglobulin-bearing B cells in a periodontitis lesion. (Source: Seymour *et al*. 2009. Reproduced with permission from John Wiley & Sons.)

The role of specific antibodies in the pathogenesis of chronic periodontitis is poorly understood. High titers of specific antibodies to *P. gingivalis* and *A. actinomycetemcomitans* have been demonstrated in the serum and GCF of subjects with periodontal disease; however, the reports are still conflicting with respect to disease activity (Baranowska *et al*. 1989; Nakagawa *et al*. 1994; Ebersole *et al*. 1995). Immunodominant antigens of *P. gingivalis* and *A. actinomycetemcomitans* have also shown different patterns of immunoreactivity, while anti-*P. gingivalis* antibodies with different avidities have been demonstrated in various forms of periodontal disease (Mooney & Kinane 1994). It has been suggested that antibodies with high avidity confer resistance to continued or repeated infection, whereas non-protective low-avidity antibodies may be incapable of effectively mediating a variety of immune responses (Lopatin & Blackburn 1992; Kinane *et al*. 2008).

While a strong antibody response has been suggested to be generally protective, facilitating bacterial clearance and arresting disease progression (Offenbacher 1996; Kinane *et al*. 2008), the mechanism by which this is achieved is unclear. Antibodies, by virtue of their molecular size, are unlikely to penetrate the biofilm and hence their ability to clear the subgingival infection is questionable. Equally, PMNs do not penetrate the biofilm, again limiting their ability to clear the infection. Nevertheless, an increased capacity of serum to opsonize *P. gingivalis* has been shown to be a distinctive feature in patients with past destructive periodontal disease (Wilton *et al*. 1993). However, this high level of opsonizing antibody is more likely to be related to past bacteremias and the ability to clear the serum, than an ability to clear the subgingival infection. On the other hand, repeated infection with *A. actinomycetemcomitans* in an animal

model has been shown to elicit an anti-leukotoxin antibody which protects PMNs from the leukocidal activity of the leukotoxin (Underwood *et al*. 1993). In this context, specific antibodies to bacterial products may be involved in controlling disease expression rather than clearing the organism from the subgingival biofilm. On the other hand, polyclonal B-cell activation by periodontopathic bacteria and the production of non-specific and/or low-avidity antibodies may not be capable of controlling the disease.

As well as producing immunoglobulins/antibodies, continued B-cell activation leads to the production of high levels of cytokines, including IL-1 and IL-10, which may contribute to subsequent tissue destruction. However, while *P. gingivalis* depresses the gene for IL-1β in T cells, it has been shown to induce an increased percentage of peripheral blood B cells from periodontitis patients to produce IL-1β (Gemmell & Seymour 1998). Since macrophages are not a dominant feature of the advanced lesion (Chapple *et al*. 1998) and suppressed cell-mediated immunity is associated with advanced periodontitis, it may be that B cells are the major source of IL-1 in periodontitis.

Macrophages in periodontitis (M1 and M2)

Activated macrophages are now recognized to display a degree of plasticity with at least two different phenotypes being identified. The classical or M1 macrophage produces proinflammatory cytokines such as IL-6 and TNF-α, while the M2 macrophage is reported to play a role in the resolution of inflammation and in the promotion of healing. Such macrophages produce increased amounts of IL-10 and low levels of IL-6 (Das *et al.* 2015). As noted above, macrophages are not a dominant feature of periodontitis (Chapple *et al*. 1998), occurring in fewer than 5% of the infiltrating cells (Berglundh *et al*. 2011). In addition, in a recent study Garaicoa-Pazmino *et al.* (2019) investigated the polarization of M1 and M2 macrophages in both gingivitis and in periodontitis. This study again confirmed the low levels of macrophages in periodontitis lesions but showed that there was no significant difference in the proportion of M1 and M2 macrophages between the two lesions, although the numbers of macrophages were much higher in the gingivitis lesions (Fig. 10-20). These results are not surprising in that both periodontitis and gingivitis are chronic inflammatory lesions and chronic inflammation is defined by the simultaneous presence of destruction and repair. In both lesions this is reflected in the proportions of destructive M1 and the prohealing M2 macrophages with tissue destruction seen in periodontitis probably being due to B cell, rather than macrophage, cytokine production.

Conversion of gingivitis to periodontitis

Why some people develop periodontitis while others do not, remains a fundamental question in periodontology. In a relatively small clinical and radiological study, Thorbert-Mros *et al*. (2017) have shown that those patients with advanced disease between the ages of 30 and 45 years had radiologically detectable bone loss between the ages of 22 and 28 years. This finding is in accord with that of Ramseier *et al*. (2017) who showed, in their 40-year longitudinal study of the natural history of periodontitis, that a mean loss of attachment of less than 1.81 mm in those under 30 years predicted a cohort with at least 20 teeth at age 60 years. The converse of this is that those with a mean loss of attachment of more than 1.81 mm had fewer than 20 teeth at age 60 years. Both these studies highlight the need to treat those under 30 years who show signs of early disease. But the question remains – why do these people develop disease at an early age? As discussed previously, a strong innate immune response in the gingival sulcus together with the epithelial barrier and antimicrobial peptides are essential in maintaining the homeostatic gingival lesion and any defect or deficiency in these mechanisms is likely to lead to the development of periodontitis.

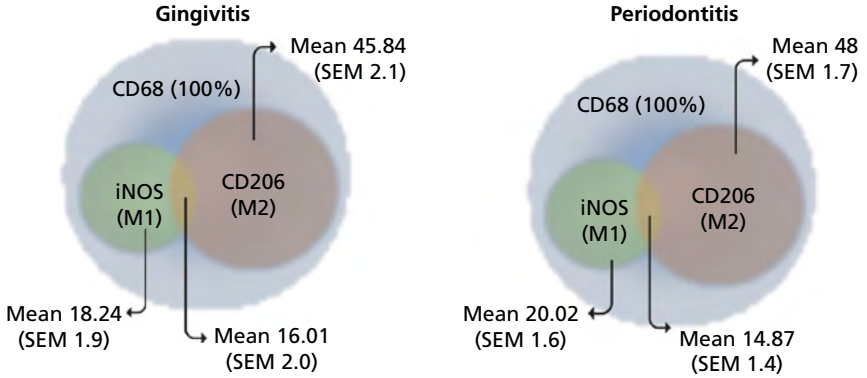

Fig. 10-20 Representation of the CD68-positive macrophage distribution in gingivitis and periodontitis showing no difference between the two lesions. Inducible nitric oxide synthase (iNOS) is expressed predominantly by M1 macrophages while the mannose receptor (CD206) is expressed predominantly by M2 macrophages, (Source: Garaicoa-Pazmino *et al*. (2019). Reproduced with permission from John Wiley & Sons.)

The Th1/Th2 paradigm

Clearly the development of periodontitis involves a switch from a predominantly T cell/macrophage lesion (Brecx *et al*. 1988; Seymour *et al*. 1988) to one involving large numbers of B cell and plasma cells (Seymour *et al*. 1979). The question then arises as to what are the controlling mechanisms of this switch? The fact that the development of gingivitis is identical to the development of DTH and that progressive chronic periodontitis is fundamentally a B-cell lesion, led to the concept that gingivitis and hence the stable periodontal lesion is mediated by Th1 cells, while periodontitis is mediated by Th2 cells (Seymour *et al*. 1993) and the conversion of gingivitis to periodontitis involves a shift from a Th1 to a Th2 mediated response. In this concept it was proposed that a strong innate immune response leads to the production of high levels of IL-12 by both PMNs and macrophages, which in turn leads to a Th1 response, cell-mediated immunity, protective antibody, and a stable periodontal lesion. In contrast, a poor innate immune response with polyclonal B-cell activation leads to a Th2 response, non-protective antibody, and a progressive periodontal lesion. Since being put forward over 25 years ago, this hypothesis has attracted a lot of attention with a number of studies supporting the hypothesis by showing either depressed Th1 responses or increased Th2 responses in periodontitis. In contrast, other studies (primarily in animal models) have implicated increased Th1 responses in periodontitis, while others have highlighted a role for Th0 cells. Nevertheless, it is now generally agreed that periodontitis in humans is mediated by a balance in Th1 and Th2 cells with a shift towards a Th2 profile (Berglundh & Donati 2005; Kinane & Bartold 2007).

Suppression of cell-mediated immunity

The first study to report a possible suppression of cell-mediated immunity in advanced periodontitis subjects was by Ivanyi and Lehner (1970). Subsequently, a number of studies have shown that periodontopathic bacteria, including *P. gingivalis, A. actinomyetemcomitans*, *T. denticola, Capnocytophaga ochracea*, and *F. nucleatum* (Shenker *et al*. 1982; Shenker & Slots 1989; Shenker & Datar 1995) could induce lymphocyte suppression *in vitro*. In addition, T cells extracted from periodontitis lesions not only have a reduced ability to respond in an autologous mixed lymphocyte reaction (AMLR), but also fail to produce IL-2, suggesting that this suppression of cell-mediated responses in periodontitis may also occur *in vivo* (Seymour *et al*. 1985) The fact that the AMLR returns to normal following periodontal therapy (Evans *et al*. 1989) also supports the concept that the suppressive effect of plaque bacteria on cell-mediated immunity (i.e. Th1 responses) may be fundamental in the conversion of a stable to a progressive lesion.

T cells and homeostasis

T cells are involved in nearly all immunoregulatory interactions both *in vivo* and *in vitro*, and a delicate balance between effector and regulatory subsets is required for immune homeostasis. Th1 cells not only mediate DTH but also increase the ability of macrophages to kill intracellular and extracellular pathogens (Romagnani 1992). Further, there is evidence that T cells are involved in the recruitment and activation of PMNs at the site of infection (Campbell 1990), suggesting that in the stable lesion, activation of PMNs may be crucial in keeping the infection under control. Indeed, a strong innate immune response in the gingival tissues and the production of IL-12 could be critical in the establishment of a Th1 response. The presence of natural killer (NK) cells in gingival tissues has also been demonstrated (Wynne *et al*. 1986) and may also be significant in the establishment of a Th1 response. The production of IFN-γ enhances the phagocytic activity of both PMNs and macrophages, and hence containment of the infection.

In contrast, the B-cell nature of the progressive periodontitis lesion suggests either an increase in production of Th2 cytokines or a decline in the production of Th1 cytokines, in other words a shift in the balance towards Th2.

Cytokine profiles

Studies over the past decade have supported the hypothesis that Th1 cells are associated with the stable lesion and Th2 cells with disease progression (for review, see Gemmell *et al*. 2007). However, other studies have reported a predominance of Th1-type cells or reduced Th2 responses in diseased tissues (Ebersole & Taubman 1994; Salvi *et al*. 1998; Takeichi *et al*. 2000). More recently, the involvement of both Th1 and Th2 cells in periodontal disease in humans (for review, see Gemmell *et al*. 2007) has been suggested. However, although cytokine patterns reflecting both subsets can be found in periodontitis tissues (Yamamoto *et al*. 1997), as previously noted, it is now agreed (Berglundh & Donati 2005; Kinane & Bartold 2007) that periodontitis in humans is associated with a shift towards a Th2 response. Further circumstantial evidence for this concept is seen in the fact that *P. gingivalis* cysteine proteases (gingipains) hydrolyze IL-12, thereby having the capacity to reduce IL-12-induced IFN-γ production by CD4 cells and so favor a shift to a Th2 response and subsequent disease progression (Yun *et al*. 2001). Also, peripheral blood cells from periodontitis patients produce significantly lower levels of IL-12 (Fokkema *et al*. 2002) and the numbers of IgG4-positive B cells in the gingival tissues have been shown to increase relative to IgG2-positive cells with increasing inflammation, indicating the influence of IL-4 and Th2 responses and a corresponding decrease in IFN-γ and Th1 responses in large infiltrates in periodontitis.

CD8 T cells

The CD4:CD8 ratio in gingivitis is approximately 2:1 (Seymour *et al*. 1988; Berglundh *et al*. 2002a; Zitzmann *et al*. 2005). This is consistent with the ratio seen in peripheral blood, in secondary lymphoid organs, and in the development of DTH (Poulter *et al*. 1982). In contrast, early studies on cells extracted from periodontitis lesions (Cole *et al*. 1987; Stoufi *et al*. 1987) reported the CD4:CD8 ratio in periodontitis to be around 1:1. Despite this obvious increase in CD8-positive T-cells, their functional activity in the context of periodontitis is poorly understood. While the majority of CD4 clones established from periodontitis tissues have Th2 phenotypes producing high levels of IL-4 and low levels of IFN-γ, the majority of CD8 clones produce equal amounts of IL-4 and IFN-γ, that is they have a Th0 phenotype (Wassenaar *et al*. 1995). Similar to CD4 cells, two subsets of CD8 clones exist. One, whose primary function is to mediate cytolytic activity, produces high levels of IFN-γ, but no IL-4 or IL-5. These are the classic CD8-positive cytotoxic T cells. The secondary function of this subset is to suppress B cells. The other subset of CD8 cells, whose primary function is to suppress the proliferative response of cytotoxic CD8 T-cell clones and to suppress cell-mediated immunity, produce high levels of IL-4 together with IL-5. These are the classic CD8-positive suppressor cells. The secondary effect of these cells is to provide help to B cells. It has been shown that peripheral blood CD8 cells from highly susceptible patients with severe periodontitis produce high levels of intracellular IL-4. If these cells also occur locally within the periodontal tissues of these susceptible patients, they may participate in the local response by suppressing IFN-γ-producing cells and favoring humoral immune responses (Wassenaar *et al*. 1995), and hence a shift towards a type 2 function. Teng (2003), however, has played down a role for CD8 cells in periodontal disease by concluding that this subset does not participate directly in the destruction during disease progression. Although they may not play a direct role in tissue destruction, CD8-positive T cells do produce cytokines which play a role in both innate and adaptive immune responses and are important in the lysis of bacteria-infected or bacteria-damaged tissues and cells. Overall, the role of CD8-positive T cells in the pathogenesis of periodontitis has been largely overlooked. However, determination of the functions of this subset is paramount in fully understanding the pathogenesis of periodontal disease.

Control of the Th1/Th2 balance

While the Th1/Th2 paradigm provides a possible mechanism by which periodontal lesions become progressive or remain stable, an important question that remains is, what causes some lesions to show Th1 characteristics while others show Th2 characteristics? The answers may lie in the nature of the microbial challenge, as well as particular genetic and environmental susceptibility factors. Importantly, some of these factors may be clinically identifiable and modifiable.

It is likely that different T-cell subsets predominate at different phases of disease and the inability to determine disease activity clinically has been a major limitation in all studies. However, it remains clear that the balance of cytokines in inflamed periodontal tissues is what determines whether the disease remains stable or leads to progression and tissue destruction (Seymour & Gemmell 2001). In this context, the control of Th1 and/or Th2 expression is therefore fundamental in understanding the immunoregulatory mechanisms in chronic periodontitis. Factors that control Th1 and Th2 expression include:

- Genetics
- Innate immune response
- Nature of the antigen
- Nature of the antigen-presenting cell
- Hypothalamic–pituitary–adrenal axis and the sympathetic nervous system
- Treg/Th17 axis.

Genetics

Study of identical twins who were raised apart indicates that between 38% and 80% of the variation in periodontal disease is due to genetics (for review, see Michalowicz 1994). Susceptibility to *P. gingivalis* infection in mice is also genetically determined (Gemmell *et al*. 2002b), although the relevance of this to human periodontal disease remains to be ascertained. However, it is interesting to note that the susceptible strains of mice show low Th1 responses, while the resistant strains show moderate-to-high Th1 responses to *P. gingivalis*.

Innate immune response

It is generally stated that there are two distinct arms of the immune response; the non-specific natural or innate response and the specific or adaptive immune response. In recent years, however, the distinction between these has become blurred with the discovery that, in many respects, the innate immune response determines the nature of the subsequent adaptive response and at the same time aspects of the adaptive response control the effectiveness of the innate response.

IL-12

As noted earlier, PMNs are a consistent feature of the periodontal lesion in both gingivitis and periodontitis, and deficiencies in PMN function are associated with severe and rapidly progressive periodontitis. A strong innate immune response will result in high levels of IL-12 and is therefore

associated with a Th1 response, while a poor innate immune response and relatively low levels of IL-12 favor a Th2 response. Support for the concept of a Th1 response in gingivitis came from a study demonstrating significantly higher levels of IL-12 in the GCF from gingivitis sites in both gingivitis and periodontitis patients compared with periodontitis sites from the same periodontitis patients (Orozco *et al*. 2006).

Toll-like receptors

As noted earlier, TLRs occur on a number of cells including dendritic cells, PMNs, and macrophages among others, and have the ability to recognize PAMPs such as LPS, peptidoglycan, bacterial DNA, double-stranded RNA, and lipoprotein.

Given their role in innate immunity, it is likely that TLRs are important in determining the nature of the host response to plaque. TLR-2 and TLR-4, upon stimulation, may induce markedly different immune responses as determined by the resulting cytokine profiles. When stimulated, TLR-4 has been shown to promote expression of IL-12 and INF-γ-inducible protein-10 (IP-10), which is indicative of a Th1 response. Conversely, TLR-2 promotes the inhibitory IL-12p40, which is characteristic of a Th2 response (Re & Strominger 2001). These differences are reflected in differential cytokine expression by *Escherichia coli*-derived LPS and *P. gingivalis*-derived LPS. *E. coli*-derived LPS, which activates TLR-4, induces a strong Th1 response, while *P. gingivalis*-derived LPS, which activates TLR-2 (Hirschfeld *et al*. 2001), induces a strong Th2 response (Pulendran *et al*. 2001). These findings may indicate a further mechanism of susceptibility to periodontitis.

Nature of the antigen

Biofilms containing complexes of bacteria including *P. gingivalis, T. forsythia,* and *T. denticola* have been related to periodontitis, such that it is unlikely that a single antigen or a single organism is responsible for the disease. Further, there is the possibility that different people may have individually specific pathogenic complexes such that any single complex may not be pathogenic in all people. Indeed, little is actually known of the biofilm-specific antigens involved in periodontal disease and of the immune response to them. T-cell clones derived from mice immunized with *P. gingivalis* alone were found to have a Th1 profile, whereas T-cell clones derived from mice immunized with *F. nucleatum* followed by *P. gingivalis* demonstrated a Th2 profile (Choi *et al*. 2000). This may be due to the fact that *F. nucleatum* is a polyclonal B-cell activator such that B cells subsequently present the *P. gingivalis* antigen. Further, mice immunized with *F. nucleatum* were subsequently unable to make antibody to *P. gingivalis* (Gemmell *et al*. 2002a, 2004). This was not the case if bacteria were injected in reverse order. These findings, albeit preliminary, nevertheless show that it is possible for co-infection with multiple organisms to modulate the immune response. The level and relevance of this modulation to human periodontal disease, however, remains to be demonstrated but it is likely to involve the Th1/Th2 balance.

Nature of the antigen-presenting cell

It has been suggested (Kelso 1995) that Th1 and Th2 cells actually represent a spectrum of cells and, depending upon the conditions, can produce either Th1 or Th2 cytokines. In this context, Th0 cells may represent cells midway in the spectrum as well as naïve or non-committed cells.

The predominant APC in gingivitis tissues is a CD14-positive, CD83-positive dendritic cell (Gemmell *et al*. 2002c). In periodontitis tissues, the predominant APC is a CD19-positive, CD83-positive B cell, although a large number of CD83-positive endothelial cells are also present (Fig. 10-21), suggesting that these cells may also be involved in antigen presentation. Bacterial antigen presentation by endothelial cells induce anergy in transmigrating Th1 cells (Kanwai *et al*. 2000) which may also favor a move to a Th2 profile.

The cytokine profile of *P. gingivalis*-specific CD4 T-cell lines can be modified by changing the APC. When autologous peripheral blood mononuclear cells are used as APCs, the cell lines are predominantly IFN-γ producing, with a Th1 profile, but if autologous Epstein–Barr virus-transformed B cells are used, the same cell lines become predominantly IL-4 producing, that is they have a Th2 profile (Gemmell & Seymour 1998). These findings suggest that it is possible to modulate the Th1/Th2 profile by varying the nature of the APC. In gingivitis, the predominant APC is a dendritic cell, whereas in periodontitis it is primarily a B cell.

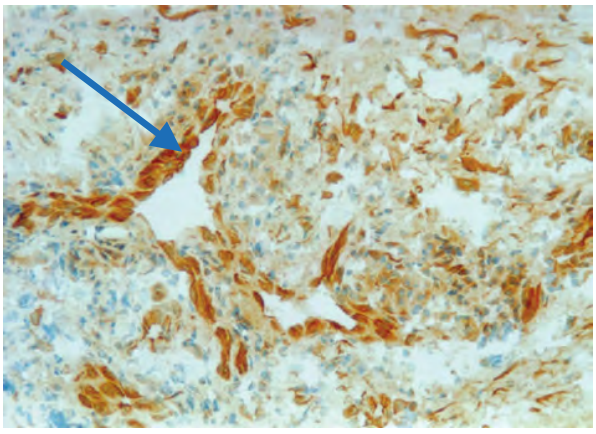

Fig. 10-21 CD83-positive endothelial cells (arrow) in periodontitis. (Source: Gemmell *et al*. 2002c. Reproduced with permission from John Wiley & Sons.)

Hypothalamic–pituitary–adrenal axis and the sympathetic nervous system

It is well accepted that stress, or at least the inability to cope with stressful situations, results in rapid progression of periodontitis. Stimulation of the sympathetic nervous system as well as hypothalamic–pituitary–adrenal axis activation leads to a selective suppression of Th1 responses, a shift towards Th2 dominance, and an increase in periodontitis (Breivik *et al*. 2000; Elenkov 2002).

Treg/Th17 axis

Regulatory T cells

Regulatory T cells (Tregs) are a specialized T cell subset characterized by the forkhead/winged helix transcription factor Foxp3. They primarily control exacerbated immune responses as well as the development of autoimmunity and do so through both contact dependent and contact independent mechanisms. They suppress effector T cells (Th1/Th2 and possibly Th17) and increased numbers have been found in periodontitis lesions where there are increased proportions of B cells compared with gingivitis tissues (Nakajima *et al*. 2005; Parachuru *et al*. 2014). Indeed, the numbers of Foxp3-positive cells significantly correlate with the B- and plasma-cell/T cell ratio in lesions dominated by B cells and plasma cells (Parachuru *et al*. 2014). Double labelling immunofluorescence revealed that CD4 but not CD8 cells were Foxp3-positive (Fig. 10-22) and that there was a significant upregulation of the Treg-related gene, signal transducer and activator of transcription (STAT5A), as well as the genes for TGFβ1 and IL-10 in B- and plasma cell dominated periodontitis lesions compared with T cell dominated gingivitis lesions (Parachuru *et al*. 2018). Protein analysis of the same specimens confirmed the gene expression data and showed higher levels of TGFβ1 and IL-10 in B- and plasma cell dominated lesions compared with T cell dominated lesions (Parachuru *et al*. 2018). Although the role of these cells in periodontal disease in humans is still speculative it may be that they are suppressing Th1 mediated responses while contributing to the proliferation of B cells via the production of IL-10. In contrast, da Motta *et al*. (2019) found slightly more Foxp3-positive cells in stage III grade B periodontitis lesion compared with stage IV grade C lesions.

Th17 cells

Over the past two decades most attention has focused on Th1 and Th2 cells; however, a third lineage of T cells has been described, the so-called Th17 cells which selectively produce IL-17. IL-17 induces the secretion of IL-6, IL-8, and PGE_2; hence, these cells are thought to play a crucial role in regulating inflammation. IL-17 is also thought to affect osteoclast activity and thereby mediate bone resorption.

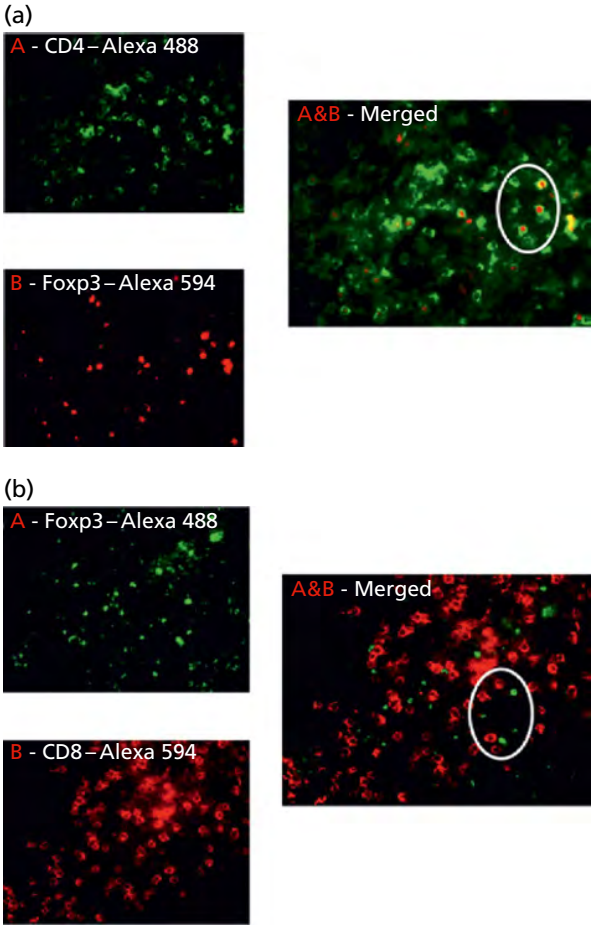

Fig. 10-22 Double labeling immunofluorescence for (a) CD4/Foxp3 and (b) CD8/Foxp3 showing all Foxp3-positive cells are CD4-positive and not CD8-positive. (Source: Parachuru *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

In the mouse, naïve T cells when incubated with transforming growth factor beta (TGF-β) and IL-2 upregulate the transcription factor Foxp3 and develop into the so-called Tregs which have an important function in suppressing autoimmune responses. In contrast, when incubated in the presence of TGF-β and IL-6, CD4-positive T cells express the transcription factor RORγt and become Th17 cells. While these cells are thought to have a protective role against bacterial infections, they may on the other hand contribute to autoimmune disease. There are, however, some important differences between mouse and human Th17 cells. In the human for example, TGF-β is not necessary for Th17 differentiation and there is some doubt over the role of IL-23, with some studies showing that IL-23 is a potent inducer of Th17 cells and others, showing that IL-23 alone is relatively ineffective. Activation of monocytes via TLR-2 is an effective stimulus for Th17 differentiation and, while IL-2 initially inhibits Th17 differentiation, ultimately it leads to Th17 expansion (for review, see Laurence & O'Shea 2007).

P. gingivalis leads to the downregulation of the IL-17 receptor (*IL-17r*) gene in mice (Gemmell *et al*. 2006). *IL-17r*-deficient mice have a defect or

display a significant delay in neutrophil recruitment into infected sites, resulting in susceptibility to infection (Kelly *et al*. 2005). This may account partly for the reported inhibition of entry of PMNs into *P. gingivalis*-induced lesions in mice (Gemmell *et al*. 1997). These studies seem to suggest that IL-17 and its ability to enhance PMN activity would have a protective effect in periodontal disease. In contrast to this mouse study, IL-17 expression in human periodontitis tissue is controversial. In periodontitis patients, 51% of gingival T-cell clones were found to express IL-17 compared with only 11% of peripheral blood T-cell clones (Ito *et al*. 2005). Also, stimulation of peripheral blood mononuclear cells by *P. gingivalis* antigen enhanced not only transcription but also translation of the *IL-17* gene (Oda *et al*. 2003). Thorbert-Mros *et al*. (2019) showed both CD3-positive and CD3-negative CD161-positive cells in gingivitis and periodontitis lesions and claimed that an increase in CD161-positive T cells was a marker of a destructive lesion. On the other hand, immunohistology and gene expression studies on diseased human tissue suggest low levels of IL-17 and low expression of IL-17 pathway genes (Okui *et al*. 2012). These results were confirmed by Parachuru *et al*. (2014, 2018) who demonstrated very few IL-17-positive cells (<1%) in B-cell/plasma cell-dominated periodontitis lesions in humans. They further showed that IL-17-positive cells had an ovoid/plasmacytoid morphology and were larger than the surrounding inflammatory cells (Fig. 10-23). Double immunofluorescence further showed that these IL-17-positive cells are not CD4- nor CD8-positive and hence are not T cells (Figs. 10-24, 10-25). Double labelling with tryptase, however, showed that they are in fact mast cells (Fig. 10-26) (Parachuru *et al*. 2018). This, in fact, is not surprising as it confirms earlier preliminary findings (Culshaw *et al*. 2011) and is consistent with the fact that mast cells appear to be the major source of IL-17 in many lesions including rheumatoid arthritis synovium (Hueber *et al*. 2010; Moran *et al*. 2011), psoriasis (Lin *et al*. 2011; Truchetet *et al*. 2013), renal allograft rejection (Velden *et al*. 2012), atherosclerosis (De Boer *et al*. 2010), and some tumors (Wang *et al*. 2013; Liu *et al*. 2014).

T cells have a high degree of plasticity and while Th17 cells are the major producers of IL-17 in peripheral blood and in culture, within the tissues the nature of the APC together with the cellular microenvironment determines the T cell phenotype. In this context, a Th17 cell entering the periodontal tissues may, under the influence of IL-4, become a Th2 cell and a Th2 cell under the influence of IL-12 and dendritic APCs may become a Th1 cell (Fig.10-27). It is possible therefore that the T cell cytokine profile will change over the course of the disease. It has further been shown that Foxp3 cells can become Th17 cells in autoimmune arthritis (Komatsu *et al*. 2014) and in keeping with this a small number of Foxp3/IL-17 double positive cells have been identified in periodontal disease tissues (Okui *et al*. 2012). Although the role of IL-17 in human periodontal disease remains to be determined it would appear that Th17 cells either do not exist in the tissues or do so in only small numbers and that the source of the low levels of IL-17 may in fact be mast cells.

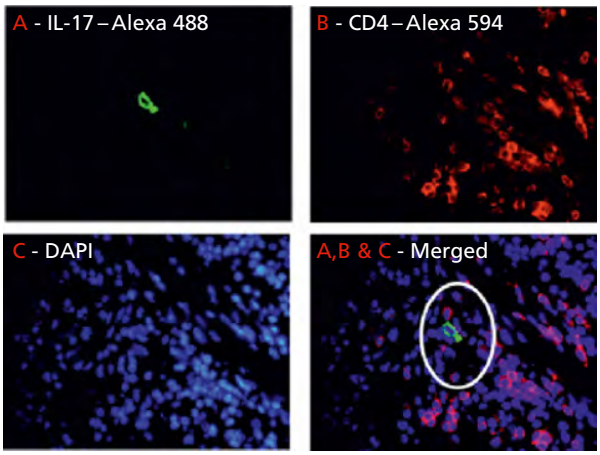

Fig. 10-24 Double labeling immunofluorescence for CD4/IL-17 showing IL-17-positive cells are not CD4-positive. (Source: Parachuru *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

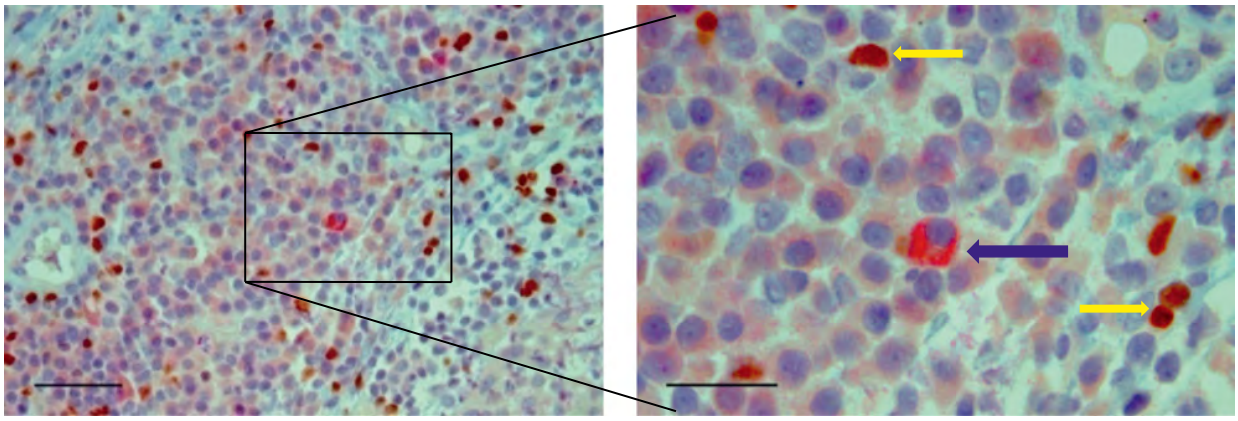

Fig. 10-23 Double labeling immunohistochemistry for Foxp3-positive (DAB-brown, yellow arrow) and IL-17-positive (AP-red, blue arrow) in the inflammatory infiltrate of B-cell/plasma cell predominant gingival tissues. (Source: Parachuru *et al*. 2014. Reproduced with permission from John Wiley & Sons.)

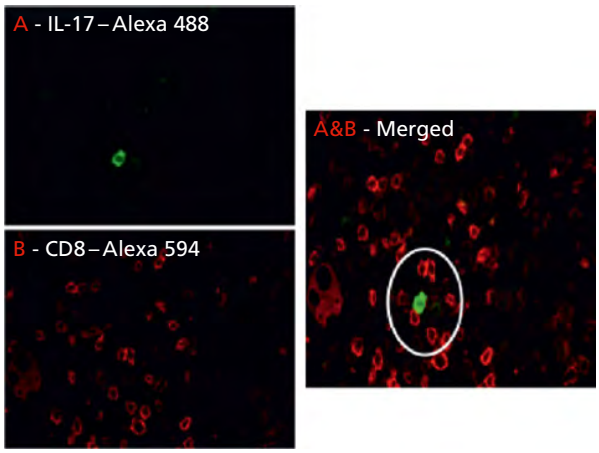

Fig. 10-25 Double labeling immunofluorescence for CD8/IL-17 showing IL-17-positive cells are not CD8-positive. (Source: Parachuru *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

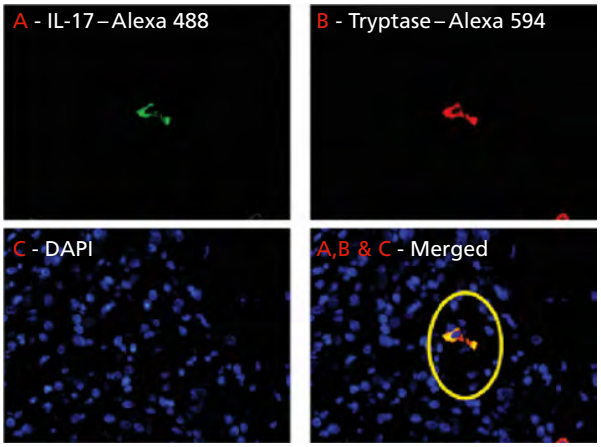

Fig. 10-26 Double labeling immunofluorescence for IL-17/tryptase showing IL-17-positive cells are tryptase positive mast cells. (Source: Parachuru *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

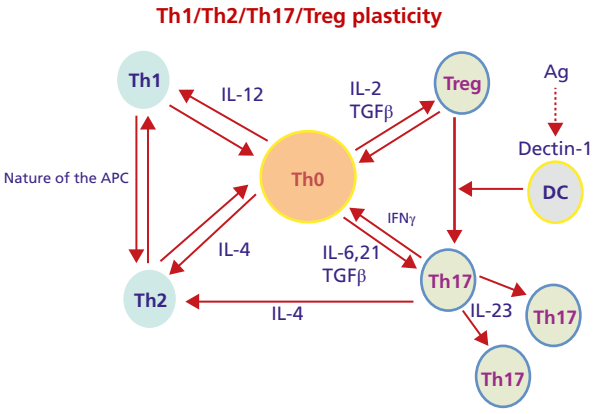

Fig. 10-27 T cell plasticity where the cellular microenvironment and the presence of different cytokines and APCs determine the T cell phenotype. A Th17 cell in the tissues under the influence of IL-4 can become a Th2 cell.

Autoimmunity

Natural killer T cells

Autoimmunity has been suggested to be a feature of periodontal disease. Cross-reactivity of human heat shock protein (HSP) 60 and *P. gingivalis* GroEL, a bacterial homolog, has been observed in periodontal disease (Tabeta *et al*. 2000; Ford *et al*. 2005). HSP60-specific as well as *P. gingivalis* cross-reactive T cells have also been demonstrated to accumulate in periodontitis lesions (Yamazaki *et al*. 2002). Taken together, these data suggest that both a humoral and a cell-mediated specific immune response to HSP60 may be important in the disease process. Additionally, anticollagen type I and III antibodies have been demonstrated in the gingivae of periodontitis patients (Hirsch *et al*. 1988) and collagen type I-specific T-cell clones have been identified in inflamed tissues of periodontitis patients (Wassenaar *et al*. 1995).

A subset of T cells that express NK surface receptors are thought to play an important autoimmune immunoregulatory role. An immunohistologic study found that NK T cells were more numerous in periodontitis lesions compared with gingivitis tissues or peripheral blood. These NK T cells also appeared to associate with CD1d-positive cells and it was suggested that they play a regulatory role in periodontal disease (Yamazaki *et al*. 2001).

The role of autoimmunity in chronic inflammation is still not clear. It is possible that autoimmunity is a feature of all chronic inflammatory processes. In this context, it has been known for many years that gingival fibroblasts are able to phagocytose collagen such that anticollagen antibodies may facilitate this phagocytosis and hence the removal of the broken down collagen. At the same time, an anti-HSP response may enhance the removal of dead and dying cells such that these autoimmune responses may be a natural part of chronic inflammation. Control of these responses would therefore be essential. This concept further illustrates that the role of T cells in periodontal disease may be one of immune homeostasis. Further studies are clearly needed to test this hypothesis and to determine the role of regulatory T cells in periodontal inflammation.

B-cell subsets

There are two major subsets of B cells: B-1 and B-2 cells. B-2 cells are recognized as conventional B cells and represent the traditional group of B cells that take an active part in the adaptive host response. They interact with T cells and develop into memory cells and long-lived plasma cells that produce antibodies with high affinity.

B-1 cells, on the other hand, may either be T-cell independent and responsible for early antibody responses with low affinity, or interact with T cells

and undergo class switching and produce IgG autoantibodies with high affinity. A specific subset of B-1 cells is the B-1a cell, which expresses the surface marker CD5. B-1a cells produce autoantibodies and are found in large proportions in subjects with autoimmune diseases and periodontitis (Afar *et al*. 1992; Berglundh *et al*. 2002b). The proportions of B-1a cells in peripheral blood are reported to be five to six times greater in subjects with periodontitis than in controls, and up to 40–50% of circulating B cells were positive for the B-1a cell marker CD5 in periodontitis (Berglundh *et al*. 2002b). B-1a cells also occur in large proportions in the gingival lesions of periodontitis patients such that the abundance of plasma cells seen in periodontitis lesions may be the result of both B-2 and B-1a proliferation and differentiation (Donati *et al*. 2009a). A study on experimental gingivitis in periodontitis patients has also demonstrated that B-1a cells are involved in the host response to microbial challenge (Donati *et al*. 2009b).

The large proportion of B-1a cells in periodontitis has also been associated with elevated levels of IL-10. B cells are one source of this cytokine and although IL-10 was previously regarded to play mainly anti-inflammatory roles, it also exhibits several proinflammatory functions, including activation of B cells, and serves as an autocrine growth factor for B-1a cells.

Connective tissue matrix destruction

Connective tissue remodeling is regulated by the interplay of cell–cell and cell–matrix interactions involving the production of enzymes, activators and inhibitors, and cytokines and growth factors (Reynolds & Meikle 1997). Proteinases such as the MMPs are key enzymes in tissue degradation. They are produced by resident cells, including fibroblasts, macrophages, and epithelial cells, and are regulated by tissue inhibitors of metalloproteinases (TIMPs).

It has been suggested that tissue destruction in disease processes may be due to an imbalance of MMPs over tissue inhibitors. Greater collagenase activity, which was demonstrated to derive mostly from PMNs, has been found in the GCF of periodontitis patients compared with the GCF of control subjects (Villela *et al*. 1987). MMP-9, which is produced by PMNs, was shown to be prominent not only in the GCF but also in gingival tissue samples from patients with periodontitis. Latent MMP-2 and MMP-9 have been shown to be expressed in the gingival tissues of patients with periodontitis, with the active forms being detected only in tissues associated with clinical disease (Korostoff *et al*. 2000; Seguier *et al*. 2001). Increases in the amounts of MMP-1, -2, -3, and -9, and the active form of MMP-9 have in fact been correlated with the number of CD22-positive B cells. This again suggests a possible mechanism by which B cells contribute to tissue destruction in periodontitis.

Up to 97–99% of the collagen in normal gingiva is made up of collagen types I and III. Collagen type III represents a minor fraction (about 10%). All other types (IV, V, VI, and VII) are related to basement membranes and together do not exceed 1–3%. Transmission electron microscopy of biopsies from periodontitis patients demonstrated the almost complete destruction of collagen types I and III in areas with leukocyte infiltration, while the basement membrane-associated collagen types V and Vl seem to remain and are related to the increased vascularity and epithelial proliferation in the inflamed tissue.

Bone loss

Bone resorption in periodontitis is regulated by the interplay between osteoblasts and the activation of osteoclasts. Osteoclasts share a common origin with cells of the macrophage/monocyte lineage and respond to and produce cytokines that regulate cells of this lineage. Osteoblasts originate from bone marrow stromal stem cells of mesenchymal origin and also have the capacity to produce factors which influence lineage development. Upon stimulation, osteoblasts produce a molecule known as receptor activator of nuclear factor-kappa B (NF-κB) ligand (RANKL), also known as osteoprotegerin-L (OPG-L), which regulates osteoclast differentiation and functions via its receptor (RANK). These activated osteoclasts then produce a number of acids and acid hydrolases which decalcify the mineral content of the bone and break down the organic matrix. The osteoclasts further phagocytose the broken-down organic matrix, thus resorbing the bone. A variety of cells produce a decoy receptor osteoprotegerin (OPG), which when released binds RANKL to prevent activation of RANK and hence osteoclasts (Simonet *et al*. 1997).

While these factors have potent effects on osteoclast development, they also have regulatory effects on immune cell function (Lorenzo 2000), being critical for T-cell maturation and the production of cytokines such as IFN-γ, IL-2, and IL-4 (Kong *et al*. 1999).

Studies have reported increased concentrations of RANKL and decreased concentrations of OPG in the GCF and tissues from periodontitis patients (Mogi *et al*. 2004; Vernal *et al*. 2004). However, the relationship between this observation and the progression of periodontitis is speculative. Interestingly, human gingival fibroblasts stimulated with bacterial LPS have been shown to express OPG and OPG mRNA rather than RANKL. Supernatants of LPS-stimulated fibroblasts reduced the numbers of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts generated by monocytes cultured in the presence of RANKL and macrophage colony-stimulating factor (M-CSF), suggesting the inhibition of monocyte-derived osteoclasts via the OPG pathway (Nagasawa *et al*. 2002). RANKL and RANKL mRNA are expressed by

inflammatory lymphocytes and macrophages as well as by proliferating epithelium in the vicinity of inflammatory cells. Thus, the high levels of RANKL seen in the GCF of periodontitis patients may be a reflection of the degree of inflammation rather than of bone loss and disease progression *per se*. Although both soluble and membrane-bound RANKL can be produced by activated T cells (Kong *et al*. 1999) and B cells (Taubman *et al*. 2005; Horowitz *et al*. 2010), it is the coupling of osteoblast-produced RANKL with osteoclast-expressed RANK that results in bone loss in periodontitis.

As already stated, IL-1 has a major role in bone resorption in periodontal disease, and both IL-1 and TNF-α have been reported to regulate the balance of RANKL and OPG (Hofbauer *et al*. 1999). Increased IL-1β production by B cells in periodontitis may therefore provide the link between increasing numbers of B cells and alveolar bone destruction in human periodontitis.

Conclusion

While there is no doubt that plaque is the cause of periodontal disease, its expression is the result of the interaction of bacterial, host, environmental, and systemic factors. This interaction leads to individuality of disease expression which in turn leads to individuality of treatment.

Despite over 50 years of research into the immunology of periodontal disease, the precise mechanisms and the role of many cell types remain an enigma. It is clear from the data obtained from a number of human studies that the function of the immune response in periodontal disease is to maintain homeostasis in the presence of the plaque biofilm. In this context, the development of the T-cell response in gingivitis represents the default homeostatic response where the host is in balance with the plaque biofilm. It is when this balance is disturbed, resulting in a dysbiosis between the biofilm and the host, that disease progression occurs. This periodontitis lesion is dominated by B cells and plasma cells and the uncontrolled production of B cell cytokines, including IL-1 and TNF-α, leads ultimately to destruction of the connective tissue attachment, loss of alveolar bone, and apical migration of the junctional epithelium. The B cell nature of this progressive lesion has been clearly demonstrated by Coat *et al*. (2015), who showed that pocket depth and attachment loss were significantly decreased 6 months after treatment with the anti-B cell monoclonal antibody rituximab and that the periodontal status of the subjects followed for up to 48 months after rituximab treatment was improved irrespective of the clinical parameter observed.

The equal proportion of M1 and M2 macrophages reflects the simultaneous presence of destruction and repair that is characteristic of chronic inflammation. Control of this T- to B-cell/plasma cell shift, however, probably involves the balance between Th1 and Th2 cells. While the interplay between a number of mechanisms, including the presence of inflammation in the gingival tissues and its influence on the ecology of the biofilm together with the PMN response in the gingival sulcus, are integral in maintaining homeostasis, control of the Th1/Th2 balance involves genetics, the innate immune response, and the nature of the antigen-presenting cell. The PMN response in the gingival sulcus is critical and any deficiencies in this response either qualitative or quantitative results in advanced disease. The epithelial barrier, IL-17, and the formation of NETs within the gingival sulcus are fundamental. The major source of IL-17 in the gingival sulcus is probably the PMNs themselves while mast cells and not Th17 cells are the major source of the very low levels found in the tissues.

The role of autoimmunity in chronic inflammation is also of major interest. In this context it can by postulated that autoimmunity is a critical and integral part of chronic inflammation in that it enhances the removal of collagen by enhancing fibroblast phagocytosis of protease-digested collagen fragments, as well as the removal of destroyed or dying cells. Control of this process by regulatory T cells (Tregs/NK T) then becomes fundamental and, again, if there is a disturbance in this homeostatic mechanism, enhanced tissue destruction could result.

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Chapter 11

Systemic and Environmental Modifying Factors

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Introduction

This chapter discusses systemic and environmental factors that may modify the host's susceptibility to periodontitis and the disease's clinical phenotype, including its extent, severity, progression, and response to therapy. The emphasis is on the two major modifying factors, diabetes mellitus and tobacco smoking. Aspects related to the epidemiologic evidence for the effect of these factors on periodontitis are reviewed in Chapter 6; thus, here we focus on underlying mechanisms, clinical presentation of affected individuals, and treatment considerations. A list of potential modifiers of periodontal health is shown in Table 11-1. Among these, factors such as puberty, menstruation, pregnancy, and medications that affect only the gingival status are discussed in Chapter 15, and the impact of HIV/AIDS on the periodontium is covered in Chapter 19.

Diabetes mellitus

Diabetes mellitus is a common, chronic condition with serious health implications. It comprises a group of metabolic disorders characterized by defects in insulin production, insulin action, or both, leading to abnormal glucose metabolism. The resulting hyperglycemia that characterizes both major types of diabetes (type 1 and type 2) is associated with a range of acute and chronic complications, and may eventually affect all organs of the body, including the periodontal tissues. Indeed, diabetes is established as a major risk factor for periodontitis.

Mechanisms underlying the effect of diabetes on periodontitis

Early studies exploring the mechanisms that may contribute to the increased prevalence and severity of periodontal destruction observed in patients with diabetes suggested the existence of distinct subgingival microbial profiles (Zambon *et al*. 1988). Subsequent reports concluded that the nature of the bacterial challenge in patients with diabetes and periodontitis does not appear to differ from that in those without diabetes (Feitosa *et al*. 1992; Thorstensson *et al*. 1995; Novaes *et al*. 1997; Sbordone *et al*. 1998). Many of these studies included small numbers of individuals, assessed only a handful of bacterial species, and most importantly compared patients with diabetes and periodontitis to controls without diabetes who were periodontally healthy. Taking these limitations into consideration, the subgingival microbial challenge in diabetes was later revisited using a cohort of subjects

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Table 11-1 Potential modifiers of periodontal health.

- Diabetes mellitus
- Tobacco smoking
- Obesity and nutrition
- Osteoporosis
- Stress
- Menstrual cycle
- Pregnancy
- Medications
  - Oral contraceptives
  - Anticonvulsants
  - Immunosuppressants
  - Calcium channel blockers
- HIV/AIDS
- Other systemic diseases and developmental and acquired conditions affecting the periodontal supporting tissues (Jepsen *et al*. 2018)

with type 1 diabetes and a control group of age- and gender-matched individuals without diabetes but with similar levels of periodontitis (Lalla *et al*. 2006b). Bacterial profiles, based on 12 species, as well as the homologous serum antibody responses were found to be comparable between the two groups. Still, this and most other studies of periodontal microbiota changes in diabetes to date were cross-sectional, used traditional microbiological approaches, and were restricted to known biofilm species. Emerging results from molecular microbiome studies have reported alterations in the composition of the oral microbiota in diabetes (Casarin *et al*. 2013; Zhou *et al*. 2013; Matsha *et al*. 2020) and, therefore, larger studies employing global analyses of the periodontal microbiome may be needed to shed light on this issue. For now, it appears that it is mostly the host response to the bacterial challenge that drives the enhanced susceptibility to periodontitis in diabetes.

Indeed, it was proposed early on that impairment of neutrophil function may facilitate bacterial persistence and increase periodontal destruction (Manouchehr-Pour *et al*. 1981a, b; McMullen *et al*. 1981). Subsequently, neutrophil priming in moderately and poorly controlled patients with diabetes, caused by increased levels and activity of protein kinase, was demonstrated (Karima *et al*. 2005). Other studies suggested a hyperinflammatory monocytic phenotype in diabetes characterized by enhanced levels of proinflammatory mediators in gingival crevicular fluid (GCF) or following challenge with lipopolysaccharide (LPS) in culture (Yalda *et al*. 1994; Salvi *et al*. 1997, 1998; Duarte *et al*. 2014).

In a study employing the experimental gingivitis model approach (i.e. 3-week cessation of oral hygiene resulting in gingivitis, followed by 2 weeks of optimal plaque control resulting in resolution of gingival inflammation), individuals with diabetes were found to develop accelerated and exaggerated gingival inflammation compared with controls without diabetes, despite a similar bacterial challenge (Salvi *et al*. 2005). Effects on other relevant cell types have also been reported, such as decreased collagen production and increased collagenolytic activity by gingival and periodontal ligament fibroblasts (Ramamurthy & Golub 1983; Sasaki *et al*. 1992; Yu *et al*. 2012), and hyperinflammatory response by oral epithelial cells (Amir *et al*. 2011).

Consistent with the evidence in humans, a number of animal studies have demonstrated that diabetes may increase the inflammatory response to bacteria. *Porphyromonas gingivalis* injection into the calvariae of diabetic mice was shown to stimulate an exaggerated cytokine expression and inflammatory infiltrate compared with the response observed in non-diabetic mice (Naguib *et al*. 2004; Graves *et al*. 2005; Nishihara *et al*. 2009). Reduction of inflammation and lesion size by specific inhibition of tumor necrosis factor-alpha (TNF-α) in these studies suggested that cytokine dysregulation represents a mechanism through which diabetes alters the host response to the bacterial challenge (Naguib *et al*. 2004; Takano *et al*. 2010).

A number of other reports, including human studies, have focused on osteoclastogenesis-related factors and explored the role of the receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin (OPG) in diabetes associated periodontal infections (Mahamed *et al*. 2005; Duarte *et al*. 2007; Lappin *et al*. 2009; Santos *et al*. 2010; Wu *et al*. 2015). These studies have suggested that hyperglycemia in diabetes may modulate the RANKL:OPG ratio in periodontal tissues and thus contribute to alveolar bone destruction. Along this line, the cycle of bone loss and subsequent bone formation was examined in a model of ligature-induced alveolar bone loss in rats (Liu *et al*. 2006b). Osseous repair was significantly limited by diabetes and the level of apoptosis of bone-lining cells was higher. In the calvarial model, diabetic mice also displayed increased fibroblast apoptosis and reduced fibroblast density following *P. gingivalis*-induced injury (Liu *et al*. 2004). Healing was significantly improved by blocking apoptosis with a caspase inhibitor (Al-Mashat *et al*. 2006) or by anti-TNF-α treatment (Liu *et al*. 2006a). These results were confirmed in diabetic mice with intraoral wounds (Desta *et al*. 2010; Siqueira *et al*. 2010). TNF-α inhibition in diabetic rats with ligature-induced periodontitis was also shown to impair expression of growth factors that control proliferation, differentiation, or apoptosis of osteoblasts, to restore the bone coupling process, and to increase the capacity of the animals to form new bone (Pacios *et al*. 2012).

The first attempt to explore more upstream changes induced by diabetes that may explain the observed hyperinflammatory response to infection, focused on the role of the receptor for advanced glycation end products (RAGE), a multiligand signaling receptor and member of the immunoglobulin superfamily of cell-surface molecules. RAGE expression is increased in diabetes and its activation through ligand interaction has an established role in the development and progression of other diabetic complications (Yan *et al*. 2009). First, expression of AGE

ligands and of markers of oxidative stress was demonstrated in gingival tissues of patients with diabetes and periodontitis (Schmidt *et al*. 1996). Subsequently, levels of serum AGEs were shown to be significantly associated with the extent of periodontitis in adults with type 2 diabetes (Takeda *et al*. 2006) and increased AGE and RAGE expression was reported in gingival tissues and saliva of individuals with diabetes and periodontitis (Yoon *et al*. 2004; Katz *et al*. 2005; Abbass *et al*. 2012; Chang *et al*. 2012a; Yu *et al*. 2012; Zizzi *et al*. 2013). More recently, delayed polymorphonuclear apoptosis in individuals with periodontitis and type 2 diabetes was shown to occur through an AGE–RAGE interaction (Manosudprasit *et al*. 2017).

In a model of oral infection and diabetes in mice, *P. gingivalis*-induced alveolar bone loss was increased in diabetic animals compared with non-diabetic controls and was accompanied by enhanced expression of RAGE, inflammatory AGEs, and tissue destructive matrix metalloproteinases (MMPs) in the gingival tissues (Lalla *et al*. 1998). In subsequent studies, treatment with soluble RAGE (sRAGE), the extracellular ligand-binding domain of RAGE which antagonizes interaction of ligands with the whole receptor, decreased levels of TNF-α, interleukin-6 (IL-6), and MMPs in gingival tissues and suppressed alveolar bone loss in a dose-dependent manner in diabetic animals (Lalla *et al*. 2000). Importantly, the beneficial effects of RAGE blockade were paralleled by suppressed expression of the receptor and its ligands in gingival tissues and were independent of the level of glycemia. These findings demonstrated that AGE–RAGE interaction leads to the exaggerated inflammatory response to the bacterial challenge and subsequent tissue destruction seen in diabetes-associated periodontitis. Accumulation of AGEs and their interaction with RAGE have been also shown to contribute to osteoclastogenesis via increased RANKL expression and OPG downregulation in various cell types (Ding *et al*. 2006; Yoshida *et al*. 2009).

Moreover, RAGE may contribute to impaired repair following injury, as shown in studies of excisional dermal wounds in diabetic mice (Goova *et al*. 2001) and of osseous defects following tooth extraction in diabetic rats (Chang *et al*. 2012b). Studies of osteoblast cultures and craniotomy defects in mice in the absence of infection have demonstrated the role of RAGE and its interaction with the AGE ligand carboxymethyl-lysine (CML)–albumin in delayed bone healing (Santana *et al*. 2003). Using the same experimental approach, the apoptotic effect of CML–collagen on osteoblasts was shown to be mediated through RAGE (Alikhani *et al*. 2007).

The basic mechanisms involved in the pathogenesis of diabetes-associated periodontitis are summarized in Fig. 11-1: the hyperglycemia that characterizes diabetes drives the formation of AGEs and leads to increased expression and activation of their chief receptor RAGE. AGEs can impact cellular phenotype directly via receptor-independent pathways but, importantly, the AGE–RAGE interaction negatively affects cellular phenotype and function, leading to enhanced inflammation, production of reactive oxygen species or oxidative stress, and

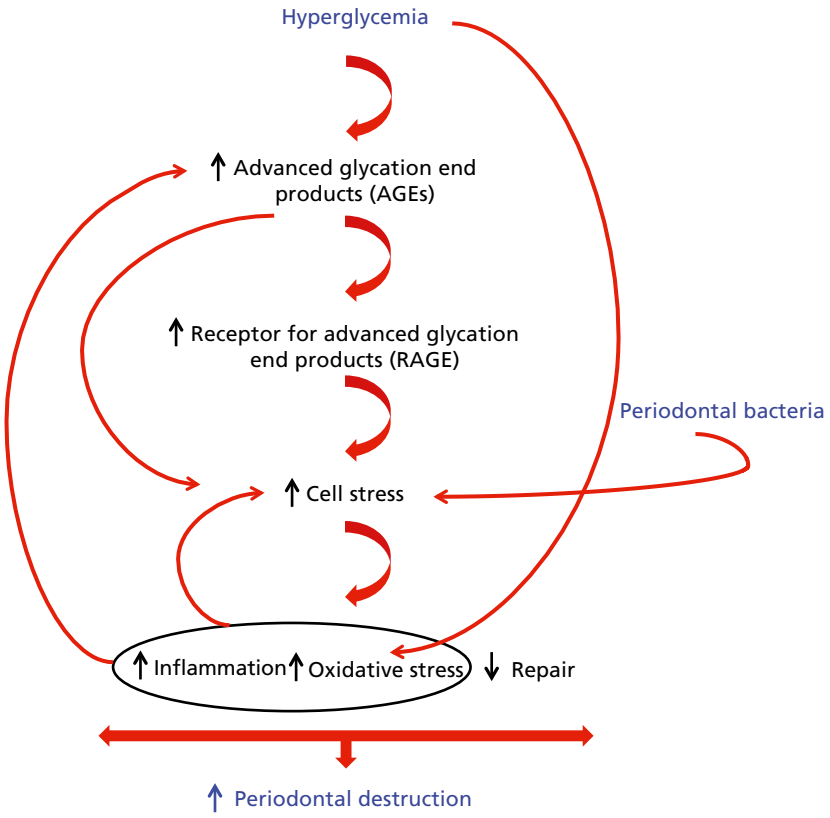

Fig. 11-1 Potential mechanisms in the pathogenesis of diabetes-associated periodontitis (see text).

compromised tissue repair. Hyperglycemia also promotes oxidative stress directly, and both inflammation and oxidative stress can contribute to further AGE formation. These mechanisms coupled with the impact of the periodontal pathogens perpetuate this vicious cycle of inflammatory stress and impaired repair in the diabetic periodontium. Of note, there are several links between the various elements shown in Fig. 11-1, but they cannot all be demonstrated in a single diagram. For example, inflammation and oxidative stress amplify one another and can also promote shifts in the subgingival biofilm. The net result of all these complex pathways is the accelerated periodontal tissue destruction observed in diabetes.

Clinical presentation of the periodontal patient with diabetes

The current consensus is that there are no characteristic phenotypic features unique to periodontitis in patients with diabetes and, on this basis, diabetes-associated periodontitis is not a distinct disease (Jepsen *et al*. 2018). Nevertheless, since diabetes is an important modifying factor of periodontitis, according to the 2018 classification (Papapanou *et al*. 2018), the level of glycemic control is taken into consideration in the assessment of grade of periodontitis.

Patients with diabetes will often present with pronounced clinical and radiographic signs of periodontitis, including gingival inflammation, increased pocketing, and increased attachment, bone, and tooth loss (Figs. 11-2, 11-3, 11-4, 11-5). It is recognized that among those affected by diabetes, patients with poor glycemic control are at a higher risk for presenting with more severe periodontitis (Garcia *et al*. 2015; Genco & Borgnakke 2020). In addition, clinical and radiographic signs of periodontitis progression may be evident (Figs. 11-6, 11-7), especially in periods when glycemic control deteriorates over time (Westfelt *et al*. 1996; Demmer *et al*. 2012; Costa *et al*. 2013b). Beyond the typical appearance of amplified gingival inflammation and bone or attachment loss, poorly controlled or undiagnosed/untreated patients with diabetes may present with or experience multiple recurring periodontal abscesses (Harrison *et al*. 1983; Ueta *et al*. 1993; Herrera *et al*. 2014). Given that many of the effects of hyperglycemia discussed in the section above are irreversible and may have long-lasting effects, poor periodontal status may also be present in patients with adequate current glycemic levels, but past periods of poor metabolic control.

Importantly, even children and adolescents with diabetes may present with significant periodontal changes (Cianciola *et al*. 1982). A series of reports in 6–18-year-old individuals (Lalla *et al*. 2006a, 2007a, b) has demonstrated that increased attachment loss manifests much earlier in life in diabetes than previously recognized and is associated with poor glycemic control. These findings have been supported by subsequent studies and have led to the recommendation that a thorough periodontal evaluation is needed in patients with diabetes across all age groups to allow for early intervention (Jensen *et al*. 2020).

With respect to periodontal therapy outcomes, patients with adequately controlled diabetes can respond well to non-surgical treatment and achieve reduced probing depths and attachment gain (Christgau *et al*. 1998; Hsu *et al*. 2019). In such patients, periodontal status can remain stable over time following therapy (non-surgical and surgical) and appropriate maintenance (Westfelt *et al*. 1996). However, in patients with poor glycemic control, long diabetes duration, and other diabetic complications, response to periodontal therapy appears to be unpredictable as tissue repair and wound healing are often compromised (Tervonen & Karjalainen 1997). There is little available evidence to date on specific responses to different types of surgical therapy in patients with diabetes. Clinicians may use early responses to non-surgical therapy, especially at the more "predictable" sites (e.g. shallow–moderate pockets, accessible sites, single-rooted teeth), in order to identify potential non-responders early, properly inform/advise such patients, and plan further treatment accordingly.

Concepts related to patient management

Studies suggest that oral disease awareness among individuals with diabetes is low (Moore *et al*. 2000; Tomar & Lester 2000; Sandberg *et al*. 2001; Jansson *et al*. 2006; Allen *et al*. 2008; Al Habashneh *et al*. 2010; Poudel *et al*. 2018; Siddiqi *et al*. 2019; Parakh *et al*. 2020). Therefore, dental professionals need to educate their patients with diabetes, young and old, about the link between diabetes and periodontitis, and stress that the two conditions may amplify one another.

Managing the periodontal patient with diabetes who is under good medical care and maintains adequate glycemic control should not generally be difficult. However, as the concepts discussed earlier suggest, patients with poor metabolic control and those who present with other complications and co-morbidities may present a challenge when treated for periodontal conditions. Therefore, special considerations must be taken into account to ensure that the oral care provided is safe and that it leads to predictable outcomes. These considerations include: (1) taking a thorough medical history with a focus on understanding the patient's metabolic profile; (2) establishing communication with the treating physician; (3) performing a careful intraoral evaluation and a comprehensive periodontal examination; (4) addressing other risk factors present, such as smoking or overweight/obesity; and (5) considering co-morbidities and other complications, such as hypertension and vascular or kidney disease.

Initial therapy should focus on the control of acute infections, if present, as these may also have a direct adverse effect on the level of the patient's glycemic control. Good oral and overall health behaviors along

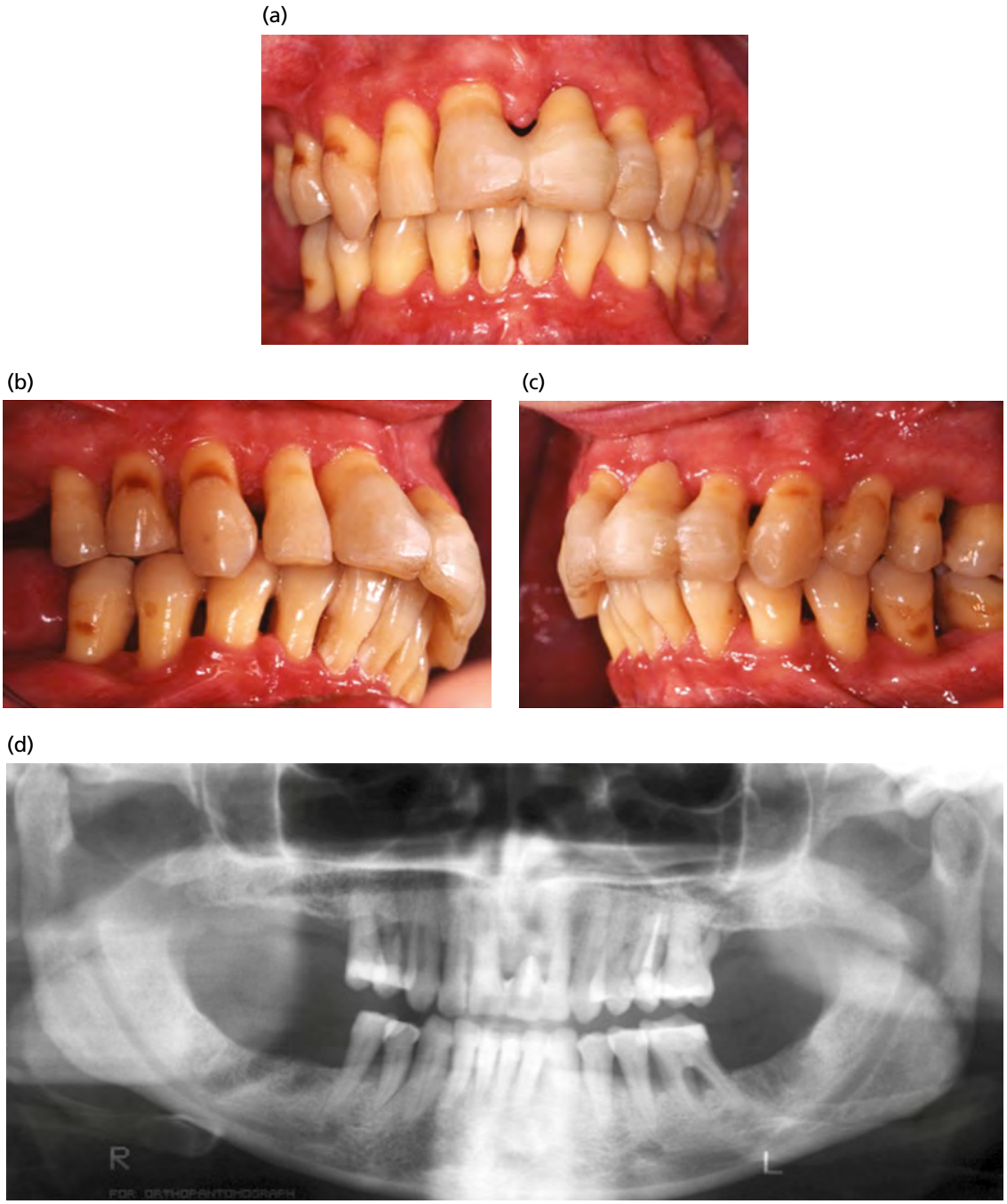

Fig. 11-2 (a–c) Clinical and (d) radiographic presentation of a 38-year-old female patient with type 1 diabetes and generalized Stage IV, Grade C periodontitis. The patient was diagnosed with diabetes at the age of 10 years, has poor glycemic control, and is also a smoker. (Source: Courtesy of Dr. Tellervo Tervonen.)

with lifestyle changes, as needed, must be promoted. Recommendations for proper home care are very important and a less complex, stepwise periodontal therapy plan should be offered whenever possible. Clinical protocols should be in place for determining frequency of maintenance care (to reinforce oral hygiene and prevent, monitor, and treat any disease reactivation), the need for referral to a periodontist, and the need for medical consultation, referral, and follow-up. An interdisciplinary approach and collaboration beyond professional boundaries is essential.

Furthermore, extreme glycemic variability is a relatively common medical emergency in a dental care setting. Prevention, early recognition, and proper management of potential hypo- and hyperglycemic episodes are very important. Dental professionals need to remember that, for all people with type 1 and many with advanced type 2 diabetes, episodes of hypoglycemia are very common and can be precipitated by several factors, including missed or delayed meals, excessive physical activity, stress, or alcohol consumption. Acute hyperglycemic episodes are less common, but also serious. They can be precipitated by pain and stress, that antagonize insulin action, or by under-dosing of diabetic medications prior to the dental appointment. Therefore, consideration must

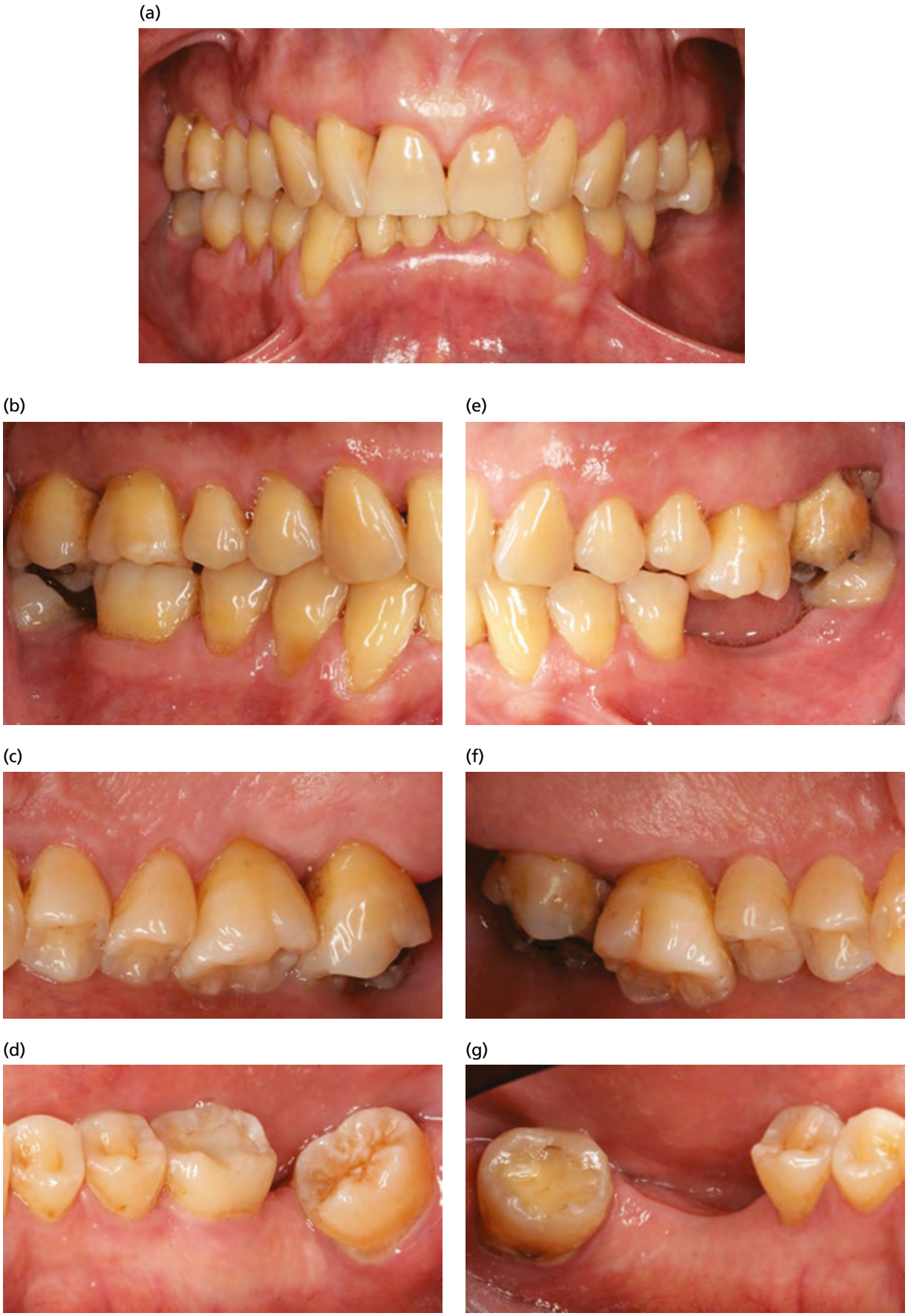

Fig. 11-3 Clinical presentation of a 50-year-old male patient with type 2 diabetes. (a) Anterior view; (b–d) right side view; (e–g) left side view. The patient was diagnosed with diabetes 8 years earlier, is poorly controlled, and is a former smoker. Periodontal examination revealed probing depths of up to 10 mm and multiple sites with gingival recession. (Source: Courtesy of Dr. Thomas Spinell.)

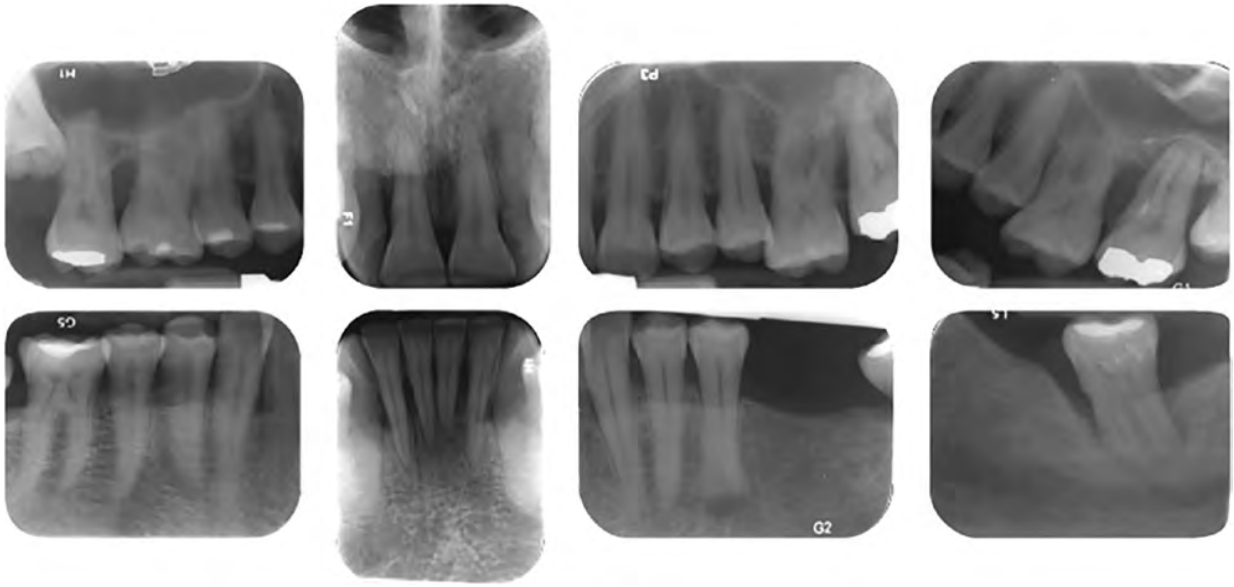

Fig. 11-4 Periapical radiographs of the patient shown in Fig. 11-3 reveal areas of severe bone loss. (Source: Courtesy of Dr. Thomas Spinell.)

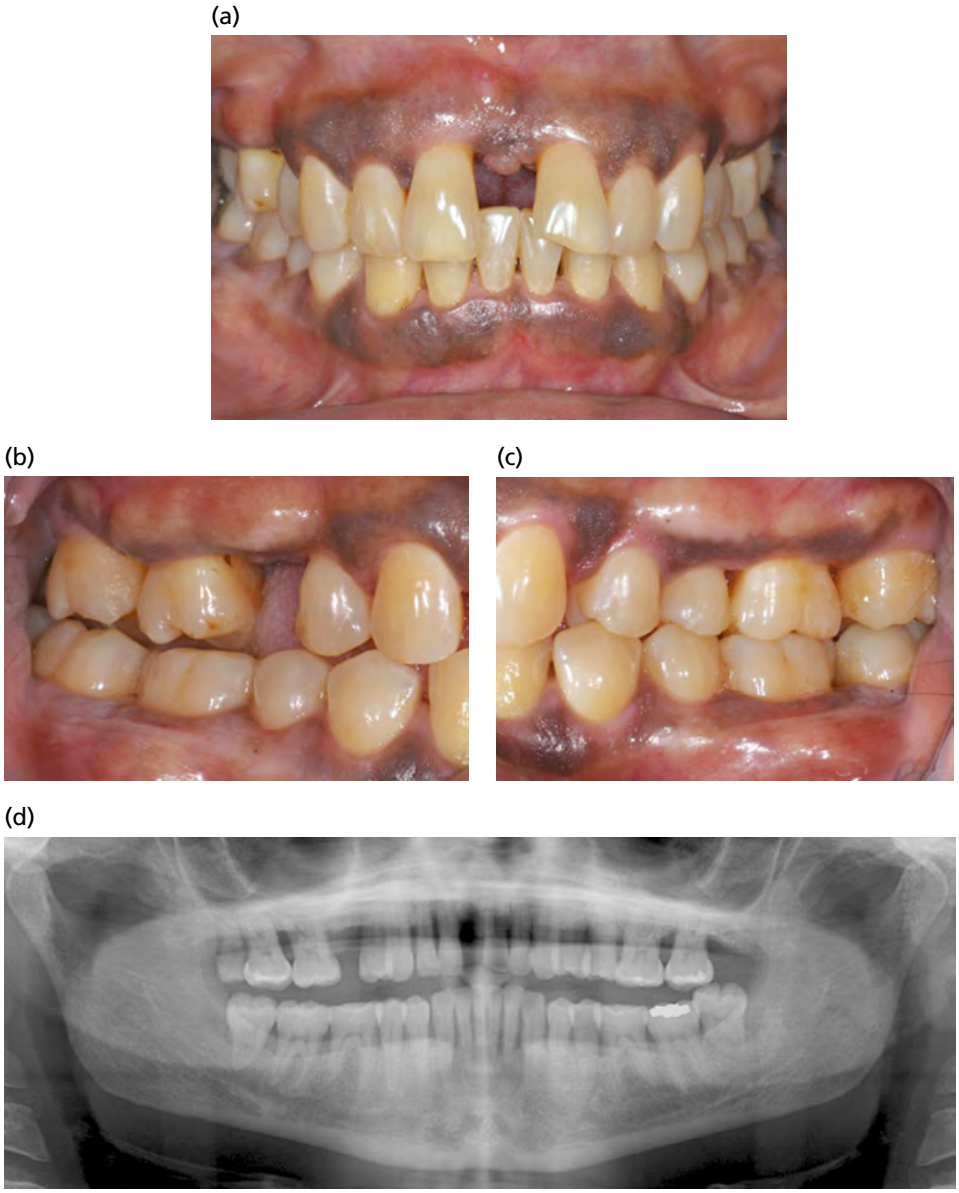

Fig. 11-5 (a–c) Clinical and (d) radiographic presentation of a 41-year-old female patient with type 1 diabetes. The patient was diagnosed with diabetes at the age of 26 years, has poor glycemic control, and is a former smoker. Periodontal examination revealed generalized Stage III, Grade C periodontitis with probing depths ranging between 5 and 9 mm on most teeth. (Source: Courtesy of Dr. Shota Tsuji.)

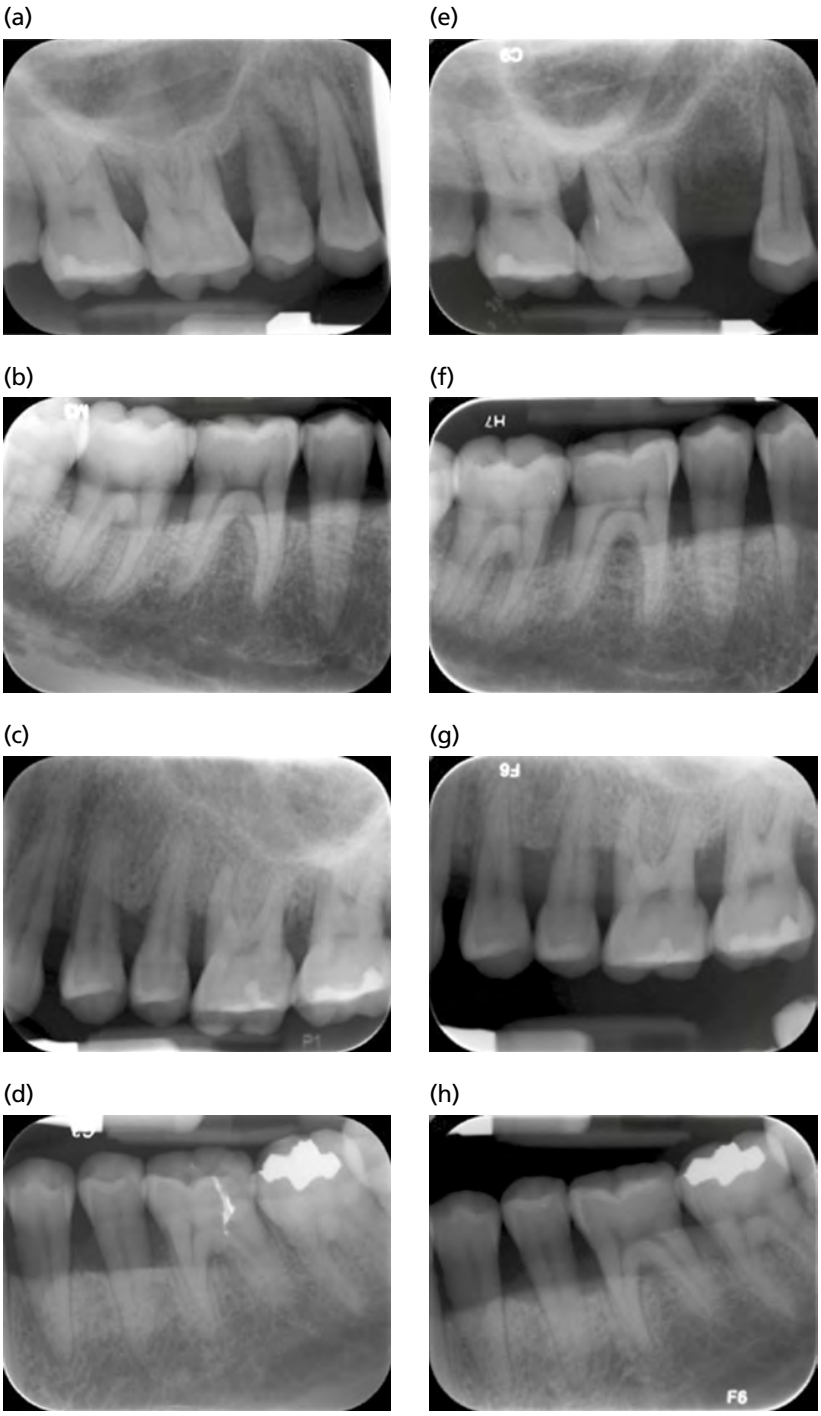

Fig. 11-6 Same patient as in Fig. 11-5. Posterior periapical radiographs at presentation (e–h), and corresponding radiographs taken 17 months earlier (a–d). Comparison reveals progression of bone loss and loss of the upper right second premolar within this short time period, during which glycemic control was poor (HbA1c values of 9–10%). (Source: Courtesy of Dr. Shota Tsuji.)

be given to the appropriate timing and duration of appointments: early mornings are preferable, as patients can tolerate stress better due to higher levels of endogenous corticosteroids. Likewise, procedures should preferably be brief and as atraumatic and pain free as possible, requiring profound anesthesia and adequate post-treatment analgesic coverage. In addition, since the patient's ability to eat may be affected by a periodontal procedure, a change in diabetic regimen may be necessary and should be explored in consultation with the treating physician.

A preoperative determination of glucose levels using the patient's glucometer can be very helpful in prevention and/or early identification of episodes of extreme glycemic variability. Early signs of hypoglycemia (glucose levels <70 mg/dL) include shakiness, weakness, hunger, cold and clammy skin, and nausea, and later symptoms include increasingly bizarre behavior, mental confusion, hypotension, and loss of consciousness. If the patient is conscious, 15–20 g of simple carbohydrates should be given orally (e.g. glucose tablets or gel, 120 mL of fruit juice, 1 tablespoon

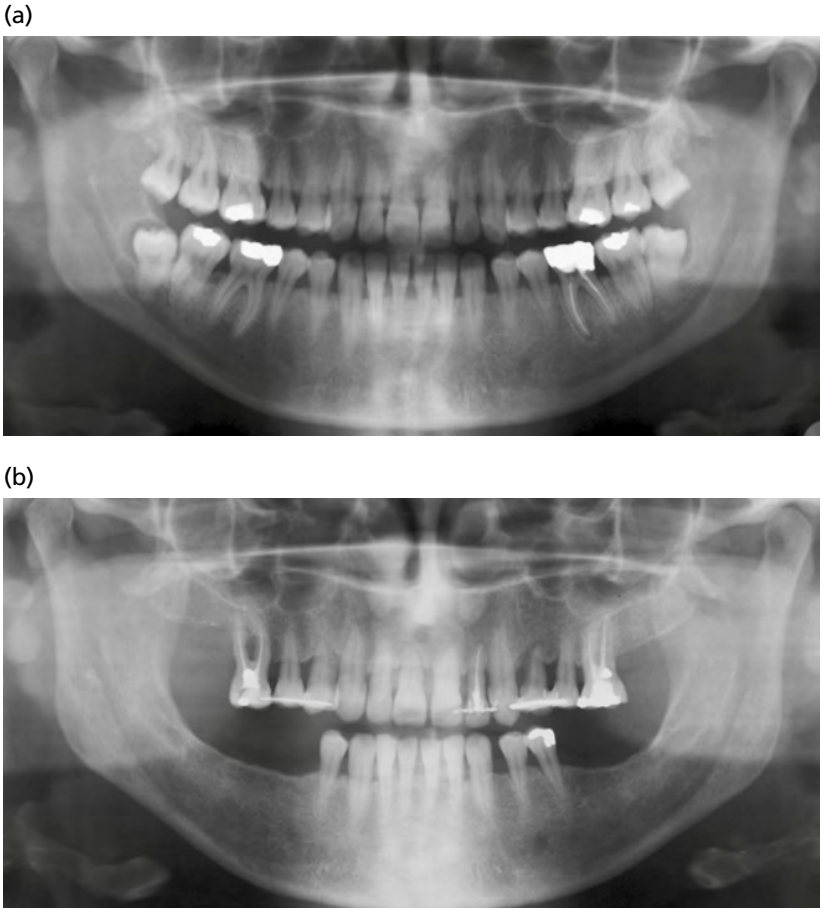

Fig. 11-7 Panoramic radiographs of a female patient with type 1 diabetes (a) at presentation at the age of 29 years and (b) 12 years later. The patient had been diagnosed with diabetes at the age of 12 years, was poorly controlled, and a smoker. She developed nephropathy and was on peritoneal dialysis. Despite comprehensive periodontal therapy, her periodontal status deteriorated significantly. The patient died of a myocardial infarction at age 41. (Source: Courtesy of Dr. Tellervo Tervonen.)

of table sugar). The patient should respond in about 15 minutes and should be then given a snack with complex carbohydrates and protein. If the patient does not respond, treatment can be repeated. If the patient becomes unconscious, glucagon (available as a kit with a 1-mg ampule, diluents, and syringe) can be injected into the upper arm or thigh muscle and medical emergency services must be called. When the patient responds to the glucagon injection and is able to swallow, the oral carbohydrate administration steps described above can be followed until the patient is stabilized. A patient with an acute hyperglycemic emergency (glucose levels >250–300 mg/dL) can present disoriented, thirsty, fatigued, or nauseated, with rapid and deep breathing, hot and dry skin, and fruity breath, and can progress to hypotension and loss of consciousness. Such patients require transfer to an emergency room/hospital setting and immediate medical intervention. Again, having a glucometer at hand is very helpful; glucose levels can be assessed when symptoms arise to confirm whether the episode is because of hypo- or hyperglycemia, and in the case of a hypoglycemic episode, to reassess levels following initial treatment. If a glucometer is not available and the dental professional is unable to differentiate whether the patient is hypo- or hyperglycemic, treatment for hypoglycemia should be initiated. The patient's treating physician should always be informed of extreme glycemic emergencies that occurred in the dental setting and provided with all related information.

Finally, another concern relates to the large number of people worldwide who have diabetes, but remain undiagnosed, and the even larger number of individuals at risk for diabetes who are unaware of it. Since diabetes has early oral effects and many patients visit a dentist annually, often returning for multiple non-emergent visits, dental care settings are ideal healthcare sites that can be used for the early identification of undiagnosed diabetes. Dental professionals can assess risk factors, refer for testing or "formally" screen, and follow up on outcomes.

Early studies aiming to explore the ability of clinical periodontal parameters to identify patients with undiagnosed diabetes were based on national US data and suggested that such an approach is promising (Borrell *et al*. 2007; Strauss *et al*. 2010). The first study to collect data prospectively in a clinical setting in order to discern a simple and efficient protocol to identify people with undiagnosed prediabetes or diabetes revealed that two dental parameters (number of missing teeth and percent of teeth with deep

periodontal pockets) were effective in correctly identifying the majority of cases of unrecognized dysglycemia (Lalla *et al*. 2011, 2013). The addition of a point-of-care HbA1c test result was found to improve significantly the performance of the screening algorithm in the population under investigation. Other approaches to screening in dental settings have since been reported with consistent results (Genco *et al*. 2014; Herman *et al*. 2015; Lalla *et al*. 2015; Holm *et al*. 2016; Acharya *et al*. 2018; Estrich *et al*. 2019). Findings from these studies suggest that incorporating assessment for undiagnosed diabetes into the periodontal evaluation of patients at risk is of value as it can raise patients' awareness and contribute to early diagnosis and treatment of those affected, and highlight a new set of responsibilities for dental professionals.

Tobacco smoking

Tobacco smoking is a prevalent behavior with widespread and severe health consequences. Although tobacco use was once classified as a habit, it is now considered an addiction to nicotine and a chronic relapsing medical condition. Smoking has several effects on the oral cavity, ranging from simple tooth staining to oral cancer.

As reviewed in Chapter 6, tobacco smoking is recognized as an important risk factor for periodontitis, and a multitude of epidemiologic and clinical studies have established its detrimental effect not only on the prevalence and severity of periodontitis, but also on its incidence and progression (Zeng *et al*. 2014; Nociti *et al*. 2015; Leite *et al*. 2018). These effects have been shown to be dose-dependent and can be particularly evident in younger individuals (Kibayashi *et al*. 2007; Stabholz *et al*. 2010; Costa *et al*. 2013a; Zeng *et al*. 2014). There is also evidence for a link between passive, also termed environmental or second-hand, smoking and periodontal disease (Arbes *et al*. 2001; Nishida *et al*. 2008; Akinkugbe *et al*. 2016; Sutton *et al*. 2017). Tobacco smoke contains thousands of different substances (Talhout *et al*. 2011) and most of its harmful effects result through systemic exposure following lung absorption, in addition to the obvious absorption in the oral cavity (Palmer *et al*. 1999).

Electronic nicotine delivery systems (e-cigarettes) are alternative, non-combustible tobacco products that generate an inhalable aerosol. E-cigarette use, or vaping, appeals to current smokers, former smokers, and young people who have never smoked, and e-cigarette use by adolescents is highly prevalent and has been associated with a two- to four-fold increase in cigarette smoking over the following year (Asher *et al*. 2019; Cullen *et al*. 2019). Evidence on the effects of vaping on the oral cavity is currently limited (Yang *et al*. 2020). E-cigarettes have been marketed as useful tools in smoking cessation, but evidence is inadequate to infer that they actually increase quit rates (Lindson-Hawley *et al*. 2016; El Dib *et al*. 2017; Dunbar *et al*. 2019). Importantly, the extent of health risks posed by ingredients that are unique to e-cigarettes but not present in conventional cigarettes must be considered. Also of importance in this context is the changing characteristics of e-cigarettes, the many different contexts in which they are used, and the limited number of studies on their long-term health effects conducted to date (Clapp & Jaspers 2017; Gotts *et al*. 2019).

Mechanisms underlying the effect of smoking on periodontitis

The mechanisms by which cigarette smoking affects periodontal status are not fully understood; however, various potential pathways have been discussed in the literature, including effects on the oral microbiota, the gingival tissues, the inflammatory and immune response, and the healing capacity of the periodontium.

Early reports suggested that the amount of plaque in smokers is higher compared with non-smokers (Preber *et al*. 1980), but studies controlling for confounding factors revealed that smoking does not appear to affect plaque scores, and indeed, in experimental gingivitis models, the rate of plaque formation was similar between smokers and non-smokers (Bergstrom 1981; Preber & Bergstrom 1986; Lie *et al*. 1998). Further, certain studies focused on smoking and qualitative changes in subgingival plaque. Zambon *et al*. (1996) found higher prevalence of *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *P. gingivalis* in current and former smokers compared with never-smokers. Similarly, Haffajee and Socransky (2001b) found a higher prevalence of eight bacterial species in current smokers compared with past smokers and non-smokers. Studies employing traditional culture or targeted molecular methods have not always reported consistent findings (Kubota *et al*. 2011; Heikkinen *et al*. 2012; Lanza *et al*. 2016; Joaquim *et al*. 2018), but altered subgingival microbial communities due to smoking are generally revealed using 16S sequencing (Jiang *et al*. 2020). Indeed, tobacco smoking has been shown to affect bacterial acquisition and aggregation, and to promote colonization with key periodontal pathogens (Shchipkova *et al*. 2010; Bagaitkar *et al*. 2011; Brook 2011; Kubota *et al*. 2011; Kumar *et al*. 2011; Bizzarro *et al*. 2013).

Based on the above, it appears that microbiologic differences exist between smokers and non-smokers, but they primarily concern the composition rather than the amount of the subgingival biofilm. No unified conclusion can be drawn currently, however, on how smoking-induced microbial diversity changes contribute to periodontitis.

Importantly, it is well accepted that smoking has the potential to impair several aspects of the innate and immune response and, in the setting of periodontitis, this can tip the balance towards an exaggerated tissue breakdown and impaired repair (Lee *et al*.

2012). To this end, it has been reported that neutrophil migration and chemotaxis in the periodontal tissues are negatively affected in smokers (Pabst *et al*. 1995; Persson *et al*. 2001; Soder *et al*. 2002). Interestingly, neutrophils express functional receptors for many tobacco smoke components and, for example, the numbers of nicotine receptors are increased in smokers and have been shown to decrease following smoking cessation (Ackermann *et al*. 1989; Lebargy *et al*. 1996). Not all data on neutrophil effects are consistent, but overall cigarette smoke appears to shift the balance of neutrophil activities in the more destructive direction (White *et al*. 2018). The effects of tobacco smoking on T- and B-cell numbers and function are more complex and less consistent across studies, as both immunosuppressive and inhibitory processes have been described (Palmer *et al*. 1999; Loos *et al*. 2004). There is also, mostly *in vitro*, evidence suggesting that gingival and periodontal ligament fibroblast recruitment and adhesion may be negatively affected in smokers, and that collagen production is decreased while collagenolytic activity is increased (Tipton & Dabbous 1995; James *et al*. 1999; Gamal & Bayomy 2002; Poggi *et al*. 2002; Karatas *et al*. 2020). Finally, the reported suppressed gingival inflammation in smokers as evidenced by clinical signs of reduced gingival bleeding and bleeding on probing (Preber & Bergstrom 1985, 1986; Bergstrom *et al*. 1988; Bergstrom & Bostrom 2001) appears to be related to fewer gingival vessels (Rezavandi *et al*. 2002; Palmer *et al*. 2005), rather than to vasoconstriction as originally speculated. The above effects of smoking on the inflammatory response, vasculature, and fibroblast function can also explain its well-described negative effects on healing following non-surgical and surgical periodontal therapy (Kinane & Chestnutt 2000).

Much less is known about the mechanisms underlying the effects of passive smoking on the periodontium. However, there is evidence for increased levels of salivary cotinine (a nicotine metabolite), higher levels of a number of inflammatory mediators, and an increased proportion of phagocytic cells in gingival lesions of individuals exposed to second-hand smoking, possibly indicating an altered host response to the bacterial challenge (Walter *et al*. 2012).

Clinical presentation of the periodontal patient who smokes

The current consensus is that there is no unique phenotype of periodontitis in smokers and, on this basis, smoking-associated periodontitis should not be a distinct diagnosis (Jepsen *et al*. 2018). Nevertheless, since smoking is an important modifying factor of periodontitis, according to the 2018 classification (Papapanou *et al*. 2018), the current level of tobacco use is taken into consideration in the assessment of grade of periodontitis.

The periodontal effects of smoking become evident relatively early in the course of tobacco use, and smokers often present clinically and radiographically with signs of increased bone, attachment, and tooth loss (Figs. 11-8, 11-9). Deeper pockets and more attachment loss may often be seen in mandibular anterior and maxillary palatal sites (Haffajee & Socransky 2001a; Adler *et al*. 2008). At the same time, however, smoking may mask some other important clinical signs of gingivitis and periodontitis, complicating the usual approach to recognizing these conditions. Indeed, smokers often present with fibrotic gingiva and limited gingival erythema and edema relative to the amount of plaque and the severity of the underlying bone loss (Scott & Singer 2004). Bleeding on probing is reduced in a dose-dependent manner in smokers compared with non-smokers with similar levels of plaque (Bergstrom & Bostrom 2001; Dietrich *et al*. 2004), and it can re-emerge within weeks in patients who quit, even in the presence of improved plaque control (Nair *et al*. 2003).

Importantly, and as described in detail in Chapter 6, multiple studies examining the effects of smoking have demonstrated that response to periodontal therapy is compromised in smokers, with current smokers exhibiting less probing depth reduction and/or attachment gain compared to former or never smokers (Heasman *et al*. 2006). Meta-analyses of the effects of smoking on the outcomes of periodontal therapy corroborate these conclusions (Garcia 2005; Labriola *et al*. 2005; Patel *et al*. 2012; Kotsakis *et al*. 2015) and suggest that a smoker's post-treatment clinical presentation may not be compatible with the expected profile of a treated patient.

Concepts related to patient management

The evidence reviewed earlier has direct patient management implications. Patients who smoke need to be informed of their enhanced risk for limited or delayed treatment responses and this may actually provide an opportunity to further motivate a patient to consider smoking cessation.

Dental professionals are healthcare providers and, as such, have the responsibility to advocate smoking cessation among their patients. In doing so, they can contribute to improved patient oral health, overall health, and quality of life. A Cochrane review of 14 studies totaling more than 10500 participants (Carr & Ebbert 2012) reported that behavioral interventions conducted by oral health professionals in a dental office or other community setting could significantly increase cessation rates in cigarette smokers and users of smokeless tobacco.

Smoking cessation has been shown in longitudinal studies to have beneficial effects on the periodontal status (Bolin *et al*. 1993; Krall *et al*. 1997; Bergstrom *et al*. 2000; Rosa *et al*. 2014; Leite *et al*. 2018; Ramseier *et al*. 2020) and smoking cessation alone or in conjunction with non-surgical periodontal therapy appears to result in a subgingival environment that comprises higher levels of health-associated

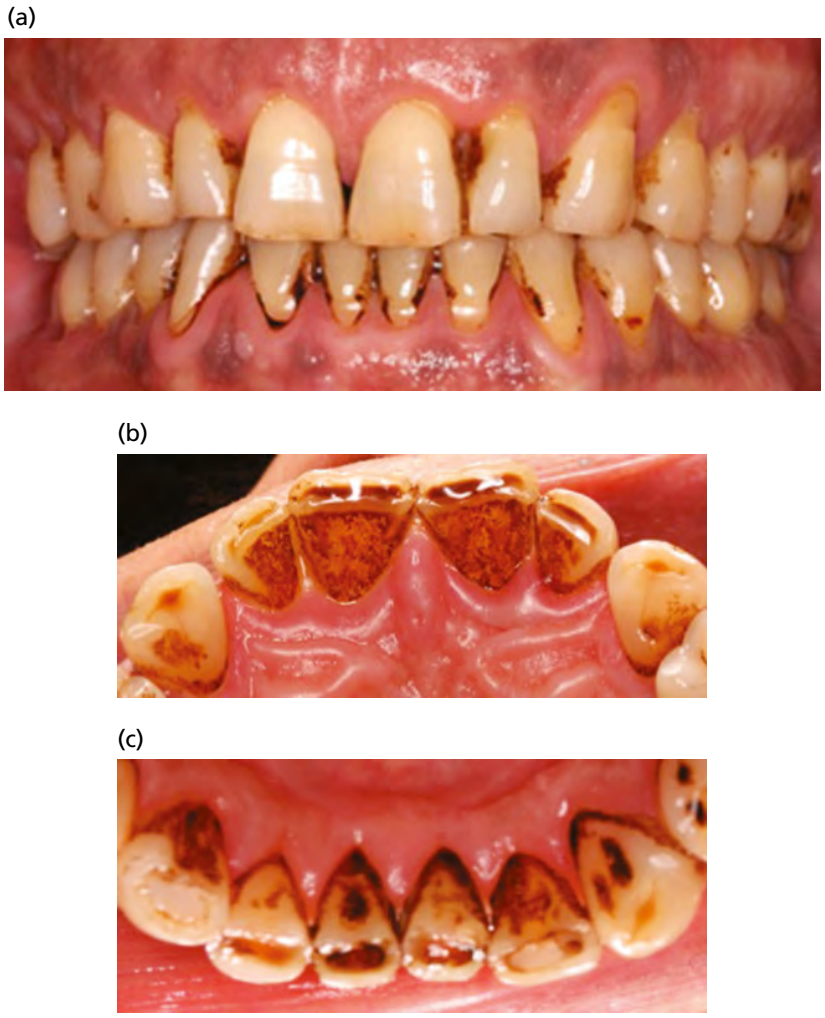

Fig. 11-8 Clinical appearance of a 53-year-old male patient who reports smoking one pack a day for 35 years. (a) Anterior view; (b) palatal view of the maxillary anterior teeth, and (c) lingual view of the mandibular anterior teeth. Note the heavy staining. Periodontal examination revealed probing depths of up to 9 mm, gingival recessions, and furcation involvements at all molars. (Source: Courtesy of Dr. Matthew Hickin.)

species and lower levels of pathogens (Fullmer *et al*. 2009; Delima *et al*. 2010).

There are multiple opportunities to interact with patients and provide tobacco use intervention, especially after initial periodontal evaluation of a new patient and during the long-term maintenance phase of periodontal therapy. Different approaches can be used. Asking every patient about tobacco use, documenting smoking status and motivation to quit, and advising patients to stop are the minimum obligations. A more comprehensive intervention that includes offering smoking cessation counseling with pharmacologic therapy and supportive follow-up is ideal. Complex patients such as those suffering from psychiatric illness or medical co-morbidities should be referred to smoking cessation specialists/clinics where comprehensive treatment can be offered. Inquiry about e-cigarette use and the reasons for it, is also appropriate. Sharing that vaping is not without risks and providing advice to reduce or quit e-cigarette use are also indicated.

Some of the different approaches to smoking cessation that can be considered in the dental setting are briefly discussed below. In general, evidence to date suggests that dental professionals often ask their patients about smoking, but don't always provide help regarding cessation, and several barriers to delivering smoking cessation intervention by dental professionals have been reported (Albert *et al*. 2005; Kunzel *et al*. 2006; Patel *et al*. 2011; Rosseel *et al*. 2011; Jannat-Khah *et al*. 2014; Chaffee *et al*. 2020). For those providers who identify lack of time or expertise/confidence as barriers, a "brief intervention" approach may be a useful model. The dental team can give patients educational brochures to take home and also provide some encouragement and support by relating tobacco use to medical and oral health risks. This strategy is often effective as the advice of a trusted healthcare provider is always valuable.

If the dental team is willing to be more proactive and the patient is motivated, a behavioral program can be introduced. The "five A's", from the United States Department of Health and Human Services

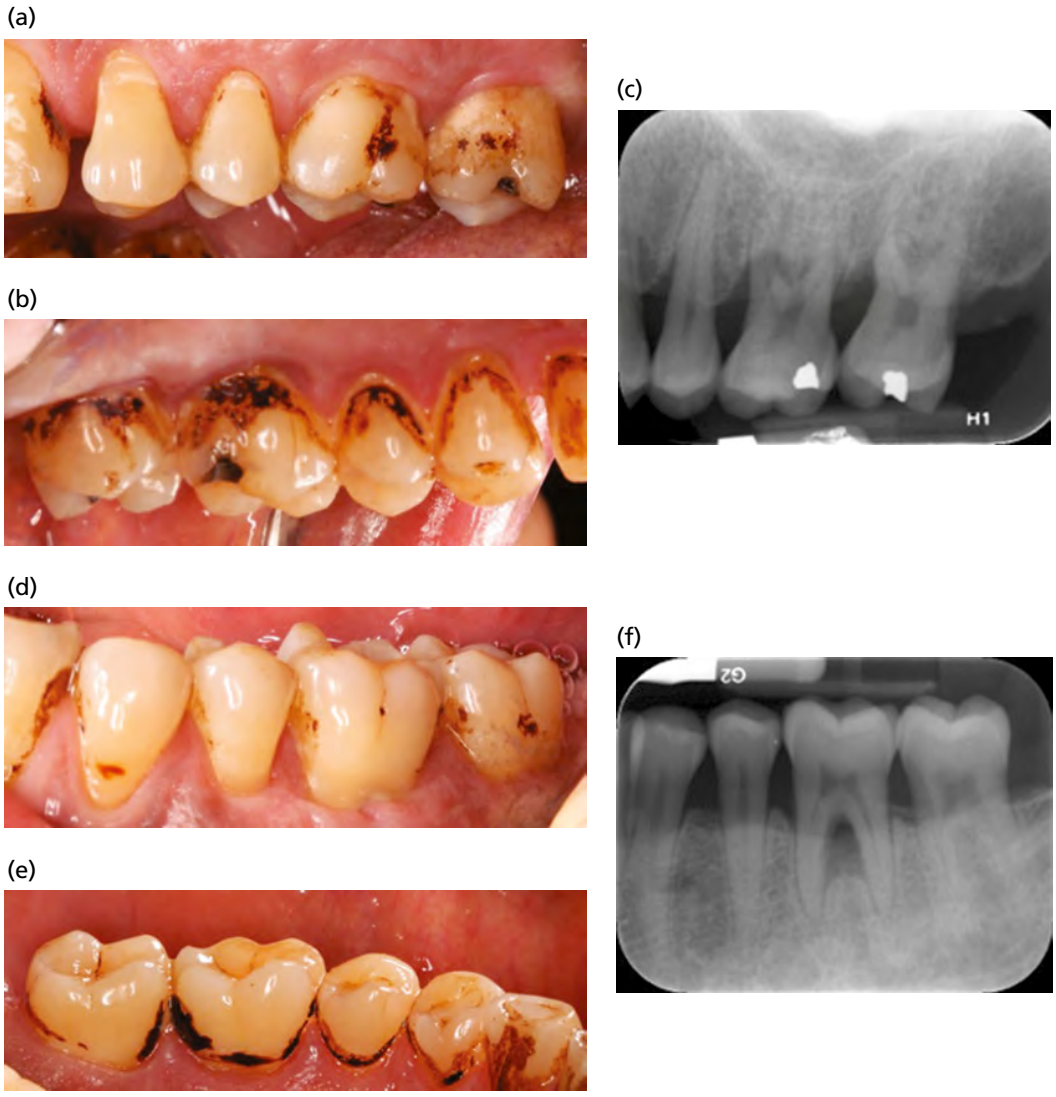

Fig. 11-9 Same patient as in Fig. 11-8. (a, b) Maxillary left buccal and palatal views and (c) corresponding radiograph; (d, e) mandibular left buccal and lingual views and (f) corresponding radiograph. Heavy staining and advanced bone loss are apparent. (Source: Courtesy of Dr. Matthew Hickin.)

(2020), is considered the gold standard approach for delivering a tobacco cessation intervention:

Ask: Ask about smoking behavior directly and document status (current, former, or never smoker; duration and number of cigarettes per day). Tobacco use status indicators on paper charts or electronic records can make screening easier.

Advise: Advise patient to quit. The message should be clear, strong, and tailored. A good time to do this is after the periodontal examination is completed and when findings, etiology, risk factors, and prognosis are discussed. Several health organizations and internet sites that provide valuable information are available.

Assess: Assess the patient's readiness and motivation to quit. If the patient is willing to attempt cessation, provide assistance as described below. If the patient is clearly unwilling to attempt quitting at this time, offer written materials about quitting and re-assess at future appointments. Improving the patient's interest and readiness level is a successful intervention, even if cessation is not immediately contemplated.

Assist: Assist the patient willing to make a quit attempt by providing a structured plan for quitting. Decide on a quit date and encourage the patient to seek support from family and friends. Consider the use of pharmacotherapies that have proven effective and are briefly described below. Anticipate challenges that might threaten smoking cessation and decide in advance on a plan of action if/when those arise.

Arrange: Arrange follow-up, including behavioral support and telephone contact/counseling. The first week of cessation is especially critical.

A variety of other approaches exist to deliver behavioral interventions for smoking cessation, and could also be considered: tobacco quitlines, web-based interventions, smartphone applications. Healthcare providers must remember that the elements that make a particular technology-mediated approach effective for cessation may shift as technologies, and the ways in which people interact with and use technology, evolve.

Based on the strong evidence available for brief tobacco cessation interventions, the US Preventive Services Task Force (Siu 2015) recommends that clinicians deliver such interventions to all adult smokers. Even brief (<3 minutes) advice from a physician significantly improves cessation rates and is highly cost-effective (Stead *et al*. 2013).

Pharmacologic treatment options to smoking cessation include nicotine replacement therapy, sustained-release bupropion, and varenicline (Aubin *et al*. 2011). Nicotine replacement therapy involves the use of products that provide low doses of nicotine, but do not contain the toxins found in smoke. The goal of therapy is to relieve cravings for nicotine and ease the withdrawal symptoms. Nicotine supplements come in different forms: transdermal patch, gum, lozenges, nasal spray, and inhaler. The different forms of replacement therapy can be used alone or in combination, and all work well if they are used correctly. The choice depends on the patient's smoking habits and preferences, and initial treatment lasts for 2–3 months. Side effects include headaches, nausea, and insomnia in the first few days, especially with the patch. Sustained-release bupropion inhibits the neuronal uptake of norepinephrine and dopamine. It can therefore control nicotine withdrawal symptoms and may also help patients manage associated anxiety and depression. Treatment with bupropion should be initiated 1–2 weeks before the quit date, because 1 week is necessary to achieve steady-state blood levels; treatment usually lasts for 2–3 months, but it can continue safely for maintenance for up to 6 months. The use of bupropion is contraindicated for patients with a history of seizures, eating disorders, and those who are on certain antidepressants. Common side effects of bupropion include insomnia and dry mouth, and patients should be monitored closely for unusual changes in behavior, such as agitation, depression, and attempted suicide (Hays & Ebbert 2010). Varenicline is the newest drug for smoking cessation. It has a structure similar to that of nicotine and thus it can antagonize nicotine binding to its receptor sites. As with buproprion, varenicline treatment starts 1 week before the quit date and continues for 3 months; maintenance treatment, if needed, may be for up to 6 months. Common side effects include nausea, trouble sleeping, and abnormal or vivid dreams (Garrison & Dugan 2009; Hays & Ebbert 2010). Patients taking varenicline should be monitored closely for any changes in mood and behavior.

Unfortunately, nicotine dependence is chronic and strong, and therefore the possibility of relapse is high. Smokers often must experience many attempts at cessation before they can remain totally tobacco free. They are certainly more likely to be successful if they have support with quitting. Providing encouragement at every appointment with the dentist and hygienist is key in helping dental patients stay smoke free.

Obesity and nutrition

Obesity, a condition characterized by accumulation of excess body fat, is defined in adults as a Body Mass Index (BMI) of ≥30 kg/m^2, while a BMI between 25 and 29.9 kg/m^2 indicates an overweight individual (WHO 2020). In the past few decades, many countries in both the industrialized and the developing world have experienced a substantial increase in the prevalence of obesity (Fox *et al*. 2019), which is known to be a major contributor to morbidity and mortality (Lenz *et al*. 2009). Concomitant occurrence of obesity, insulin resistance, dyslipidemia, and hypertension constitute the metabolic syndrome, a precursor condition to type 2 diabetes and incident cardiovascular disease (Kumari *et al*. 2019).

As discussed in Chapter 6, several studies have demonstrated a positive association between obesity/metabolic syndrome and periodontitis. Indeed, the three most recent systematic reviews that compiled the available evidence linking obesity to periodontitis have all demonstrated a positive association between the two conditions, both in adolescents and young adults (Khan *et al*. 2018) as well as across the entire age spectrum (Martinez-Herrera *et al*. 2017; Arboleda *et al*. 2019). Although the limited number of longitudinal studies of adequate quality does not facilitate the exact delineation of the temporality of this association at the present time, it is biologically plausible that obesity may contribute to a higher risk for periodontitis. However, it is unclear thus far whether presence of obesity negatively affects the treatment outcomes of non-surgical periodontal therapy; three systematic reviews published almost concurrently failed to convincingly document differences in treatment responses between obese and non-obese patients with periodontitis (Akram *et al*. 2016; Gerber *et al*. 2016; Nascimento *et al*. 2016).

The function of the adipose tissue as essentially an endocrine organ (Scheja & Heeren 2019) is central to the association between obesity and periodontitis. Adipocytes secrete a variety of metabolically and immunologically active molecules, termed adipokines, among which leptin, adiponectin, and resistin have been studied the most. The primary function of leptin is to negatively regulate appetite and weight (Charchour *et al*. 2020), but it also interacts with other hormones including insulin (Margetic *et al*. 2002; Ghadge & Khaire 2019). Interestingly, there is a negative correlation between GCF and serum levels of leptin in periodontitis, and this association was reported to become stronger with increasing levels of attachment loss (Karthikeyan & Pradeep 2007a, b). Serum levels of adiponectin are decreased in obesity, insulin resistance, diabetes, and cardiovascular disease (Matsuzawa *et al*. 2004; Maeda *et al*. 2020). *In vitro*, adiponectin has been shown to be a potent negative regulator of osteoclast formation in response to challenge by *A. actinomycetemcomitans* LPS (Yamaguchi *et al*. 2007). Its levels in GCF have been recently

reported to be significantly elevated in periodontitis (Preshaw *et al*. 2020), but there is no clear association between its serum levels and periodontal status (Furugen *et al*. 2008; Saito *et al*. 2008; Goncalves *et al*. 2015). In contrast, serum levels of resistin were found to be higher in patients with periodontitis than in periodontally healthy individuals, and to correlate with the extent of bleeding on probing (Furugen *et al*. 2008; Saito *et al*. 2008). Collectively, adipokine action and oxidative stress have been proposed to serve as the common link in the pathobiology of obesity and periodontitis (Bullon *et al*. 2009; Suvan *et al*. 2018; Jepsen *et al*. 2020). Indeed, there is evidence of higher serum levels of markers of oxidative stress and of decreased antioxidant capacity in individuals with periodontitis when compared with periodontally healthy controls (Chapple *et al*. 2007; Ling *et al*. 2016).

The role of nutritional exposures in the etiology and therapeutic management of periodontitis has not been adequately studied, but has recently gained increasing attention. Observations documented in the Ebers Papyrus (circa 1550 BC), writings by Hippocrates (460–370 BC), and eighteenth century reports of bleeding gums and tooth loss in sailors that did not have access to fresh fruit and vegetables over prolonged time periods, would later have been attributed to scurvy-associated pathologies (for a comprehensive review see Van der Velden 2020). Ascorbic acid (vitamin C) is a powerful antioxidant radical scavenger (Da Costa *et al*. 2012) that is distributed in multiple cell types including polymorphonuclear leukocytes, platelets, and endothelial cells (Evans *et al*. 1982), and which has been shown to exercise effects on osteoclasts and periodontal ligament fibroblasts (Mimori *et al*. 2007). The effects of vitamin C deficiency on the gingival tissues were demonstrated in early studies of controlled depletion and supplementation (Leggott *et al*. 1986, 1991), as well as in epidemiologic studies (Nishida *et al*. 2000). Likewise, although it has long been known that vitamin D and calcium are important for skeletal development and maintenance of bone mass, vitamin D has emerged as an important regulator of innate immune responses in infectious diseases (Adams & Hewison 2008), with positive effects on periodontal status (Miley *et al*. 2009; Garcia *et al*. 2011). Additional micronutrients that have been investigated with respect to their association with periodontal status include both antioxidant (vitamin E, carotenoids, polyphenols, glutathione) and non-antioxidant molecules (vitamin B, omega-3 polyunsaturated fatty acids). In general, epidemiologic studies reveal that periodontitis is associated with low serum/plasma micronutrient levels (Van der Velden *et al*. 2011; Lee *et al*. 2020; O'Connor *et al*. 2020), whereas early evidence from interventional studies (Campan *et al*. 1997; Staudte *et al*. 2005; Jenzsch *et al*. 2009; Chapple *et al*. 2012; Woelber *et al*. 2016, 2019; Díaz Sánchez *et al*. 2017) suggests that adjunctive nutritional supplementation may result in improved periodontal therapy outcomes. Additional research from randomized, placebo-controlled trials is needed to further document these effects, and to facilitate the development of evidence-based nutritional recommendations in the prevention and control of periodontal diseases (Dommisch *et al*. 2018).

Osteoporosis

Osteoporosis is a disease characterized by loss of bone mineral density that can lead to bone fragility and increase susceptibility to fractures (Eastell 1998; Compston *et al*. 2019). Female gender, advanced age, family history of osteoporosis, ethnicity (Caucasian or Asian), history of a low-impact bone fracture, thin skeletal frame, and early menopause are non-modifiable risk factors/markers for osteoporosis. High alcohol intake, smoking, low body mass index, vitamin D deficiency, and physical inactivity are other important modifiable risk factors. The femur and spine are most commonly affected and bone density at these sites can be quantified using dual-energy X-ray absorptiometry (DXA) scans to define a diagnostic T score (NIH Consensus Development Panel on Osteoporosis Prevention & Therapy 2001). The T score compares bone density for a given patient to the mean peak bone density for an individual of the same sex and is reported as the number of standard deviations below that mean. A T score of −1 or above is considered normal and a score of −2.5 or lower signifies osteoporosis. Scores lower than −1.0 and greater than −2.5 indicate osteopenia, an intermediate state between health and osteoporosis.

Several clinical studies have drawn attention to the possible link between osteoporosis and periodontal disease, as both conditions involve bone loss and share common risk factors and pathogenic mechanisms (Otomo-Corgel 2012). However, and as reviewed in Chapter 6, many of the clinical studies published thus far are uncontrolled, cross-sectional, had small sample sizes, or were restricted to postmenopausal women (von Wowern *et al*. 1994; Mohammad *et al*. 1996, 1997; Tezal *et al*. 2000; Renvert *et al*. 2011; Manjunath *et al*. 2019). Larger studies, such as one based on the Korean National Health and Examination Survey (Kim *et al*. 2014) and two recent reports from an epidemiologic study in Thailand (Mongkornkarn *et al*. 2019; Niramitchainon *et al*. 2020) demonstrated a negative association between bone mineral density and periodontitis severity, but data from longitudinal studies are inconclusive (LaMonte *et al*. 2013; Pereira *et al*. 2015; Kaye *et al*. 2017). Nevertheless, the most recent systematic reviews (Wang & McCauley 2016; Goyal *et al*. 2017) concluded that there is a significant, positive association between osteoporosis and periodontitis.

It has been proposed that low bone mineral density in the maxilla and mandible as a result of osteoporosis may contribute to periodontal pathology by accelerating alveolar bone resorption that is initiated by the periodontal infection (Wactawski-Wende 2001).

In addition, factors affecting systemic bone remodeling (e.g. heredity, shared risk factors such as smoking, hormonal influences [estrogen deficiency, parathyroid hormone effects], calcium and vitamin D deficiencies, effects of inflammatory mediators and disruption of the RANKL and OPG axis) appear to perturb the local homeostatic mechanisms at the dento-gingival niche and to result in enhanced destruction of the periodontal tissues (Wang & McCauley 2016).

Skeletal bone loss in those affected by osteoporosis is usually gradual and painless. Often, there are no obvious symptoms until a fracture occurs and thus early identification of those affected by or at-risk for osteoporosis is important. Dental professionals may be able to recognize clinical risk factors for osteoporosis among their patients and observe radiographic changes, such as thinning and porosity of the inferior border of the mandible in available panoramic radiographs or cone beam computed tomographs (Horner *et al*. 2010; Koh & Kim 2011; Nagi *et al*. 2014; de Castro *et al*. 2020). Discussion of such findings and referral for further investigation by a medical colleague of those identified as potentially at-risk for osteoporosis can be beneficial in prevention of osteoporotic fractures.

Finally, it is important for dental professionals to keep in mind that, with increasing longevity, osteoporosis prevalence will continue to rise and that many female, but also male, dental patients may be affected and be under lifelong antiresorptive medications. Dentists need to review medication history, including method of delivery (oral or intravenous), duration and dose, and consult with the patient's physician in view of periodontal treatment. For those patients on bisphosphonates, careful planning and consultation with the treating physician is important, especially when periodontal therapy may involve extractions or other extensive surgical procedures and the patient has been on the medication for more than 2–3 years. Such patients should be informed of the risks and possible effects of bisphosphonates on dental treatment outcomes. Any acute lesions must be treated immediately, oral hygiene instruction must be thorough, and the periodontal condition must be carefully monitored. Systemic use of antibiotics and use of antimicrobial mouth rinses can be considered. The potential complication to prevent is osteonecrosis of the jaw (ONJ), a rare condition defined as an exposure of bone in the mandible or maxilla persisting for more than 8 weeks in a patient who previously received, or is currently under, treatment with a bisphosphonate and who has no history of radiation therapy to the jaws (Khosla *et al*. 2007). More recently, additional pharmacotherapies such as treatment with vascular endothelial growth factor inhibitors, tyrosine kinase inhibitors, and humanized antibodies that affect osteoclastic action have also been reported to initiate ONJ (Kanwar *et al*. 2020).

Clinically, ONJ may present as exposed alveolar bone occurring spontaneously or after dental surgery that caused bone trauma. The sites are usually painful, have soft tissue swelling or ulceration, mobile teeth, and induration with drainage. Radiographically, if teeth are present, there may be sclerosis of the alveolar lamina dura, loss of the alveolar lamina dura, and/or widening of the periodontal ligament space. Depending on the severity of ONJ, treatment strategies may include antibacterial mouth rinses, symptomatic treatment with oral antibiotics and analgesics, superficial debridement, and in severe cases surgical debridement/resection. The patient's treating physician must always be contacted and informed. Mitigating ONJ through preventive dental care and understanding of risk factors is of paramount importance (Wan *et al*. 2020).

Stress

Stress results from interactions between individuals and their environment. It has been defined as a state of mental or bodily tension stemming from factors that tend to alter an existent equilibrium, or as a condition or feeling experienced when a person perceives that demands exceed the personal and social resources they are able to mobilize. Stressors, the stimuli that cause stress in an individual, may be acute (short term, often due to time-limited events) or chronic (longer lasting, not always attributed to a discreet event) (Herbert & Cohen 1993), and are often categorized as (1) disasters or crises (unpredictable events completely out of the control of the individual, such as natural disasters, pandemics, wars), (2) major negative life events (such as death of a loved one, divorce, a serious new diagnosis or injury, dismissal from work), or (3) micro-stressors (daily small negative events) which, as they accumulate, can have the same impact as a major stressor, but are usually different for each individual. No single assessment can accurately measure stress or stress responses. Self-perceived stress is often measured using structured interviews/surveys and other self-reported tools. Clinically, the term "allostatic load" has been used to describe the cumulative exposure to stressors and is an aggregate of multiple parameters or mediators (neuroendocrine, metabolic, immunological, respiratory, cardiovascular, and anthropometric) many of which are, as expected, biologically interconnected (McEwen 1998).

There are numerous psychological and physical conditions that have been linked to stress, including depression, anxiety disorders, hypertension, cardiovascular and cerebrovascular events, obesity, immune system disturbances that increase susceptibility to infections, viral disorders ranging from the common cold and herpes to AIDS, certain cancers, as well as autoimmune diseases like multiple sclerosis (Spiegel & Giese-Davis 2003; Ziemssen & Kern 2007; Chida *et al*. 2008; Chida & Mao 2009; Falagas *et al*. 2010; Puder & Munsch 2010; Artemiadis *et al*. 2011; Bender & Alloy 2011; Blashill *et al*. 2011; Proietti *et al*. 2011; Wardle *et al*. 2011; Rosenthal & Alter 2012). Stress can also have direct effects on the skin and

the gastrointestinal tract, and can contribute to sleep disturbances (Kim & Dimsdale 2007; Basavaraj *et al*. 2011; O'Malley *et al*. 2011).

As expected, stress can also negatively affect the periodontium. This concept is not new; stress has been reported as an important risk factor for necrotizing ulcerative gingivitis and periodontitis for many decades. The effects of stress on the periodontium can be described as indirect or direct. Indirect effects are those mediated through lifestyle changes that can exacerbate periodontal destruction, such as compromised oral hygiene, inattention to dental visits for prevention/care, deterioration of metabolic control in diabetes, increase in smoking or alcohol and illicit drug use, and inability to maintain healthy eating habits. Direct effects may be mediated both via modification of the composition of the subgingival biofilm and/or exaggeration of the host inflammatory response.

In the first large-scale study aiming to explore the link between stress and periodontal status, 1426 adults in the US were evaluated (Genco *et al*. 1999). Subjects under high levels of financial stress and with poor coping responses were reported to have significantly more severe alveolar bone loss and attachment loss than those with low levels of stress within the same coping group, after adjustment for age, sex, and cigarette smoking. Many other studies in subjects with different types of psychosocial stress, such as academic, workplace or home related, and poor coping behaviors have provided similar results (Moss *et al*. 1996; Croucher *et al*. 1997; Deinzer *et al*. 1998, 1999; Mengel *et al*. 2002; Giannopoulou *et al*. 2003; Kamma *et al*. 2004; Ishisaka *et al*. 2007, 2008; Johannsen *et al*. 2007, 2010; Furugen *et al*. 2008; Islam *et al*. 2019; Wellappulli & Ekanayake 2019; Coelho *et al*. 2020). Of interest is the fact that adequate coping behaviors, as evidenced by high levels of problem-based coping, may reduce the stress-associated risk.

The variability associated with self-reported or clinical measures of stress and the use of different periodontal parameters as outcomes across studies investigating the link between stress and periodontitis make comparisons of such studies and the interpretation or generalizability of results difficult. However, it is fair to conclude that accumulating evidence to date supports that a positive association exists between psychosocial stress and poor periodontal status.

In response to stressful events, the hypothalamus–pituitary–adrenal axis is stimulated, leading eventually to increased production and secretion of cortisol, a hormone that can dysregulate the immune system. Further, the autonomic nervous system is stimulated, leading to secretion of catecholamine and substance P that can also impact the immune/inflammatory response and affect bacterial colonization and growth. Indeed, several stress markers have been reported in the blood, saliva, and GCF of periodontitis patients, have been shown to be positively associated with the extent and severity of periodontitis, and appear to mediate the detrimental effects of stress on the periodontal tissues (Axtelius *et al*. 1998; Hilgert *et al*. 2006; Johannsen *et al*. 2006; Ishisaka *et al*. 2007, 2008; Rai *et al*. 2011; Bakri *et al*. 2013; Mesa *et al*. 2014; Cakmak *et al*. 2016). A 2020 systematic review (Decker *et al*. 2020) concluded that a positive correlation exists between stress-related biomarkers and clinically measurable periodontal outcomes, but that whether periodontal disease severity follows or stems from stress levels is still unknown. Experimental studies using animal models and cell culture systems have provided further evidence for a link between stress and the severity of periodontal inflammation/destruction, mediated at least in part through proinflammatory molecules (Gomes *et al*. 2013; Lu *et al*. 2016).

The potential effect of stress on bacterial growth and virulence, although biologically plausible, is less studied and understood. A few studies have reported that stress hormones significantly increase the growth of periodontal pathogens (Roberts *et al*. 2002; Jentsch *et al*. 2013). More recently, *in vitro* studies revealed that cortisol directly increases the transcriptional activity of certain microorganisms and, more importantly, induces shifts in the gene expression profile of the oral microbiome, leading to a community response similar to the one observed *in vivo* in periodontitis (Duran-Pinedo *et al*. 2018). It appears that human hormones can be used by the microorganisms as signals to sense challenges in their environment and modify their profile to fit the new conditions better, but the exact mechanisms by which this crosstalk may occur remain unknown.

Unequivocally, stress is part of human life, is commonly present to varying degrees, and although it may have different consequences in different individuals, its potential effect on periodontal disease presentation and the response to therapy should not be underestimated. The dental team needs to remember that identification/understanding of potential stressors, periodontal disease prevention, meticulous monitoring, and careful maintenance strategies are all important in the management of patients under stress, especially those under chronic stress and those who appear to cope inadequately.

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Chapter 12

Genetic Susceptibility to Periodontal Disease: New Insights and Challenges

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Introduction

Periodontitis is a chronic inflammatory disease of the supporting tissues of the teeth. In subjects susceptible to destructive periodontal disease, there is an imbalance between the host's immune system and the oral bacteria. In these individuals, certain microbial pathogens can proliferate and this leads to the induction of inflammatory reactions in the periodontal tissues. These inflammatory reactions slowly destroy the periodontium. If left untreated, the teeth lose their ligamentous support to the alveolar bone and alveolar bone is resorbed, with the consequence that the affected teeth become mobile and are eventually lost.

The oral cavity is one of the most complex ecosystems of the human body and contains myriads of different bacterial species. These species co-evolved with the human organism and the oral microbiota adapted to the environmental conditions provided by the host. The evolution of this ecosystem was subjected to strong selection pressures in a biologically active environment and it is considered to have largely developed for mutual benefit. The normal oral microbiota protects the host from extrinsic pathogens and the immune system controls bacterial proliferation to maintain homeostasis. The complex interplay between intrinsic and extrinsic factors, i.e. the immune system, pathogens in the oral cavity, and consequences of lifestyle factors is largely regulated by genes. Genes encode immune receptors as well as molecules, which influence receptor specificity and sensitivity to bacterial species. They regulate and influence the intensity of the inflammatory response by encoding and adapting the signal transduction pathways that mediate inflammatory signals, and allow a flexible response of the organism to external and internal stimuli.

The interplay of the microbiota, the immune system, and lifestyle habits (smoking, stress, diet, etc.) underlie the constant changes to which the host's

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

physiology must adapt to maintain health: the bacterial species change in number and proportions, and may also change in characteristics, for example by horizontal gene transfer or mutation. The host's immune system changes over time and can be positively or negatively influenced by lifestyle factors, other diseases, or age. Additionally, the genetic constitution of the host may change during life, for example by epigenetic effects or somatic mutations. As a result, periodontitis is considered to be a complex disease.

Genetic research can improve the understanding of the factors that mediate the immune response and explain why this response often greatly differs between individuals who have the same environmental context and comparable lifestyle habits. An important objective of genetic research is to identify the genes underlying disease and to estimate the genetic effects of potential risk variants within these loci. Genetic variation most often affects the regulatory regions of the genes, which lead to subtle changes in their expression. It is important to identify these genetic elements and to characterize their modes of action to understand how the expression of target genes in a tissue is regulated. This knowledge is indispensable for the understanding of the molecular etiology of periodontitis.

The genetic basis of periodontitis was demonstrated by formal genetic studies, and many genetic variants were analyzed for their involvement in disease physiology. However, within recent years, there have been enormous developments in the tools for genetic analysis and, for many common, complex human diseases, in knowledge of the relevant genetic factors. In this chapter, we will describe the underlying concepts and methodologic principles necessary for the understanding of the current genetic basis of periodontitis. We will comment on the limitations of and the progress achieved with recent studies, the different paths that are opening up in the efforts to identify the full spectrum of genetic risk factors for periodontitis, and how this newly acquired knowledge can be used to improve diagnosis and in an emerging personalized medical care. We will also illustrate the current state of genetic research in periodontitis and give an overview on the risk genes that are currently regarded as validated. Additionally, we will discuss the likely directions of genetic research in the field of periodontitis in the near future. We will provide an evaluation of the current predictive ability of genetic tests for monogenetic and complex diseases and give an outlook on future possibilities of personal genome testing.

Evidence for the role of genetics in periodontitis

Until the middle of the last century, it was thought that subjects with a longstanding history of poor oral hygiene would develop periodontitis. This was mainly because all forms of periodontitis were largely shown to be associated with bacterial pathogens and many studies demonstrated immunologic responses to these. In addition, the prevalence and proportions of periodontal pathogens were regarded to be higher in periodontitis patients compared with healthy controls (Griffen *et al*. 1998; van Winkelhoff *et al*. 2002). It remained an open discussion whether or not periodontitis was solely caused by one or more specific periodontal pathogens. If it were, periodontitis should develop in most infected subjects. However, periodontal pathogens show a relatively high prevalence in healthy subjects as well as in subjects with gingivitis or minor periodontitis. For example, in a study of 222 healthy children aged 0–18 years from Ohio, USA, pathogenic strains of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* were detected in 48% and 36% of the children, respectively, and both species were detected in infants as young as 20 days old (Lamell *et al*. 2000). Interestingly, in a large group of subjects with gingivitis or minor periodontitis (mean age 52 years), *A. actinomycetemcomitans* and *P. gingivalis* were similarly prevalent (38% and 32%, respectively) (Wolff *et al*. 1993). In the last decades, epidemiologic studies as well as longitudinal clinical studies have shown that the presence of bacteria does not invariably induce periodontal attachment loss, but that host factors are also required for periodontitis. The concept of high-risk groups was added to the pathogenesis model and was one of the factors that developed the hypothesis that periodontitis may have a genetic background.

A study from 1966 was one of the earliest to deduce that certain individuals are more at risk for periodontitis than others (Trott & Cross 1966). This study investigated the principal reasons for tooth loss in over 1800 subjects. The study showed that in each age category, many teeth are lost due to periodontitis in relatively few patients. This phenomenon was confirmed in a 28-year longitudinal study of a dentate American population. It was found that 14.4% of this population who became edentulous accounted for 64% of all teeth lost in that period. Among those who lost teeth but remained partially dentate, 13.8% were responsible for 60.2% of all teeth lost in that group. Analysis showed that gingivitis was the strongest risk factor for tooth loss (Burt *et al*. 1990). The same phenomenon was found in two longitudinal studies, which evaluated the effect of periodontal therapy in periodontitis patients over more than 15 years (Hirschfeld & Wasserman 1978). These studies showed that 20% of the patient populations accounted for about 75% of all lost teeth.

The concept of high risk for the development of periodontitis was further confirmed in longitudinal studies investigating the natural history of periodontal disease. In a population in Sri Lanka without access to dental care and absence of oral hygiene, Löe *et al*. (1986) were able to identify three subpopulations: a group with no progression (11%), a group

with moderate progression (81%), and a group with rapid progression of periodontal breakdown (8%). In a more recent study, the initiation and progression of periodontal breakdown was studied in a remote village in West Java that was deprived of regular dental care (Van der Velden *et al*. 2006). The authors found that 20% of the subjects developed severe breakdown, whereas the remaining population developed minor-to-moderate breakdown, and suggested that not everybody is equally susceptible to periodontitis. This shaped the hypothesis that host susceptibility may have a genetic background: the antimicrobial response of the host is defined in part by genes and can vary across the population. Genetic variants in the genes which encode the pathways of the host's antibacterial response, but also in the bacterial factors that are targeted by the host's immune system, have the potential to deleteriously affect the interplay of the immune system, environment, and lifestyle factors. In some cases they can lead to disease development. Figure 12.1 illustrates this hypothesis and shows how an almost continual exposure to bacteria may or may not cause disease symptoms. It also shows how interventions may be effective before disease manifestation. The individual's immune response, which determines the extent of periodontal destruction, is additionally challenged by other internal and external factors, like systemic diseases (e.g. diabetes), smoking, stress, nutrition, and age (Kinane *et al*. 2006; Jauhiainen *et al*. 2020), which are again determined by the individual's genetic constitution. This interplay between the oral microbiota, internal and external factors which influence the immune system, and the host's general genetic constitution forms the individual susceptibility of a subject to periodontitis.

Heritability

Heritability measures the proportion of phenotypic variation that can be attributed to genetic variation. For example, members of a family may have a large variation of body weight that can be expressed by the body mass index (BMI). The observed variation can be due to different dietary habits among the family members. However, genetic factors can also influence the BMI independent of diet and can be

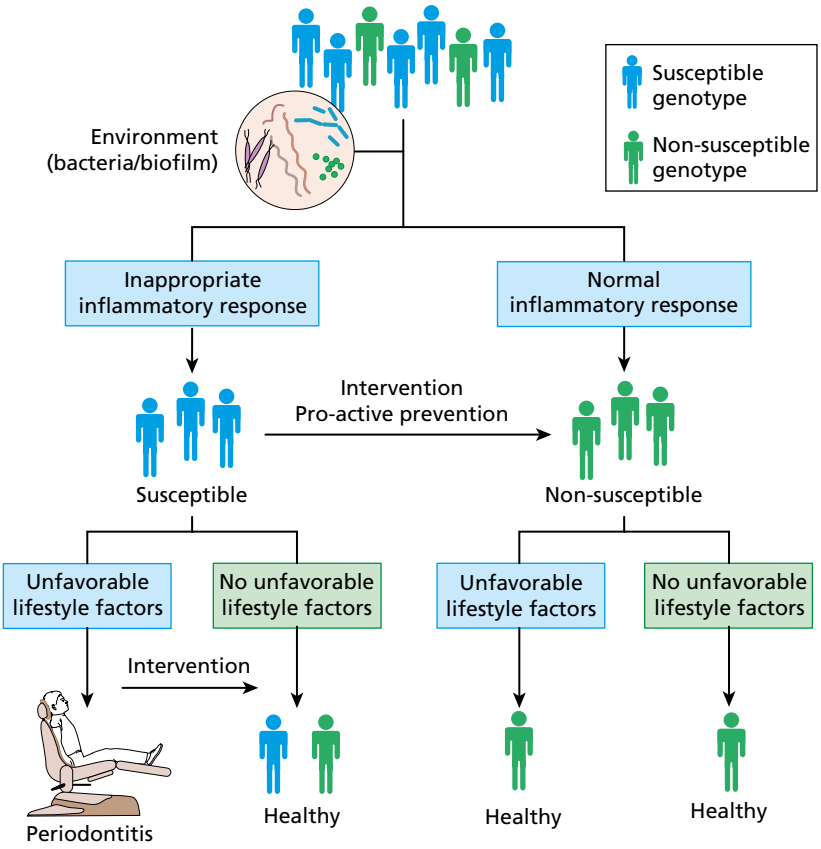

Fig. 12-1 Variations in the antimicrobial response of the host may be important features of the pathogenesis of periodontitis. In this model, the population, consisting of non-susceptible and susceptible hosts, is exposed to prevalent oral bacteria. Non-susceptible individuals with a normal, effective antibacterial response do not develop the disease, whereas susceptible individuals are at risk of developing the disease if key environmental factors are present. An understanding of the immune system alterations that make individuals susceptible may allow for interventions that aim to render the individual insensitive to the environmental stimuli that induce disease (proactive prevention), or that can alleviate or cure the disease after it has become manifest. This model suggests that it is critical to learn more about the factors that influence host–microbial homeostasis. However, it is possible that long-term effects of additive, deleterious lifestyle factors in conjunction with a compromised immune system at advanced age also lead to the manifestation of periodontitis independent of specific genetic risk factors. (Source: Adapted from Foxman & Iwasaki 2011. Reproduced with permission from John Wiley & Sons.)

shared between some of the related family members (Schousboe *et al*. 2003). Heritability measures the fraction of the phenotype variability that is due to genetic variation between the individuals of the sample. Heritability is also always specific to a particular population in particular surroundings. If, for example, a family shows uniformity in dietary habits, the heritability will be higher than if the family shows high variation in dietary habits. In the context of oral health, in a sample that shows uniformity in oral hygiene habits, the heritability will be higher compared with a sample that has strong variation in oral hygiene.

Heritability of periodontitis among young people

Siblings of young patients (e.g. 8–21 years of age) with periodontitis frequently also suffer from periodontitis. This observation was based on family studies as well as on reports of single cases. The largest family study included 227 young probands with periodontitis (Marazita *et al*. 1994). Of these probands, 104 had at least one first-degree relative who was clinically examined. Also, a segregation analysis was carried out on 100 families, which included 527 cases and healthy subjects. A segregation analysis is a method of formal genetic analysis employed to determine whether or not a phenotype is inherited. It tests whether the transmission pattern in human families over different generations is consistent with Mendelian conditions. This method allows the mode of inheritance to be determined, for example if the genetic factor has a dominant or a recessive effect on the phenotype. The authors concluded that the most likely mode of inheritance in the examined families was autosomal dominant (see Box 12-1), with a penetrance of the causative genetic factors of about 70%.

Familial segregation of cases indicates that genetic factors may be important in the susceptibility to periodontitis, but results from segregation analyses need to be interpreted with caution as they may also reflect exposure to common lifestyle factors like oral hygiene, diet, and smoking. Certain infectious agents may also cluster in families. Additionally, segregation studies with human families are hampered by various methodologic factors, which often are the lack of adequate statistical power due to small numbers of families, too small or incomplete families, and a high heterogeneity between families.

A preferred alternative method to determine the evidence for genetic factors in the familial aggregation is the study on monozygotic twins. Twins arise in two ways. The parallel fertilization of two ova by two different spermatozoa results in dizygotic (DZ) twins. These comparatively common cases have the same genetic relationship as siblings. However, infrequently after fertilization, the ovum divides in two, resulting in a pair of monozygotic (MZ) twins who are genetically identical. Severe, typically early-onset forms of periodontitis, sometimes with a molar/incisor phenotype, for which it is believed that genetic factors are particularly important in influencing disease susceptibility, have a comparatively low prevalence in the general population and it is very difficult to identify enough affected MZ twins to provide sufficient statistical power to test the concordance of this disease phenotype. Nevertheless, the most conclusive indication of whether or not the disease has a genetic cause is obtained by a comparison of the presence of the same disease phenotype in both members of a pair of twins. This is expressed by a comparison of the concordance rate of MZ and DZ twins. For example, twins are concordant when both have or both lack a given phenotype.

The degree of concordance for early-onset periodontitis was estimated by Corey *et al*. (1993). Information on periodontal disease was available for 4908 twin pairs. The mean age at diagnosis of periodontitis in these twins was 31 years. A total of 349 twins reported a history of periodontal disease in one or both pair members. Of these, 116 were MZ and 233 were DZ twins; 70 twins were concordant. The concordance rate for the history of periodontal disease in MZ and DZ twin pairs based on this study is given in Table 12-1. The proband-wise concordance rate showed more than a two-fold increased risk for early-onset periodontitis for the genetically identical MZ twins compared with the DZ twins. It also indicated that in a high proportion of cases factors other than genetic factors were important in triggering this disease phenotype. The mean age difference at diagnosis for the concordant MZ twin pairs was 1 year, while the corresponding difference in concordant DZ twin pairs was 5.4 years (information on age at diagnosis of periodontal disease was only available for both members in 34 of the 70 concordant twin pairs). This reduced mean difference of age at first diagnosis for the MZ twins may also point to an influence of heritable factors in periodontitis.

Heritability of periodontitis in adults

A few twin studies have assessed the heritability of a periodontal disease status in adults and almost all have reported a heritable component for periodontitis (Michalowicz *et al*. 1991, 2000; Corey *et al*. 1993; Michalowicz 1994). One of the first studies included 110 pairs of adult twins (mean age 40.3 years), including 63 MZ and 33 DZ twin pairs reared together, and 14 MZ twin pairs reared apart. The periodontal parameters probing depth, clinical attachment loss, gingivitis, and plaque were examined, and it was estimated that 38–82% of the variance in these measures could be attributed to genetic factors (Michalowicz *et al*. 1991). Another population-based twin study on 117 twin pairs (Michalowicz *et al*. 2000) assessed the heritability of the genetic and environmental variation in periodontitis and gingivitis. It showed that the investigated MZ twins (64 pairs) were more

Box 12-1 Human genes, genetic variation, and useful definitions.

Genes direct the production of proteins with the assistance of enzymes and messenger molecules. In humans, the genes are located on 23 pairs of chromosomes: 22 pairs of *autosomal* chromosomes (autosomes) and one pair of *sex chromosomes* (the gonosomes, XX for females and XY for males). From each pair, one chromosome is inherited from the father and one from the mother. The complete set of chromosomes is called the *genome*. Each chromosome contains a long duplex of deoxyribonucleic acid (DNA). DNA consists of sequences of nucleotides, which are chemically linked by a sugar–phosphate backbone. The nucleotides are the "building blocks" of the DNA and are made up of nitrogenous bases. Four nitrogenous bases exist: adenine (A), guanine (G), cytosine (C), and thymine (T).

In the chromosomes, DNA is arranged in a double helix: two polynucleotide chains are associated together by hydrogen bonding between the nitrogenous bases. The pairing of the two single-stranded nucleotide chains is complementary: G pairs only with C, and A pairs only with T; these are called base pairs (bp). The order of these four nucleotides determines the meaning of the information encoded in that part of the DNA molecule, just as the order of letters determines the meaning of a word. Virtually every single cell in the body contains a complete copy of the approximately 3 milliard (US; English 3 billion) DNA base pairs that make up the genome (National Human Genome Research Institute [NHGRI], National Institutes of Health [NIH], www.genome.gov). The genetic code is read in groups of three nucleotides; each trinucleotide sequence (triplet) is called a *codon*, which encodes a specific amino acid.

A gene usually consists of various parts. The *promoter region* is a specific sequence of nucleotides upstream of the coding region that is essential for the regulation and initiation of the transcription of the coding region. *Introns* are sequences of non-protein coding nucleotides and surround the *exons*, which code for the sequence of amino acids of a protein (Fig. 12-2). The collection of known exons in the genome is called the *exome*.

Genes can be transcribed in alternative ways, such that each of the estimated 20 000 protein coding genes in the human genome codes for an average of four protein variants (ENCODE-Project-Consortium 2012). Proteins make up body structures like organs and tissues, carry signals between cells, and are the enzymes that control biochemical reactions. If a cell's DNA is mutated, an abnormal protein or abnormal protein quantities may be produced, which can disrupt the body's usual processes and lead to a disease.

For translating the information contained in the DNA into cellular function, the DNA must be transcribed into corresponding molecules of ribonucleic acid (RNA), referred to as transcripts. There are various kinds of RNA transcripts. The type that carries the information that codes the amino acid sequence of the proteins is called messenger RNA (mRNA) and is transcribed from the exons. Non-protein coding RNAs, such as *microRNAs* or long non-coding RNAs (ncRNA), largely function in the regulation of gene expression. The collection of all transcripts present in a given cell is called the *transciptome*.

Sequencing technologies determine the exact order of the nucleotides in a strand of DNA. After the finished high-quality version of the sequences of all human chromosomes was published in 2006 by the international *Human Genome Project*, the 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation. By sequencing the genomes of 2504 individuals from 26 human populations, in total over 88 million variants were identified in humans (84.7 million *single nucleotide polymorphisms (SNPs)*, 3.6 million short insertions/deletions (indels), and 60 000 structural variants) (1000 Genomes Project *et al*. 2015) (Fig.12.3). The majority of these variants are rare, and only approximately 8 million have a frequency >5%. Nevertheless, the majority of variants observed in a single genome are common: just 40 000 to 200 000 of the variants in a typical genome (1–4%) have a frequency <0.5%. It was found that a typical genome contained >100 sites with protein truncating variants, >10 000 sites with peptide sequence-altering variants, about 2000 variants per genome associated with complex traits through genome-wide association studies (GWAS), and >20 variants per genome implicated in rare disease.

The alternative variants at a specific chromosomal region (*locus*) of the DNA are called *alleles*, and the collection of alleles in an individual's chromosomes is termed the *genotype*. Two or more alleles for a given locus may exist in nature and occur with different frequencies. The *minor allele frequency* (MAF) is the proportion of the least frequent allele in a population and can range from 0% to 50%. Variants with a MAF of >5% are termed *common variants*. If the MAF of a variant ranges between 1% and 5% it is called a *rare variant*. Genetic variants with frequencies of <1% are called *mutations*.

A mutation or a genetic variant may have no effects or may have moderate to strong effects. For example, if a mutation occurs within the coding region of a gene, it may result in an amino acid substitution and therefore an altered protein structure, which may affect the protein's function (non-synonymous SNP). Or, when such a mutation occurs in a regulatory region of a gene (e.g. the promoter or an enhancer element), it may alter

(*Continued*)

the gene's expression level. Accordingly, genotypic differences among individuals can contribute to phenotypic variation, termed *genetic variance*. The strength with which a genetic variant affects the susceptibility to a disease is defined as the *genotype relative risk* (GRR), the ratio of the risk of disease between individuals with and without the genotype. A ratio of 1.1 equates to a 10% increase in risk and is often expressed as the odds ratio (OR). However, carriership of a genetic variant or mutation does not inevitably lead to disease, as only a proportion of individuals with a mutation or risk variant will develop the disease. This proportion is described as the *penetrance*. The severity of the disease in individuals who have the risk variant and the disease is described as the *expressivity* of the variant.

Despite the existence of many genetic variants, only a fraction of the genotypic differences contributes to phenotypic variation. Where in the chromosomes the causative variants are located and how they interact is mostly unknown. Testing all of the several millions of common and rare SNPs in a person's chromosomes would be extremely expensive. Variants that are near each other tend to be inherited together; for example, individuals who have an A rather than a G at a particular location in the chromosome can have identical genetic variants at other SNPs in the chromosomal region surrounding the A. This non-random association between alleles at different loci is termed *linkage disequilibrium* (LD) and the regions of linked variants are known as *haplotypes* (www.hapmap.ncbi.nlm.nih.gov). Determining the identity of a common SNP on a haplotype, the *tag SNP*, uniquely identifies all other linked variants on the same haplotype. Identifying an individual's tag SNPs, a process known as *genotyping*, enables the haplotypes in the chromosomes to be identified. If patients with the same disease tend to share a particular haplotype, variants contributing to the disease might be somewhere within or near that haplotype. The number of tag SNPs that contain most of the information about the patterns of genetic variation of a genome is estimated to be 300 000–600 000, which is far fewer than 10 million common SNPs, and much less expensive to genotype. Thus, the information from the HapMap has been instrumental in mapping variants contributing to the disease.

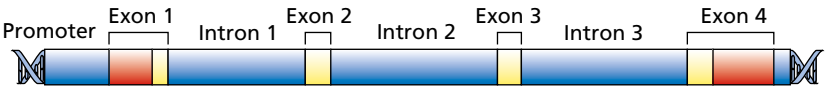

Fig 12-2 Structure of a gene. This gene has four exons (yellow bands), but in reality genes can have many more exons. The first exon is preceded by an untranslated region, the 5′-UTR (left red band), and the last exon is followed by another untranslated region, the 3′-UTR (right red band).

```
CCTCGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGACACCAC    A/GCCCGGCGGATAGAGAGAATTT
TGACAGGTGAGGAGGTATTCCAATGCAAAAGAATAATAGGAGCAAAAGCACAGTGGTGAGAAATTGGA
GGGGAACTGTGAAAATTGCCACATAGATTAGAGGCAGGAAAATAAAGGAC    A/GGCT
```

Fig 12-3 Single nucleotide polymorphisms (SNPs) in a randomly selected segment of the transcribed region of the gene *SIGLEC5*. The two alternative nucleotides (alleles) in this sequence stretch are depicted in red. The allele common in the population is given first and the rarer allele second.

Table 12-1 Concordance rates for early-onset periodontitis in twins.

	n	Concordance rate
Monozygotic	116	0.38
Dizygotic	233	0.16

A twin pair was considered to be concordant if information was provided by one or both pair members and indicated that both pair members were affected. (Source: Data from Corey *et al*. 1993. Reproduced with permission from John Wiley & Sons.).

similar than the DZ twins (53 pairs) for attachment loss and probing depth, and showed statistically significant genetic variance for the severity and extent of the disease. The heritability was estimated to be ~50%, which was unaltered following co-variate adjustments for smoking, dental hygiene, age, and gender (Table 12-2). It is noteworthy that this study showed no evidence of heritability for gingivitis and attributed this disease phenotype entirely to disease-related behaviors such as oral hygiene and smoking.

Table 12-2 Heritability estimates for clinical parameters of periodontitis.

	Age and gender adjusted	Fully adjusted[c]
Attachment loss[a] (%)	52	50
Deepened probing depth[b] (%)	50	50
Gingival index (%)	52	0

[a] Mean percentage of teeth with attachment loss of ≥3 mm.
[b] Mean percentage of teeth with probing depth of ≥4 mm.
[c] Adjustments for age, gender, and oral hygiene as described in Michalowicz *et al*. (2000).(Source: Adapted from Michalowicz *et al*. (2000). Reproduced with permission from John Wiley & Sons.)

A recent study systematically reviewed the literature to refine the heritability of gingivitis and

Box 12-2 Genetic association studies.

Studies designed to localize chromosomal regions (loci) that contribute to a disease susceptibility analyze the allele frequencies of variants in a study population and test their co-occurrence with the disease, in comparison with a study population not having the disease (control group). The intention of such *genetic association studies* (or association mapping) is to determine whether an individual carrying one or two copies of a specific allele is at increased risk of developing a disease. The principle of the commonly used case–control association study is illustrated in Fig. 12-4. This study is a powerful method to detect associations of certain alleles with a disease phenotype, and it has been employed for the identification of the genetic risk factors in periodontitis.

An important prerequisite of case–control studies is to ensure a good match between the genetic background of cases and controls, so that any genetic difference between them is related to the disease under study and not to biased sampling. Therefore, cases and controls should have similar ethnic descent. A further prerequisite is a *case selection strategy* that is designed to enrich susceptibility alleles of a specific disease. This includes efforts to minimize phenotypic heterogeneity by stringent diagnosis criteria, and should focus on extreme cases, defined, for example, by a particularly early age of disease onset or severe disease or both.

In most circumstances, and particularly when the total sample size has financial or operational constraints, efforts to enrich case selection with the most severe phenotypes are very likely to improve the *statistical power* of a study due to an increase in the frequency of the risk genotype (McCarthy *et al*. 2008). Related to this and compulsory for the identification of a true genetic risk factor, are case–control analysis populations, which are large enough to provide the necessary statistical power. The statistical power increases with sample size and correlates with allele frequency and the genetic effect of the respective variant (Kathiresan *et al*. 2004). This is why common variants or variants with a high odds ratio (OR) are more likely to be detected in genome-wide association studies (GWAS) than rare variants or variants with a small effect (Fig. 12-5). However, most disease-associated variants increase the susceptibility rather modestly and to identify a common variant with a modest genetic effect, often >1000 well-defined cases and at least the same number of controls are necessary to reach a sufficient statistical power.

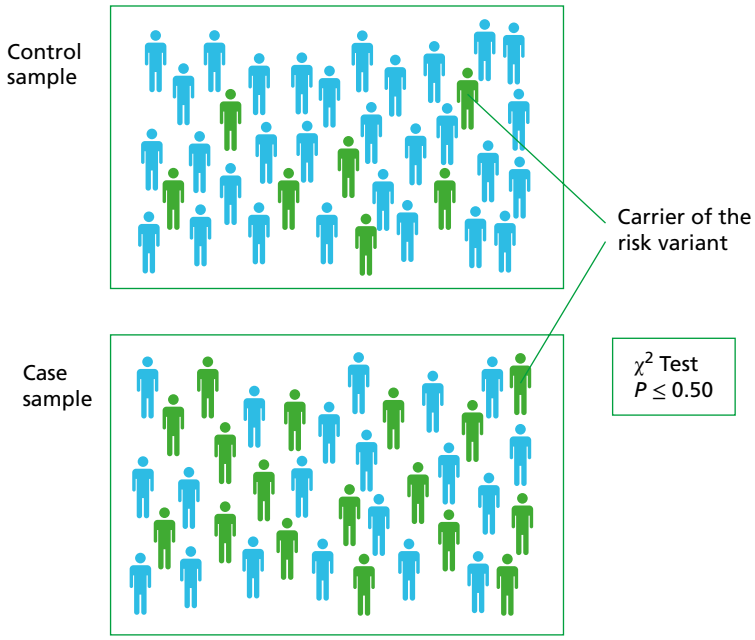

Fig 12-4 Case–control studies compare the frequency of single nucleotide polymorphism (SNP) alleles in two well-defined groups of non-related individuals: controls, who are either known to be unaffected or who have been randomly selected from the population, and cases who have been diagnosed with the disease under study. An increased frequency of an SNP allele or genotype in cases compared with controls indicates that the presence of the SNP allele may increase the disease risk. The potential association is a mere statistical association and always requires a replication in an independent sample. Significance can be assessed with various methods, but most often the χ^2 statistic is used in contingency table analyses, which provide an assessment of the departure from equal SNP allele frequencies in cases and controls (*P* value). Association studies can also be used to estimate the disease risk conferred by the SNP allele, which is expressed by the odds ratio (OR). The OR is the ratio of allele carriers to non-carriers in cases compared with that in controls, which gives the increase in disease risk for carriers compared to non-carriers (Source: Data from Lewis 2002. Reproduced with permission from John Wiley & Sons.).

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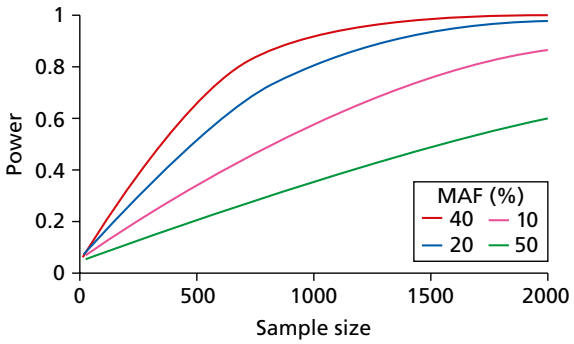

Fig 12-5 Statistical power in relation to the sample size, allele frequency, and odds ratio (OR). To identify a genetic risk variant with a minor allele frequency (MAF) of, for example, 20% in the general population, approximately 1000 cases and 2000 controls are required to achieve the necessary statistical power of 0.8. The statistical power was calculated as described by Dupont and Plummer (1998) for an average OR of 1.3, and twice as many controls as cases were considered. A power of 0.8 is regarded as statistically significant. (Source: Data from Dupont & Plummer 1998. Reproduced with permission from John Wiley & Sons.)

The findings of case–control studies are mere statistical associations, which describe differences of allele frequencies between two independent samples; importantly, they should not be regarded as causative associations. By a preassigned significance threshold of 0.05, one in every 20 allelic variants tested will pass the commonly preassigned significance threshold of a P value of <0.05 by chance alone. Allele frequencies between independently sampled populations are also liable to stochastic fluctuations (random allele drifts across and between populations, without selection pressure). For these reasons, *replication* of the initial findings is the gold standard for genetic association studies. Notably, the replication needs to be performed in an independent case–control sample of the same phenotype (diagnosis criteria) and the same ethnic background. A repetition of the study with samples from different ethnic groups, with different diagnostic criteria or with independent cases but the same controls, cannot be considered as a replication and does not test the initial finding properly. Only after confirmation by replication is it useful to validate the initial finding of an association study in different subphenotypes or in different ethnicities.

As genes are usually patchworks of different haplotypes, being mostly in poor-to-moderate linkage disequilibrium (LD), the information on the potential association of one haplotype provides little to no information on the association or non-association with another haplotype within that gene (Slatkin 2008). Thus, association studies should capture the complete haplotype information of the gene of interest before drawing an unambiguous conclusion of the association findings for that gene, positive or negative (Slatkin 2008).

Candidate gene association studies

Until the early years of this millennium, investigations of selected candidate genes based on literature reviews and perceived pathophysiologic pathways was the most important strategy for the identification of risk genes that contribute to a disease. A major disadvantage of candidate gene studies is the requirement for an *a priori* hypothesis on the involvement of the gene in disease risk and on the presence of a functional variant within this particular gene (Wilkening *et al*. 2009). Essentially, there are two different selection strategies for a candidate gene, which depend on the question addressed. When it is of interest to ask whether or not specific loci within a regulatory signaling pathway are involved in the increase of the genetic risk of periodontitis, or there is functional evidence of the effect of a variant from the study of other diseases, it is reasonable to select genes from this pathway or the specific variants. This approach will determine whether or not the selected genes carry genetic variants which increase the risk of the disease.

Another question which addresses the classical objective of molecular genetics is more difficult to answer: which specific genes and pathways influence the disease risk? As the formulation of the hypothesis for the selection of the candidate gene is entirely dependent on the current knowledge of the molecular biologic mechanisms of the disease, hundreds of loci and/or genes which can have an influence on the disease will not be selected because their function might be unknown or their function lies within pathways that have not yet been implicated in the disease. As the knowledge on these genes is very incomplete, selection of candidate genes is necessarily arbitrary. Accordingly, most associations observed in these studies cannot be successfully replicated. Obviously, this does not rule out the finding of a true positive association if the correct candidate gene was selected *a priori*, but with this approach it is not possible to identify hitherto unknown genes that are disease relevant.

Genome-wide association studies

In contrast, for 10–15 years, GWAS has provided an unbiased and hypothesis-free approach. A large number of SNPs (currently 500 000 to >1 000 000 markers) distributed across the whole genome serve as proxies for multiple other SNPs in LD. Nevertheless, genome-wide testing of polymorphisms also entails problems. First, if by chance alone, one in every 20 markers tested gives a P value of <0.05, the probability of statistical errors rises with increasing number of single SNP association tests, so-called type 1 errors (false-positive association findings). If 500 000 markers or more are independently tested, the P value obtained from the χ^2 statistics must be corrected for multiple testing. This is addressed by setting a genome-wide significance threshold by correcting

for the number of tests performed (Balding 2006). The current standard for declaring statistical significance at genome-wide level for common variants is a combined *P* value (including "initial discovery" GWAS and replication cohorts) of $<5 \times 10^{-8}$ (Manolio 2010). Because rare variants are more numerous and less correlated with each other than common variants, this threshold is not enough to declare significance in association studies that target rare variants. Thus, rare variant associations suffer from an increased multiple testing burden and a decrease in statistical power owing to the rarity of individuals carrying these variant alleles. However, the sample sizes that are required to achieve such significance thresholds may be unrealistic for the study of less common diseases. The resulting lack of statistical power is the major factor that leads to type 1 and type 2 errors (false positive and false negatives), that is, the failure to detect a true association.

periodontitis by including information from >50 000 human subjects (Nibali *et al*. 2019). The heritability of periodontitis was estimated at 0.38 in twin studies and 0.15 in other family studies, and increased with disease severity and smoking habits. No heritability was found for clinically measured gingivitis. This systematic review confirmed that a substantial proportion of the phenotypic variance of periodontitis in the population is due to genetic susceptibility and that genetic factors contribute more to disease risk for severe early-onset traits and younger individuals.

Gene mutation of major effect on human disease and its association with periodontitis

Complex diseases such as periodontitis are caused by an intricate interplay of many genetic and non-genetic factors. In contrast, monogenic diseases such as Huntington's disease and cystic fibrosis are fully heritable and people who carry a causative allele in a single gene specific for the monogenic disease will inevitably become affected, unless treated. The Papillon–Lefèvre syndrome (PLS) is relatively unique in the group of monogenic diseases, in that severe fast progressive periodontitis forms a significant component of the phenotype and is a defining clinical feature (Toomes *et al*. 1999). Both the deciduous and permanent dentitions are affected, resulting in prepubertal periodontitis and premature tooth loss. Additionally, palmoplantar keratosis, varying from mild psoriasiform scaly skin to overt hyperkeratosis, typically develops within the first 3 years of life. Keratosis also affects other sites such as the elbows and knees. Most PLS patients display both periodontitis and hyperkeratosis. Some patients have only one or the other, and periodontitis is rarely mild or of late onset.

The causative mutations of PLS are located in the *CTSC* (cathepsin C) gene on chromosome 11; over 50 mutations in the gene are now recognized. The protein encoded by this gene is cathepsin C, a lysosomal cysteine proteinase, that appears to be a central coordinator for activation of various serine proteinases. It is expressed at high levels in polymorphonuclear leukocytes (PMNs) and alveolar macrophages and their precursors (Rao *et al*. 1997). It was proposed that minimal cathepsin C activity (~13%) was necessary to prevent the clinical features of PLS, but the exact mechanism by which an altered function of cathepsin C plays a role in the pathogenesis of PLS-associated prepubertal periodontitis is unknown (Hewitt *et al*. 2004). It is speculated that cathepsin C is essential for activation of many serine proteinases in immune-inflammatory cells, including cathepsin G, neutrophil serine proteases, proteinase 3, and elastase (Dalgic *et al*. 2011). The inactive forms of these neutrophil serine proteases result in dysregulation of the host immune response. Increased susceptibility to infections has been attributed to impaired neutrophil and T- and B-cell functions (Ryu *et al*. 2005). The impaired localized PMN response in inflamed periodontal tissues leads to periodontitis, most likely due to improper phagocytosis and digestion of Gram-negative periodontal pathogens. Likewise, the mutation in the *CTSC* gene seems to result in the incapacity of PMNs to kill *A. actinomycetemcomitans* in an anaerobic environment (de Haar *et al*. 2006).

Identification of genetic risk factors of periodontitis

To reiterate the important aspects of the pathophysiology of periodontitis, we summarize here that, in contrast to monogenic diseases like PLS, periodontitis is a complex disease that is caused by a combination of genetic, environmental, and lifestyle factors. Thus, genetic factors represent only part of the risk associated with complex disease phenotypes and a genetic predisposition means that an individual has a genetic susceptibility to develop a certain disease but it does not mean that a person harboring such a genetic tendency is destined to develop the disease. Instead, the development of the disease phenotype largely depends on a person's environment and lifestyle. However, some individuals develop periodontitis at a young age. In such cases, environment and lifestyle factors only act in the short term and they are often shared with individuals who do not develop the disease. Thus, an early age of disease onset often indicates a genetic predisposition. This does not imply carriage of a single genetic variant with a strong effect; rather, patients with an early onset often carry specific combinations of various

risk alleles. In this regard, the different phenotypes of periodontitis can be considered as different parts of a large range of similar conditions, which can be attributed to the effects of different combinations of genetic risk loci that form the genetic constitution. Furthermore, different disease manifestations are not confined entities but share risk alleles and covariates. The central problem in efforts to elucidate the genetic susceptibility factors of a complex disease is that millions of genetic variants exist in the genome with most having no effects, while only a very small fraction contributes to the disease risk with minute effects of each effect allele. However, these add in specific individual combinations that make up the personal risk genotype. Because no hypotheses can be developed that allow a direct selection of the effect alleles, since in most cases the causal variants do not change the amino acid of a protein, essentially all variants of the human genome need to be tested for their role in the disease susceptibility.

About a decade ago, technical advances allowed the hypothesis-free approach of simultaneously testing millions of SNPs across the genome of a single patient. These studies are called genome-wide association studies (GWAS, see Box 12-2). In this type of study, it can be determined which alleles are more frequent in a sample with disease or the trait of interest compared with a control sample. An increased frequency of a specific allele points to a genetic location of the variant that likely has a role in the trait or disease. This new era of genetic research largely began with the milestone publication of the Wellcome Trust Case Control Consortium (2007). Because of the small effects of the risk alleles, large case–control populations are indispensable (see Box 12-2) (Visscher *et al*. 2017). Several thousands of well-defined cases and many more controls are needed to detect a genetic variant with a small effect that is observed commonly for complex diseases. This realization eventually resulted in the formation of extensive international consortia for the recruitment of the appropriate case and control numbers, which eventually included over tens of thousands of cases and controls.

In recent years, all common genetic risk factors for any complex human disease like type 2 diabetes, coronary artery disease, or rheumatoid arthritis have been unveiled. Table 12-3 gives a snapshot of the recent findings in terms of the numbers of identified genetic risk loci of major complex inflammatory diseases, some of which are co-morbidities of periodontitis, and the numbers of cases and controls employed in the largest of these studies. Most of the identified genes were initially not thought of as likely candidate genes.

For periodontitis, despite >100 candidate-gene association studies that have been performed, evidence that is based on statistically solid associations is scarce. Difficulties in generating large case samples of individuals with a homogenous ethnic background have been the major cause for the slow progress in the discovery of genetic risk loci of periodontitis compared with other complex human diseases. Consequently, few genes can currently be considered as true genetic susceptibility factors for periodontitis.

The reader who is interested in lists of genetic variants that had been proposed to be associated with periodontitis can find compilations in Schaefer *et al*. (2013) and da Silva *et al*. (2017). Many variants had been implicated as potential risk factors, but few, if any, had been established definitively. Several factors undermined the validity of previous published reports, and included inappropriately small sample sizes, multiple subgroup comparisons, and publication bias. Publication bias, a crucial stratification factor in the short-term advancement of research, is explained by the fact that positive results are much easier published than negative findings, which results in biased publications and accumulation of false positive findings in the scientific literature in contrast to publications of true negative findings. This will result in false positive results from meta-analyses of publications but not from meta-analyses that used unbiased data such as GWAS-meta-analyses.

In the following discussion, instead of compiling a long list of studies with often ambiguous results, we

Table 12-3 Number of identified risk gene variants for a selection of inflammatory diseases. The total population size included in the explorative study and the replication is given for the largest of the current studies.

Disease	Total number of associations ($P < 10^{-5}$)	Population size of largest study (cases and controls)
Coronary artery disease	928	304 591 (Klarin *et al*. 2017)
Type 2 diabetes mellitus	2244	659 316 (Xue *et al*. 2018)
Rheumatoid arthritis	1391	105 000 (Laufer *et al*. 2019)
Systemic lupus erythematosus	834	35 844 (Morris *et al*. 2016)
Crohn's disease	893	77 064 (Jostins *et al*. 2012)

(Source: Data from the NHGRI-EBI Catalog of published genome-wide association studies, 03/2020. Reproduced with permission from John Wiley & Sons.)

focus on those loci that have been identified in GWAS that fulfill at least one of the following criteria:

- genome-wide significance of association with at least a P value of 5.5×10^{-8} (as a result of the combined discovery GWAS and the replication cohort). This is the gold-standard to declare significance in GWAS.
- independent replication in samples of the same disease phenotype with sufficient statistical power.
- independent validation of the associations in samples with sufficient statistical power of different disease manifestations such as the fast-progressive periodontitis phenotype often seen in teenagers and young adults, and the moderate progressive periodontitis form mainly seen in middle-aged and older adults.
- independent identification through different systematic approaches.

For future perspectives on the discovery of the missing heritability of genetic susceptibility factors the reader is referred to Box 12-3.

Sialic acid binding IG like lectin 5 (*SIGLEC5*) and other potential variants

A GWAS on periodontitis with evidence of fast progress (1116 cases and 7654 controls from Germany, the Netherlands, and Turkey) identified associations with the gene *SIGLEC5* on chromosome 19;

Box 12-3 Future perspectives.

When GWAS began a decade ago, it was widely believed that complex disease is largely attributable to a moderate number of common variants, each of which explains several percent of the risk in a population (Pritchard & Cox 2002). In contrast to this, GWAS identified an unexpectedly large number of common variants that contribute to disease risk (Table 12-3). This means that each individual will carry a number of alleles that increase and a number of alleles that decrease a disease risk. There are so many possible combinations of these sets of alleles that each individual is likely to have a unique combination. In GWAS that are designed to detect individual associated loci, the effect size of each allele is measured across the context of an averaged background. Thus, the effect size for the individual variant is generally found to be small (Visscher *et al*. 2017). However, although the number of associations increased to hundreds for most diseases (Table 12-3), they only explain a small proportion of the disease heritability. Where the missing heritability is likely to lie is currently debated. One model argues that a very large number of the genes contribute indirectly to a disease and show relatively small effect sizes and these genes are classified as peripheral and are thought to show a large amount of pleiotropy. In this model, additional genetic variants with relatively large effects sizes also exist and play a more direct role in a disease. The genes that harbor those less common disease-specific variants are classified "core" genes (Boyle *et al*. 2017). However, this intuitive concept of only a few "core" genes with higher effects, that would also represent good diagnostic and therapeutic targets, is discussed critically (Wray *et al*. 2018). First, common diseases are actually uncommon in a population, that is. most people are healthy. This indicates an inherent robustness in the biological system, which is why an etiology of many core genes should be assumed. This implies an indistinguishability between peripheral and core genes. Accordingly, large exome and genome sequencing studies showed that rare coding-region variants at known risk loci of diseases have a negligible role in susceptibility (Hunt *et al*. 2013; Genovese *et al*. 2016), or they failed to identify rare variants that could explain the missing heritability for common diseases (Fuchsberger *et al*. 2016; Genovese *et al*. 2016). Secondly, a disease that impacts only a small fraction of the population with a genetic architecture of many risk loci with similar effect sizes can be explained by a high non-linear relationship between probability of a disease and burden of risk alleles. This implies that polygenic disease is non-additive on the disease scale but rather caused by interacting effects of the genetic variants.

However, it is likely that different diseases have different genetic architectures – the joint distributions of effect size and allele frequency at the risk loci – and contribute in various degrees to different diseases. The debate on the contribution of genetic variation to disease over the coming years will center on how variants interact. A straightforward hypothesis states that common variation influences the expression and activity of genes in molecular pathways, establishing the background susceptibility to the disease that is then further modified by other variants (Fig. 12.6). Figure 12.6 illustrates gene × gene interaction under the assumption that disease is generally a threshold-dependent response that is superimposed on a continuous physiologic characteristic.

As only a proportion of the genetically predisposed and/or pathogen-exposed individuals develop a disease, simple genetic explanations for individual susceptibility to chronic inflammatory diseases such as periodontitis have not been forthcoming. The challenge for future research will be, apart from identifying as many susceptibility factors as possible, to discern the relevant patterns within the generated data, in other words to model the effects of SNP–SNP interactions (Renz *et al*. 2011).

(*Continued*)

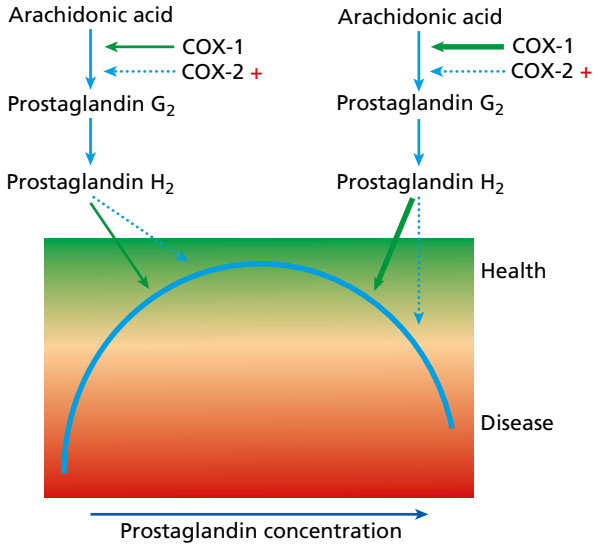

Fig 12-6 It is hypothesized that common variants influence the expression and activity of genes in pathways establishing the background susceptibility to disease that is then further modified by less common variants with larger effects. Prostaglandins are produced by a cascade of biochemical reactions following the sequential oxidation of arachidonic acid by the cyclooxygenases COX-1 and COX-2 and terminal prostaglandin synthases. Whereas COX-1 is responsible for the baseline levels of prostaglandins, COX-2 produces prostaglandins by specific stimulation in scenarios of periodontal inflammation. In this fictitious example, the half circle represents a range of prostaglandin concentrations in the lesion of a given population. The prostaglandin concentration is influenced by the interplay of the individual genetic constitutions, and the individual physiologic and environmental states. Prostaglandin concentrations at the low and high ends are associated with disease, while an intermediate concentration is physiologic and compatible with health. In this hypothetical illustration, genetic variation somewhere within the prostaglandin synthesis pathway results in some individuals having lower prostaglandin levels (left, normal COX-1 activity, indicated by the green horizontal arrow from COX-1) than others (right, genetic variation in COX-1 that establishes the background susceptibility to disease; indicated by the thick green horizontal arrow from COX-1). The variation in individuals with a background susceptibility is still within the healthy range. The effect of an additional variant that increases COX-2 synthesis (indicated by the "+" sign and blue dashed arrows) upon inflammatory stimulation is conditional on this liability, pushing those with a high concentration of prostaglandin that is genetically determined by the background susceptibility (those on the right) beyond the disease threshold and towards the development of periodontitis (into the red danger zone), whereas those with a low concentration of prostaglandin on the left can accommodate the genetic variation and remain in the green safe zone. (Source: Adapted from Gibson 2012. Reproduced with permission from John Wiley & Sons.)

this association was validated in a cohort of patients with less fast progress, consisting of 2211 cases of periodontitis and 1817 controls (Munz *et al*. 2017). A GWAS meta-analysis employing 17353 cases with moderate progressing periodontitis and 28210 controls, replicated the association of *SIGLEC5* variants with periodontitis (Shungin *et al*. 2019). *SIGLEC5* is a member of the human CD33-related siglecs and is broadly expressed in various myeloid cells of the innate immune system and in B-cells. It is classified as an inhibitory receptor with a function in maintaining leukocytes in the quiescent state until activation is triggered via appropriate receptors. Accordingly, *SIGLEC5* seems to modulate the activation of myeloid cells to prevent inappropriate reactivity against self-tissues, which is important during wound healing, for example. The ability to distinguish foreign pathogens from self and to make an appropriate response is also essential to avoid bystander damage to host cells.

Another large GWAS on periodontitis was performed with genotypes from the Hispanic Community Health Study/Study of Latinos that included 10935 participants (Sanders *et al*. 2016). As the most significant finding, an association of a rare variant at the gene *TSNAX-DISC1* on chromosome 1 was reported (SNP rs149133391, minor allele [C] frequency = 0.01%) to pass the genome-wide significance threshold ($P = 5 \times 10^{-8}$) with $P = 7.9 \times 10^{-9}$. However, owing to the rarity of individuals carrying these variant alleles, and because rare variants are more numerous and less correlated with each other than common variants, rare variant associations suffer from an increased multiple testing burden and a decrease in statistical power. Thus, a $P = 5 \times 10^{-8}$ threshold is not enough to declare significance in association studies that target rare variants (Auer & Lettre 2015). Therefore, this association should be regarded with caution.

No further associations that met the genome-wide significance thresholds for common or rare alleles were directly identified in other GWAS in studies including patients with the slow or moderate progressing rate of the disease. On the one hand it is discussed that these unremarkable results are reflections of an underlying trait heterogeneity of periodontitis. However, on the other hand, the non-findings of these studies are more likely caused by

the small sample sizes that were employed in most GWAS on periodontitis. Complex diseases with an adult onset and moderate progression usually have a large contribution of additive effects of non-genetic factors, for example for periodontitis this is smoking, oral hygiene, nutrition, stress, and the general decline of the immune system during ageing. The effects of simple genetic variants are weak. Consequently, increased sample sizes are required in GWAS that focus on a complex, moderate progressive, and adult-onset disease phenotype.

Defensin alpha-1 and -3 (*DEFA1A3*)

In the GWAS of 2017, in addition to the discovery of *SIGLEC5* as a risk gene for periodontitis, associations for periodontitis with the *DEFA1A3* gene at a genome-wide significance level were also identified (Munz *et al*. 2017). The association located at the intergenic region that separates the antimicrobial peptides *DEFA1* and *-4*. These genes belong to the family of alpha defensins that cluster on chromosome 8 and are believed to play a role in phagocyte-mediated host defense against bacteria, fungi, and viruses. The genes *DEFA1* and *DEFA3* are highly copy variable and differ only by a single base substitution in the coding sequence. They seem to be interchangeable occupants of a 19-kb-long copy-variable repeat unit, with both *DEFA1* and *DEFA3* gene numbers showing variation (Khan *et al*. 2013). For this reason, the composite designation *DEFA1A3* was suggested (Aldred *et al*. 2005).

CDKN2B antisense RNA 1 (*CDKN2B-AS1*)

CDKN2B-AS1 (also known as *ANRIL*) was identified by GWAS as the first genetic risk factor for myocardial infarction (Wellcome Trust Case Control Consortium 2007). Strong evidence of association between the presence of coronary artery disease (CAD) and periodontitis was derived from multiple randomized clinical trials, demonstrating that the association between both diseases is independent of smoking, which is the shared risk factor (Lockhart *et al*. 2012). In this context, *CDKN2B-AS1* was selected as a candidate gene for periodontitis in the investigation of a putative shared genetic basis for coronary artery disease and periodontitis. Early-onset forms (<35 years of age at first diagnosis) were chosen because of the higher heritability and to ensure that shared covariates of periodontitis and CAD, such as smoking, type 2 diabetes mellitus, and age contribute less to the development of the disease. *CDKN2B-AS1* was the first published genetic risk factor for these early-onset forms of periodontitis (Schaefer *et al*. 2011). This finding was independently replicated (Ernst *et al*. 2010; Munz *et al*. 2018). *CDKN2B-AS1* is associated with highly severe early-onset periodontitis but not with more moderate late onset forms. Because of this, it has not yet reached genome-wide significance because the analyses samples were too small to reach the very stringent threshold of genome-wide significance of $P < 5\times 10^{-8}$). However, because of the repeated replication of associations of the same variants, it is considered as a true genetic risk factor of severe early-onset periodontitis.

Miscellaneous genetic associations with periodontitis

The largest meta-analysis that combined genotype data from various GWAS (Divaris *et al*. 2013; Teumer *et al*. 2013; Munz *et al*. 2017) employing a total of 5095 periodontitis cases and 9908 controls of North-West European descent, additionally identified an association of genome-wide significance with the SNP rs729876 ($P = 2.1 \times 10^{-8}$). The variant is located within the intronic region of the long intergenic noncoding RNA (lincRNA) LOC107984137, the function of which is unknown. Currently, it is not clear if this SNP does affect the function of this lincRNA and/or of other genes. Experimental work suggests that it is linked to the function of RUNX1 (runt-related transcript factor 1) (Huang *et al*. 2004). RUNX1 plays a role in hematopoiesis and bone formation (Ono *et al*. 2007).

Epigenetic signatures

The strategies described previously for identifying genetic risk factors of periodontitis explore changes within the nucleotide sequence in the DNA. However, it is now becoming clear that a full understanding of the interactions of the environment and lifestyle factors with the genome will also require the consideration of epigenetic mechanisms. Epigenetics can be defined as the structural (mitotically or meiotically) heritable or reversible adaptation of chromosomal regions so as to register, signal, or perpetuate altered gene activity states (Bird 2007), which refers to changes in gene expression that do not involve a change in the DNA nucleotide sequence, but encompass an array of molecular modifications to both DNA and chromatin (Li 2002; Klose & Bird, 2006). These modifications are conferred by methylation of cytosines in CpG dinucleotides, changes to chromatin, and packaging of DNA by post-translational histone modifications, mechanisms that control the higher level organizations of chromatin within the nucleus, which have a range of effects on gene expression. In this context, the low concordance rates in MZ twins, who do not always show the same disease susceptibility, also raised the possibility of epigenetic differences arising during early development as well as with aging (Wong *et al*. 2005). Accordingly, it has been reported that young twins have similar amounts of DNA methylation, whereas older twins differ considerably in the amounts and patterns of this modification (Fraga *et al*. 2005). It is a subject of speculation whether the amounts and patterns of

epigenetic alterations could give rise to the divergent disease predispositions of some MZ twins. However, unambiguous, reliable epigenetic data for twins and unrelated humans are scarce and generalizations and interpretations should be handled with prudence. Data from model organisms have suggested long-term and transgenerational epigenetic effects on gene expression (Morgan *et al*. 1999; Rakyan *et al*. 2003; Anway *et al*. 2005). Evidence for potential mechanisms that modify the epigenome of the gingiva and link environmental and lifestyle influences to the genetic constitution was given for tobacco smoking by two epigenome-wide association studies (EWAS) of buccal cells and solid gingival tissues (Teschendorff *et al*. 2015; Richter *et al*. 2019). These studies showed that the genes *CYP1B1* (cytochrome P450 family 1 subfamily B member 1) and *AHRR* (aryl-hydrocarbon receptor repressor) have an important role in xenobiotic metabolism of tobacco smoke in the oral mucosa. For periodontitis, no EWAS was performed with gingival tissues to date. However, an EWAS with individuals who self-reported gingival bleeding and tooth mobility was conducted in whole blood (Kurushima *et al*. 2019). For tooth mobility, the two most associated CpG sites were located in the gene body of the *IQCE* (IQ Motif Containing E) gene and in the gene body of the *XKR6* (XK Related 6) gene. *IQCE* is associated with a variety of different traits like alcohol consumption, food allergy, and underweight. *XKR6* is associated with a variety of different traits like alcohol consumption, smoking behavior, body mass index or wellbeing, but also with co-morbidities of periodontitis such as diabetes mellitus and systemic lupus erythematosus. It is possible that the different methylation of these genes in blood is not directly related to periodontitis but related to exposure of risk factors of periodontitis. This underlines the necessity to use oral mucosal tissues to identify differential methylation caused by oral inflammation or environmental factors that exert their effects in the oral cavity.

From genetic disease susceptibility to improved oral care

Despite great breakthroughs in human genetics in recent years, in a substantial number of inflammatory diseases few direct improvements in clinical care have resulted to date. This is largely because of the complexity of most heritable diseases, as described earlier. Most of the identified common risk factors have only moderate effects, and in most cases the true causative variants that mediate the effect at the molecular biologic level, as well as the underlying mechanism, still await elucidation. In this context it is of interest to look at the present potential of genetic health tests. Over time, these tests have evolved from testing a few variants for the prediction of a single disease, to testing hundreds of thousands of genetic variants genome-wide for multiple diseases simultaneously (Janssens & van Duijn 2010). The prediction ability of these tests is very imprecise and differs considerably between monogenic and complex diseases,

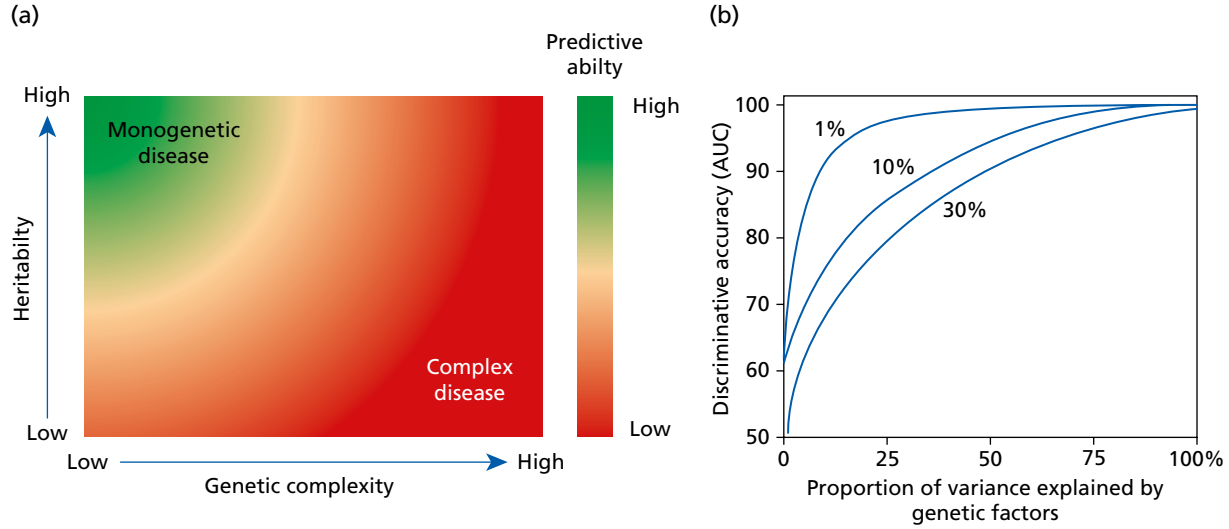

Fig 12-7 (a, b) Relationship between the heritability, genetic complexity, and predictive ability in personal genome testing. The predictive ability is highest if the heritability is high and the genetic complexity is low. The discriminative accuracy, assessed as the area under the operating characteristic curve (AUC), is the extent to which predicted risks can discriminate between individuals who will develop a disease of interest, like periodontitis, and those who will not. The AUC is the probability that the test correctly identifies the person who will develop the disease from a pair of whom one will be affected and one will remain unaffected, and ranges from 50% (complete lack of discrimination) to 100% (perfect discrimination). The percentages on the graph refer to the risk of disease prevalence in the population. Underlying this is the assumption that the total heritability can be explained, but whether or not this is realistic depends on the complexity of the genetic etiology. The discriminative accuracy for the more moderate or slow progressing phenotype of periodontitis often with the adult onset, will always be low; however, for the fast-progressing phenotype of periodontitis with often a more early onset history, the discriminative accuracy is expected to be higher. (Source: Data from Janssens *et al*. 2008. Reproduced with permission from John Wiley & Sons.)

which is explained by the different genetic complexities of these diseases (Fig. 12-7). Monogenic diseases such as cystic fibrosis or Huntington's disease are fully heritable and a mutation in a single specific gene is sufficient to cause these diseases. Testing for the absence or presence of these mutations gives an accurate estimate of future disease development. When diseases have a high heritability and a low genetic complexity, such as monogenetic disorders, genetic tests will be very accurate. In contrast, for complex diseases, the predictive ability of genetic tests is determined by the combined effect of all genetic, environmental, and lifestyle factors tested (Janssens & van Duijn 2010). Only when diseases have a high heritability can we expect that the maximum discriminative accuracy is reliable, nevertheless only under the assumption that all variants are identified. A good predictive ability of a genetic test will theoretically be possible for a disease with a very high heritability and a low genetic complexity. Such diseases are commonly severe and have an early age of onset and a low frequency (<1%) in the population. Thus, reliable genetic testing may become possible for the early-onset and relatively fast progressing forms of periodontitis, on the condition that the genetic susceptibility factors are completely identified. In contrast, late-onset periodontitis being diagnosed in middle-aged or older individuals, having moderate and greatly variable phenotypes as well as a high risk in the population, have numerous underlying low-risk genetic variants, which may interact with each other and with other non-genetic risk factors in countless different ways. Therefore, currently, predictive testing models of increased or decreased risks for periodontitis based on genetic testing, are highly unreliable due to the very complex multidimensional interactions between multiple genes, lifestyle factors, microbial factors, and present or hidden comorbidities.

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Part 5: Trauma from Occlusion

Chapter 13

Effect of Load on Periodontal and Peri-Implant Tissues

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INTRODUCTION

The tissues surrounding teeth and implants are presented in Chapters 1, 4, and 5. It is documented that the periodontal ligament plays an important role in responding to the occlusal forces to the crown portion of a tooth during function. The corresponding tissue around implants is comprised of bone that has formed in direct contact with the metal surface. While the periodontal ligament harbors a large number of cells that are capable of responding to alterations in occlusion, the bone tissue in the zone of osseointegration contains groups of cells apparently less able to respond to altered load conditions during function (see Chapter 5) This is one important reason why the effect of load on implants and teeth is described in different sections (Part I and Part II).

PART I: PERIODONTAL TISSUES

Definition and terminology

Trauma from occlusion is a term that was used to describe pathologic alterations or adaptive changes which develop in the periodontium as a result of undue force produced by the masticatory muscles. It is only one of many terms that have been used to describe such alterations in the periodontium. Other terms often used are: *traumatizing occlusion*, *occlusal trauma*, *traumatogenic occlusion*, *periodontal traumatism*, and *overload*. In addition to damaging the periodontal tissues, traumatic occlusal force may also injure, for example, the temporomandibular joint, the masticatory muscles, and the pulp tissue. This part of the chapter deals exclusively with the effects of occlusal trauma on the periodontal tissues.

The World Health Organization (WHO) in 1978 defined trauma from occlusion as "damage in the periodontium caused by stress on the teeth produced directly or indirectly by teeth of the opposing jaw". Occlusal trauma is an injury to the attachment apparatus that results from excessive occlusal force(s). A new terminology was proposed at the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions (Jepsen *et al*. 2018). Thus, *traumatic occlusal force* was defined as any occlusal force resulting in injury of the teeth and/or the periodontal attachment apparatus, while *occlusal trauma*

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

describes the injury to the periodontal attachment apparatus.

Traumatizing forces may act on an individual tooth or on groups of teeth in a premature contact relationship; they may occur in conjunction with parafunctions such as clenching and bruxism, or in conjunction with loss or migration of premolar and molar teeth with an accompanying, gradual spread of the anterior teeth of the maxilla.

The tissue injury associated with trauma from occlusion is often divided into *primary* and *secondary*. The *primary* form includes tissue reactions (damage) elicited around a tooth with normal periodontium height, while the *secondary* form is related to situations in which occlusal forces cause injury to a periodontium of reduced height. The distinction between a primary and a secondary form of injury–primary and secondary occlusal trauma–serves no meaningful purpose, since the alterations which occur in the periodontium as a consequence of occlusal trauma are similar and independent of the height of the target tissue, that is the periodontium. It is, however, important to understand that symptoms of occlusal trauma may develop only in situations when the magnitude of the load elicited by occlusion is so high that the periodontium around the exposed tooth cannot properly withstand and distribute the resulting force without altering the position and stability of the tooth involved. This means that in cases of severely reduced height of the periodontium, even comparatively small forces may produce adaptive changes in the periodontium.

Occlusal trauma and plaque-associated periodontal disease

Ever since Karolyi (1901) postulated that an interaction may exist between "*trauma from occlusion*" and "*alveolar pyrrohea*", different opinions have been expressed regarding the validity of this claim. In the 1930s, Box (1935) and Stones (1938) reported experiments in sheep and monkeys, the results of which seemed to indicate that "trauma from occlusion is an etiologic factor in the production of that variety of periodontal disease in which there is vertical pocket formation associated with one or a varying number of teeth" (Stones 1938). The experiments by Box and Stones, however, have been criticized because they lacked proper controls and because their design did not justify the conclusions drawn.

The interaction between occlusal trauma and plaque-associated periodontal disease in humans was frequently discussed in the period 1955–1970 in connection with "case reports", "in my opinion" statements, etc. Even if such anecdotal data may have some value in clinical dentistry, it is obvious that conclusions drawn from research findings are much more pertinent. Research-based conclusions are not always indisputable, but they invite the reader to critique them, which anecdotal data do not. In this section, therefore, the presentation will be limited to findings from endeavors involving clinical and preclinical research.

Clinical trials

In addition to the presence of angular bony defects and infrabony pockets, *increased tooth mobility* is frequently listed as an important sign of occlusal trauma. Conflicting data have been reported regarding the periodontal condition of mobile teeth. In one clinical study by Rosling *et al*. (1976), patients with advanced periodontal disease associated with multiple angular bony defects and mobile teeth were exposed to subgingival scaling after flap elevation followed by meticulous supportive therapy. Healing was evaluated by probing attachment level measurements and radiographic monitoring. The authors reported that "the infrabony pocket located at hypermobile teeth exhibited the same degree of healing as those adjacent to firm teeth". In another study, however, Fleszar *et al*. (1980) reported on the influence of tooth mobility on healing following periodontal therapy, including both subgingival scaling and occlusal adjustment. They concluded that "pockets of clinically mobile teeth do not respond as well to periodontal treatment" (including tooth debridement) "as do those of firm teeth exhibiting the same disease severity".

Pihlstrom *et al*. (1986) studied the association between occlusal trauma and periodontitis by assessing a series of clinical and radiographic features at maxillary first molars: probing depth, probing attachment level, tooth mobility, wear facets, plaque and calculus, bone height, and widened periodontal space. The authors concluded from their examinations that teeth with increased mobility and widened periodontal ligament space had deeper pockets, more attachment loss, and less bone support than teeth without these symptoms.

In another clinical trial, Burgett *et al*. (1992) studied the effect of occlusal adjustment in the treatment of periodontitis. Fifty patients with periodontitis were examined at baseline and subsequently treated for their periodontal condition with root debridement ± flap surgery. Twenty-two of the 50 patients additionally received comprehensive occlusal adjustment. Re-examinations performed 2 years later disclosed that probing attachment gain was on average about 0.5 mm greater in patients who received the combined treatment, that is debridement and occlusal adjustment, than in patients who did not receive occlusal adjustment.

Nunn and Harrel (2001) and Harrel and Nunn (2001) examined the relationship between occlusal discrepancies and periodontitis in two studies. Their sample included about 90 patients who had been referred for treatment of periodontal disease and who had at least two (≥1 year apart) complete periodontal records, including an analysis of their occlusion. The patients were examined with respect

to probing pocket depth, tooth mobility, and furcation involvement (at multirooted teeth). In addition, occlusal contact relationships were studied, such as (1) discrepancies in centric relation and centric occlusion and (2) premature occlusal contacts in protrusive movements (lateral and frontal) of the mandible in working and non-working quadrants. A treatment plan, including both periodontal and occlusal measures, was subsequently designed for each patient. About one-third of the patients decided to abstain from treatment, about 20 accepted only a non-surgical approach to periodontal therapy (scaling and root planing [SRP]), and about 50% accepted and received comprehensive treatment that included surgical pocket elimination (tooth debridement; SRP + surgery) as well as occlusal adjustment (if indicated). Some teeth in the SRP group received occlusal therapy, whereas other teeth with occlusal discrepancies were left untreated. It was observed that teeth with occlusal discrepancies had significantly deeper pocket depth values and higher mobility scores than teeth without occlusal "trauma", and also that teeth exposed to occlusal adjustment responded better (reduction in pocket depth) to SRP than teeth with remaining occlusal discrepancies.

Mobile teeth and probing depth

The findings in some of the clinical studies referred to above lend some support to the concept that occlusal trauma (and increased tooth mobility) may have a detrimental effect on the periodontium. Neiderud *et al*. (1992), however, in a Beagle dog study demonstrated that tissue alterations which occur at mobile teeth with clinically healthy gingivae (and normal height of the tissue attachment) may reduce the resistance offered by the periodontal tissues to probing. In other words, if the probing depth at two otherwise similar teeth–one non-mobile and one hypermobile–is recorded, the tip of the probe will penetrate 0.5 mm deeper at the mobile than at the non-mobile tooth. This finding must be taken into consideration when the above clinical data are interpreted.

Preclinical studies

Orthodontic-type trauma

In early experiments, the reaction of the periodontium was studied following the application of forces applied to teeth in one direction only. Biopsy specimens, including tooth and periodontium, were harvested after varying intervals and prepared for histologic examinations. Analysis of the sections (Häupl & Psansky 1938; Reitan 1951; Mühlemann & Herzog 1961; Ewen & Stahl 1962; Wærhaug & Hansen 1966; Karring *et al*. 1982) revealed that when a tooth is exposed to unilateral forces of a magnitude, frequency, or duration that its periodontal tissues are unable to withstand and distribute while maintaining the stability of the tooth, certain well-defined reactions develop in the periodontal ligament, eventually resulting in an adaptation of the periodontal structures to the altered functional demand. If the crown of a tooth is affected by such horizontally directed forces, the tooth tends to tilt (tip) in the direction of the force (Fig. 13-1). The forces result in the development of *pressure* and *tension zones* within the marginal and apical parts of the periodontium. The tissue reactions which develop in the *pressure zone* are characteristic of a mild inflammation (increased number of vessels, increased vascular permeability, vascular thrombosis, and disorganization of cells and collagen fiber bundles). If the magnitude of forces is within certain limits, the vitality of the periodontal ligament cells is maintained and bone-resorbing osteoclasts soon appear on the bone surface of the alveolus in the *pressure zone*. A process of *direct bone resorption* is initiated.

If the force applied is of higher magnitude, the periodontal ligament tissue in the *pressure zone* may become necrotic and undergo *hyalinization*. "Direct bone resorption", therefore, cannot occur. Instead, osteoclasts appear in marrow spaces within the adjacent bone tissue where the stress concentration is lower and a process of undermining or "*indirect bone resorption*" is initiated. Through this reaction the surrounding bone is resorbed until there is a breakthrough to the hyalinized tissue within the *pressure zone*. This breakthrough results in a reduction of the stress in this area, and cells from the neighboring bone or adjacent areas of the periodontal ligament can proliferate into the *pressure zone* and replace the previously hyalinized tissue, thereby re-establishing

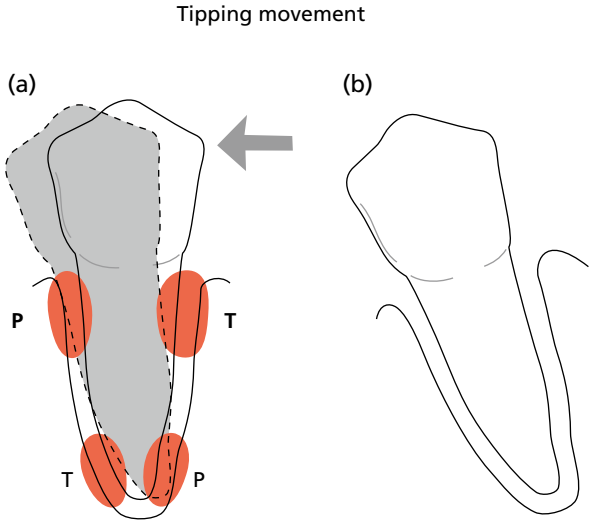

Fig. 13-1 (a) If the crown of a tooth is exposed to excessive, horizontally directed forces (arrow), pressure (P) and tension (T) zones will develop within the marginal and apical parts of the periodontium. The supra-alveolar connective tissue remains unaffected by force application. Within the pressure and tension zones, tissue alterations take place and eventually allow the tooth to tilt in the direction of the force. (b) When the tooth is no longer subjected to the trauma, complete regeneration of the periodontal tissues takes place. There is no apical downgrowth of the dentogingival epithelium.

the prerequisites for "direct bone resorption". Irrespective of whether the bone resorption is of a direct or an indirect nature, the tooth moves (tilts) further in the direction of the force.

Concomitant with the tissue alterations in the *pressure zone*, apposition of bone occurs in the *tension zone* in order to maintain the normal width of the periodontal ligament in this area. Because of the tissue reactions in the *pressure* and *tension* zones, the tooth becomes hypermobile. When the tooth has moved (tilted) to a position where the effect of the forces is nullified, healing of the periodontal tissues takes place in both the *pressure* and the *tension zones*, and the tooth becomes stable in its new position. In orthodontic tilting (tipping) movements, neither gingival inflammation nor loss of connective tissue attachment will occur at teeth with a healthy periodontium.

These tissue reactions do not differ fundamentally from those which occur as a consequence of *bodily tooth movement* in orthodontic therapy (Reitan 1951). The main difference is that the *pressure* and *tension zones*, depending on the direction of the force, are more extended in an apicocoronal direction along the root surface than in conjunction with the tipping movement (Fig. 13-2). The supra-alveolar connective tissue is not affected by the force, either in conjunction with tipping or in conjunction with bodily movements of the tooth. Unilateral forces exerted on the crowns of teeth, therefore, will not induce inflammatory reactions in the gingiva or cause loss of connective tissue attachment.

Studies have demonstrated, however, that orthodontic forces producing bodily (or tipping) movement of teeth may result in gingival recession and loss of connective tissue attachment (Steiner *et al*. 1981; Wennström *et al*. 1987). This breakdown of the attachment apparatus occurred at sites with gingivitis when, in addition, the tooth was moved through the envelope of the alveolar process. At such sites bone dehiscence became established and, if the covering soft tissue was thin (in the direction of the movement of the tooth), recession (attachment loss) occurred.

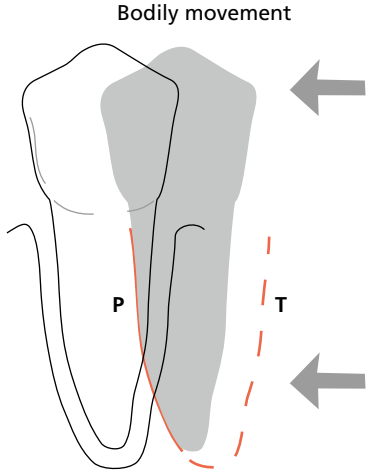

Fig. 13-2 When a tooth is exposed to forces which produce "bodily tooth movement", for example in orthodontic therapy, the pressure (P) and tension (T) zones, depending on the direction of the force, are extended over the entire tooth surface. The supra-alveolar connective tissue is not affected in conjunction either with tipping or with bodily movements of teeth. Forces of this kind, therefore, will not induce inflammatory reactions in the gingiva. No apical downgrowth of the dentogingival epithelium occurs.

Criticism has been directed at experiments in which only unilateral trauma is exerted on teeth (Wentz *et al*. 1958). It has been suggested that in humans, unlike in the animal experiments described above, the occlusal forces act alternately in one and then in the opposite direction. Such forces have been termed *jiggling forces*.

Jiggling-type trauma

Healthy periodontium with normal height

Experiments have been reported in which traumatic forces were exerted on the crowns of the teeth, alternately in the buccal/lingual or mesial/distal directions, and the teeth were not allowed to move away from the force (e.g. Wentz *et al*. 1958; Glickman & Smulow 1968; Svanberg & Lindhe 1973; Meitner 1975; Ericsson & Lindhe 1982). In conjunction with "*jiggling-type trauma*" no clear-cut *pressure* and *tension zones* can be identified, but rather there is a combination of pressure and tension on both sides of the jiggled tooth (Fig. 13-3).

The tissue reactions in the periodontal ligament provoked by the combined *jiggling* forces were found to be rather similar to those reported to occur in the pressure zone at orthodontically moved teeth, but with one important difference. The periodontal ligament space at jiggled teeth gradually increased in width on both sides of the tooth. During the phase when the periodontal ligament gradually increased in width, (1) inflammatory changes were present in the ligament tissue, (2) active bone resorption occurred, and (3) the tooth displayed signs of gradually increasing (*progressive*) mobility. When the effect of the forces applied had been compensated for by the increased width of the periodontal ligament space, the ligament tissue showed no signs of increased vascularity or exudation. The tooth was hypermobile but the mobility was no longer *progressive* in character. Distinction should thus be made between *progressive* and *increased* tooth mobility.

In *jiggling-type trauma* experiments performed in animals with a normal periodontium, the supra-alveolar connective tissue was not influenced by the occlusal forces. This means that a gingiva which was healthy at the start of the experiment remained healthy. It was also observed that an overt gingival lesion was not aggravated by the jiggling forces.

Healthy periodontium with reduced height

Progressive periodontal disease is characterized by gingival inflammation and a gradually developing loss of connective tissue attachment and alveolar bone. Treatment of periodontal disease, that is removal of plaque and calculus and elimination of

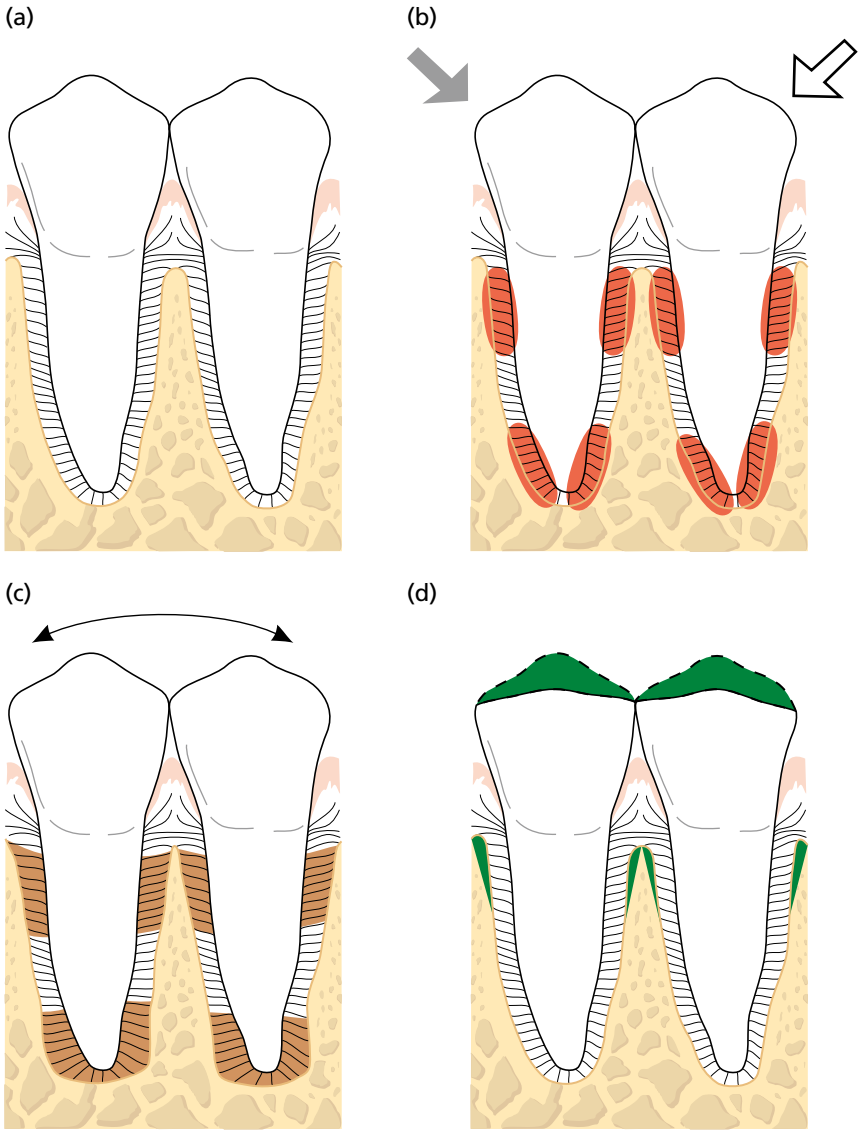

Fig. 13-3 Two mandibular premolars with normal periodontal tissues (a) are exposed to jiggling forces (b), as illustrated by the two arrows. The combined tension and pressure zones (encircled areas) are characterized by signs of acute inflammation, including collagen resorption, bone resorption, and cementum resorption. As a result of bone resorption, the periodontal ligament space gradually increases in size on both sides of the teeth as well as in the periapical region. (c) When the effect of the force applied has been compensated for by the increased width of the periodontal ligament space, the ligament tissue shows no signs of inflammation. The supra-alveolar connective tissue is not affected by the jiggling forces and there is no apical downgrowth of the dentogingival epithelium. (d) After occlusal adjustment the width of the periodontal ligament becomes normalized and the teeth are stabilized.

pathologically deepened pockets, will result in the re-establishment of a healthy periodontium but with reduced height. The question is whether a healthy periodontium with reduced height has a capacity similar to that of the normal periodontium to adapt to traumatizing occlusal forces (secondary occlusal trauma).

This problem has also been examined in a preclinical study (Ericsson & Lindhe 1977). Destructive periodontal disease was initiated in premolars of dogs by allowing the animals to accumulate plaque and calculus. When around 50% of the periodontal tissue support had been lost, the involved teeth were exposed to debridement and surgical pocket elimination. Following healing, these teeth had a reduced but healthy periodontium (Fig. 13-4a). During the subsequent months of continued plaque control, certain premolars were exposed to traumatizing jiggling forces (Fig. 13-4b). The periodontal tissues in the combined *pressure* and *tension zones* reacted to the application of forces with inflammation as well as by bone resorption. In the initial phase, the traumatized teeth displayed signs of *progressive* tooth mobility and a progressive increase of the size of the periodontal ligament. After several weeks of jiggling, there was no further increase in the mobility (Fig. 13-4c). The active bone resorption had ceased and the markedly widened periodontal ligament tissue had regained its normal composition. The teeth were hypermobile at this stage, but surrounded by a periodontal ligament which had adapted to the altered functional demands.

During the entire experimental period the supra-alveolar connective tissue remained unaffected by the jiggling forces. There was no further loss of connective tissue attachment and no further downgrowth of dentogingival epithelium. The results from this study clearly revealed that, within certain limits, a healthy periodontium with reduced height has a capacity similar to that of a periodontium with normal height to adapt to altered functional demands. Removal of the jiggling forces ("occlusal adjustment") will in this situation result in a normalization of the width of the periodontal ligament (Fig. 13-4d).

Plaque-associated periodontitis

Experiments carried out on humans and animals have demonstrated that *occlusal trauma* cannot induce pathologic alterations in the supra-alveolar connective tissue, in other words cannot produce inflammatory lesions in a normal gingiva or aggravate a gingival lesion and cannot induce loss of connective tissue attachment. The question remains whether or not abnormal occlusal forces can influence the spread of the plaque-associated lesion and enhance the rate of tissue destruction in periodontal disease. This has been studied in animal experiments (Lindhe & Svanberg 1974; Meitner 1975; Nyman *et al*. 1978; Ericsson & Lindhe 1982; Polson & Zander 1983) in which progressive and destructive periodontal disease was first initiated in dogs or monkeys by allowing the animals to accumulate plaque and calculus. Some of the premolars that were involved in a progressive periodontal disease process (periodontally involved) were also exposed to occlusal trauma.

"Traumatizing" jiggling forces (Lindhe & Svanberg 1974) were exerted on periodontally involved

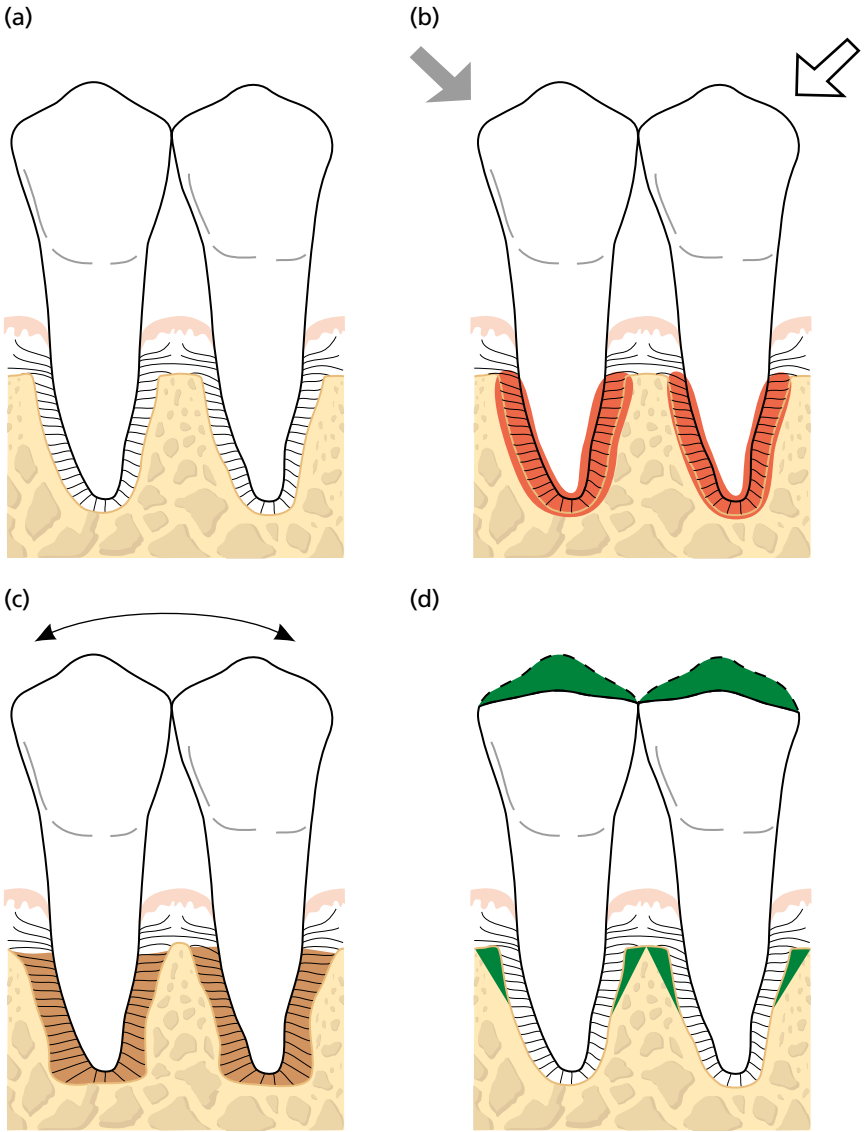

Fig. 13-4 (a) Two mandibular premolars are surrounded by a healthy periodontium with reduced height. (b) If such premolars are subjected to traumatizing forces of the jiggling type, a series of alterations occurs in the periodontal ligament tissue. (c) These alterations result in a widened periodontal ligament space and increased tooth mobility, but do not lead to further loss of connective tissue attachment. (d) After occlusal adjustment, the width of the periodontal ligament is normalized and the teeth are stabilized.

premolars and were found to induce certain tissue reactions in the combined *pressure/tension zones*. Within a few days of the onset of the jiggling forces, the periodontal ligament tissue in these zones displayed signs of inflammation. On the adjacent bone surfaces a large number of osteoclasts were present. Since the teeth could not orthodontically move away from the jiggling forces, the periodontal ligament on both sides of the tooth gradually increased in width, the teeth became hypermobile (*progressive* tooth mobility), and angular bony defects could be detected on the radiographs. The effect of the forces was eventually nullified by the increased width of the periodontal ligament.

If the forces applied were of a magnitude to which the periodontal structures could adapt, the *progressive* increase of the tooth mobility terminated within a few weeks. The active bone resorption ceased, but the angular bone destruction persisted as well as the increased tooth mobility. The periodontal ligament had an increased width, but a normal tissue composition. Biopsy specimens including the periodontally involved teeth revealed that this process of adaptation had occurred with no further attachment loss (Fig. 13-5) (Meitner 1975). This means that occlusal forces which allow adaptive alterations to occur in the *pressure/tension* zones of the periodontal ligament will not aggravate a plaque-associated periodontitis (Fig. 13-6).

If, however, the magnitude and direction of the jiggling forces were such that, during the course of the study, the tissues in the pressure/tension zones could not adapt, the injury had a more permanent character. For several months the periodontal ligament in the pressure/tension zones displayed signs of inflammation and osteoclastic bone resorption. This resulted in a gradual widening of the periodontal ligament (Fig. 13-7). As a consequence, the resulting angular bone destruction was continuous and the mobility of the teeth remained progressive. In this dog model, additional portions of the connective tissue attachment were lost and periodontal tissue destruction became more severe (Figs. 13-8, 13-9) (Lindhe & Svanberg 1974).

On the other hand, findings from more short-term experiments using a monkey model (Polson & Zander 1983), failed to support the observations of Lindhe and Svanberg (1974) and Ericsson and Lindhe (1982). Polson and Zander (1983) reported that trauma superimposed on periodontal lesions associated with angular bony defects caused increased loss of alveolar bone, but failed to produce additional loss of connective tissue attachment.

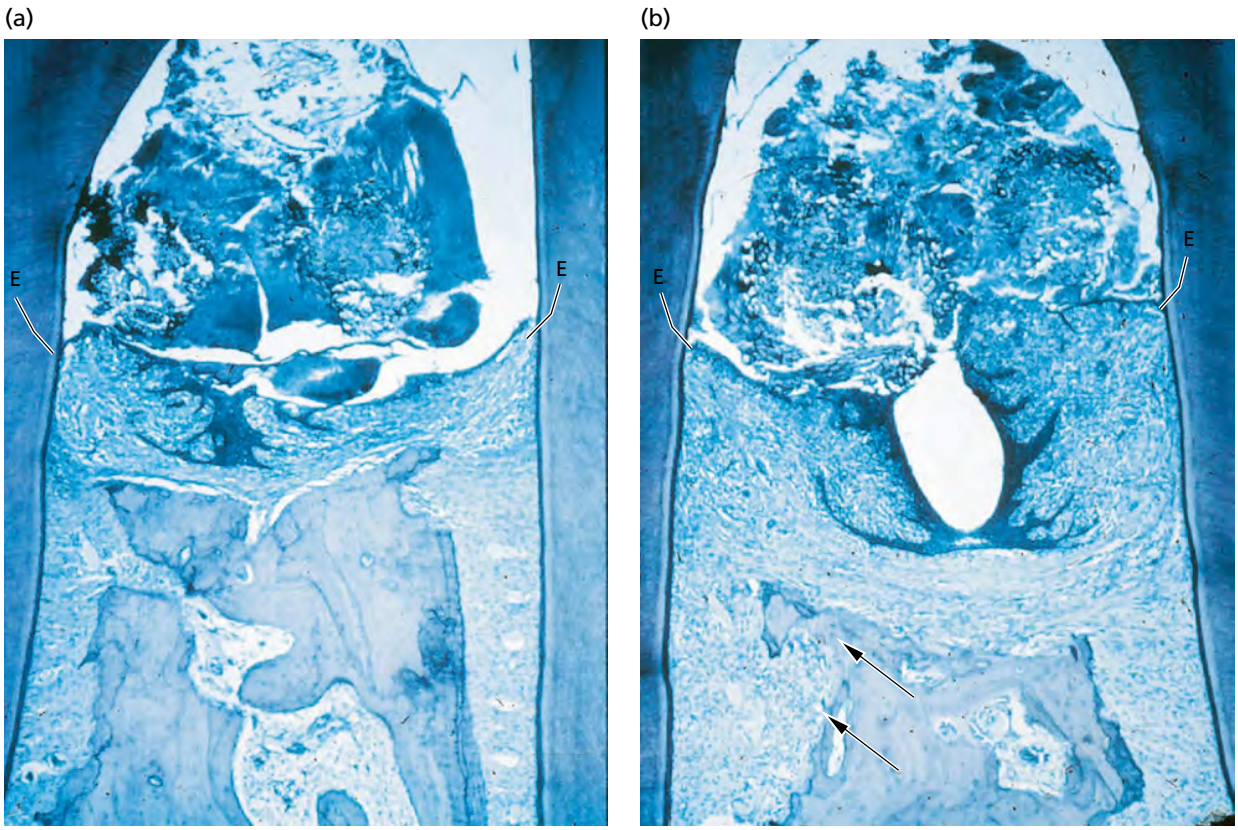

Fig. 13-5 (a) A composite photomicrograph illustrating the interdental space between two pairs of teeth. The teeth have been subjected to experimental, ligature-induced periodontitis and in (b) also to repetitive mechanical injury. In (b), there is considerable loss of alveolar bone and an angular widening of the periodontal ligament space (arrows). However, the apical downgrowth of the dentogingival epithelium in the two areas in (a) and (b) is similar. E indicates the apical level of the dentogingival epithelium. (Source: Courtesy of S.W. Meitner.)

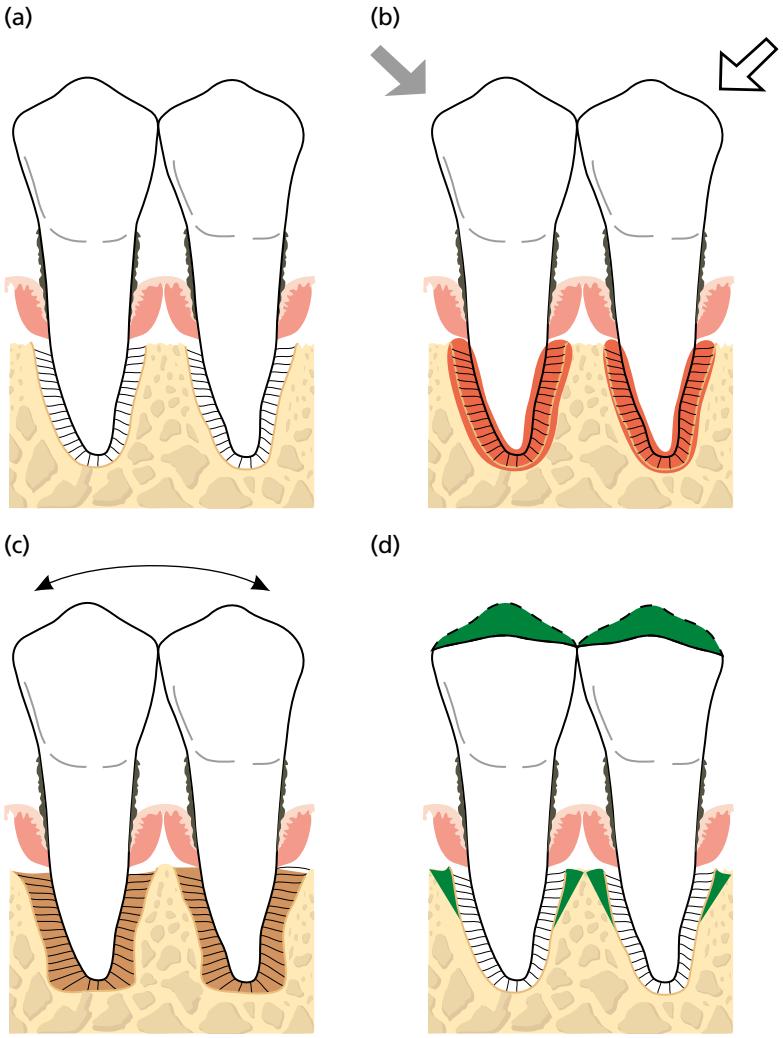

Fig. 13-6 (a) Two mandibular premolars with supra- and subgingival plaque, advanced bone loss, and periodontal pockets of a suprabony character. Note the connective tissue infiltrate (shadowed areas) and the uninflamed connective tissue between the alveolar bone and the apical portion of the infiltrate. (b) If these teeth are subjected to traumatizing forces of the jiggling type, pathologic and adaptive alterations occur within the periodontal ligament space. (c) These tissue alterations, which include bone resorption, result in a widened periodontal ligament space and increased tooth mobility, but no further loss of connective tissue attachment. (d) Occlusal adjustment results in a reduction of the width of the periodontal ligament and in less mobile teeth.

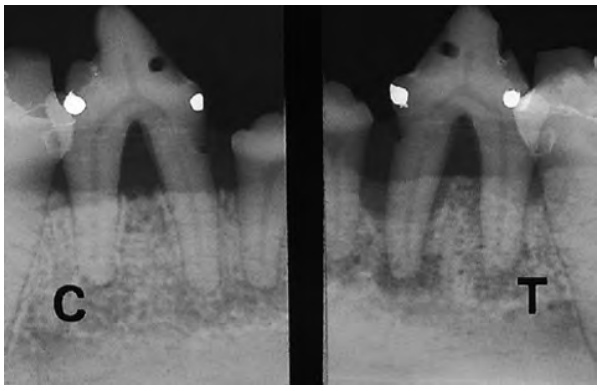

Fig. 13-7 Radiographic appearance of one test tooth (T) and one control tooth (C) at the termination of an experiment in which periodontitis was induced by ligature placement and plaque accumulation, and in which trauma of the jiggling type was induced. Note the angular bone loss particularly around the mesial root of the mandibular premolar (T) and the absence of such a defect at the mandibular premolar (C). (Source: Lindhe & Svanberg 1974. Reproduced with permission from John Wiley & Sons.)

Conclusion

Clinical and preclinical studies have produced convincing evidence that neither unilateral forces nor jiggling forces, applied to teeth with a healthy periodontium, result in pocket formation or in loss of connective tissue attachment. *Occlusal trauma cannot induce periodontal tissue breakdown*. Occlusal trauma does, however, result in resorption of alveolar bone, leading to an increased tooth mobility which can be of a transient or permanent character. This bone resorption with resulting increased tooth mobility should be regarded as a physiologic adaptation of the periodontal ligament and surrounding alveolar bone to the traumatizing forces, that is to altered functional demands.

In teeth involved in progressive periodontitis, occlusal trauma may, under certain conditions, enhance the rate of progression of the disease. It is important to realize that in such cases, treatment directed towards the trauma alone, that is occlusal adjustment or splinting, may reduce the mobility of

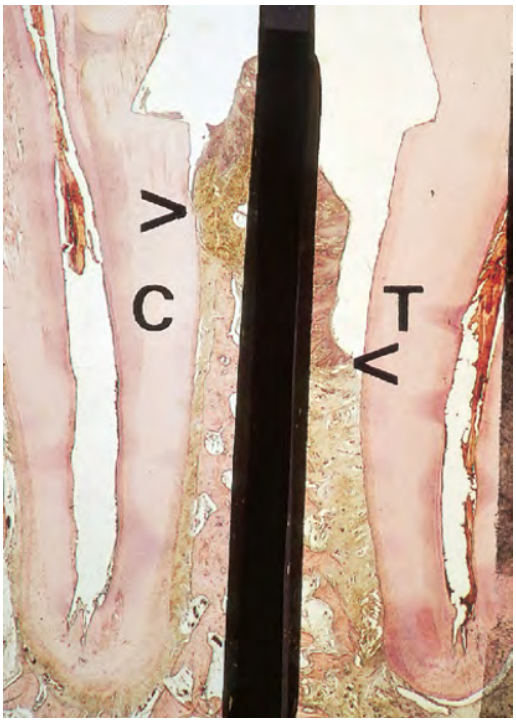

Fig. 13-8 Microphotographs from one control (C) and one test (T) tooth after 240 days of experimental periodontal tissue breakdown and 180 days of trauma from occlusion of the jiggling type (T). The arrowheads denote the apical position of the dentogingival epithelium. The attachment loss is more pronounced in T than in C. (Source: Lindhe & Svanberg 1974. Reproduced with permission from John Wiley & Sons.)

the traumatized teeth and result in some regrowth of bone, but it will not influence the features of the plaque-associated lesion.

PART II: PERI-IMPLANT TISSUES

Endosseous osseointegrated oral implants have been suggested to serve as anchorage for orthodontic appliances where the existing dentition does not provide sufficient anchorage. Both clinical (Turley *et al*. 1988; Ödman *et al*. 1988; Haanaes *et al*. 1991; Ödman *et al*. 1994) and experimental (Wehrbein & Diedrich 1993; Wehrbein *et al*. 1996) studies have demonstrated that osseointegrated implants were able to provide sufficient and stable anchorage for tooth movement during the time period of orthodontic therapy, thereby eliminating the need to observe Newton's third law according to which an applied force can be divided into an *action* component and an equal and opposite *reaction* moment.

In long-term clinical studies of various two-stage submerged implant systems, however, implant losses have been attributed to *overloading* or *excessive loading*. In patients with edentulous (Adell *et al*. 1981; Lindquist *et al*. 1988) and partially edentulous jaws (Jemt *et al*. 1989; Quirynen *et al*. 1992), most of the implant losses were considered to be the result of excessive occlusal loading. Although it has been shown that early loading of oral implants may impede successful osseointegration (Sagara *et al*. 1993), the effect of excessive occlusal functional forces following successful osseointegration has not been documented so far. However, studies by Isidor (1996, 1997) have demonstrated that loading of implants through the creation of a massive supraocclusion, leading to excessive–and most likely non-physiologic–laterally directed occlusal forces, established a high risk for the loss of osseointegration in loosely trabecular bone. Nevertheless, in one of four experimental animals, even such excessive loading forces were unable to jeopardize the interfacial union of the alveolar bone with the implant surface.

The forces applied in the studies mentioned were characterized as being very high and of short duration. However, they could not be quantified. None of the experimental studies analyzed the direct relationship between changes in the stress and strain applied to oral implants during functional loading, and the tissue reactions of the surrounding alveolar bone. For the evaluation of the etiology and pathogenesis of implant losses due to overload, such information would appear to be of crucial importance.

Orthodontic loading and alveolar bone

In order to evaluate the tissue reactions adjacent to oral implants following loading with well-defined forces and to relate these to the strain values applied on the trabecular surface of the alveolar bone, an animal study was performed using finite element analysis (FEA) to determine the cellular activity (Melsen & Lang 2001). In six adult monkeys, the lower first and the second premolars as well as the second molars were removed. After 6 months, two specially designed screw implants were inserted in the region of the lower left second premolar and second molar. After a further 3 months, a square rod with three notches at different levels was inserted and tightened to the top of the implants. The notches served as a reference for the measurements of the implant displacement. A flat disk was placed between the implant and the rod. To this disk two extensions were welded buccally and lingually in a way that allowed a coil spring to be placed as close as possible to the estimated level of the center of resistance (Fig. 13-10). Immediately before the buccal and lingual springs were inserted, the extensions were placed on the occlusal surface of the implants. Impressions of each segment were taken. Subsequently, two measurements were performed with an electronic strain gauge-based measuring device. For anchorage of the device, a cast splint was fitted to the anterior segment of the dentition and each of the implant screws. One measurement was taken between the notches close to the implant connection, and another between the notches close to the top of the square rod extensions. These were repeated after 11 weeks, in other words at the termination of the orthodontic loading period.

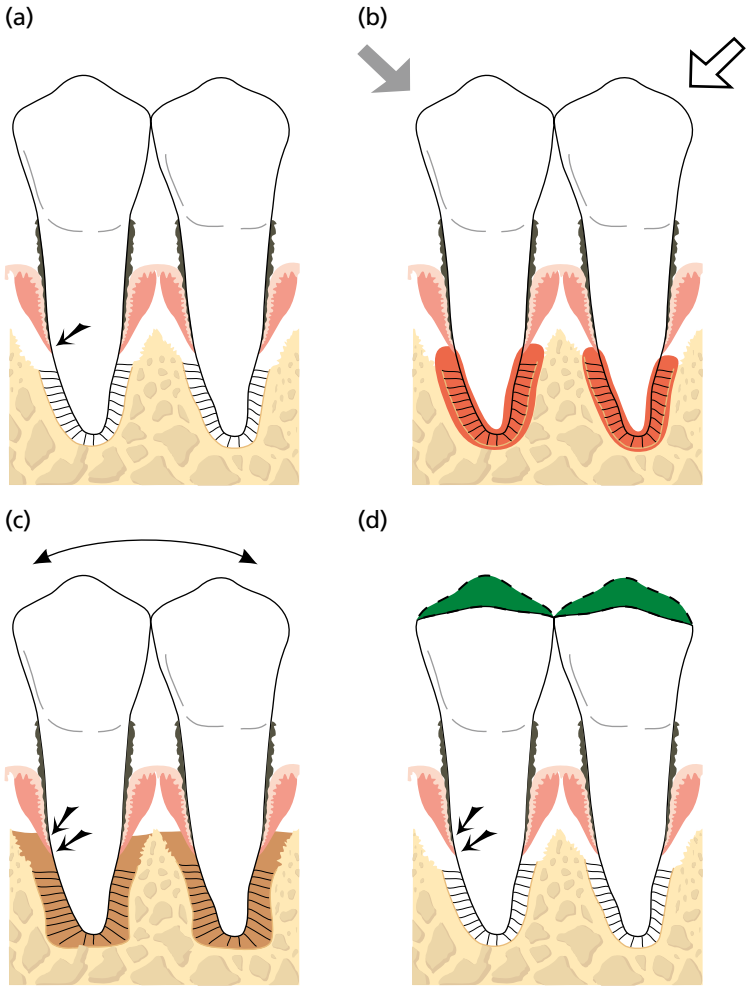

Fig. 13-9 (a) A tooth where subgingival plaque has mediated the development of an infiltrated soft tissue (shadowed area) and an infrabony pocket. (b) When trauma from occlusion of the jiggling type is inflicted (arrows) on the crown of this tooth, the associated pathologic alterations occur within a zone of the periodontium which is also occupied by the inflammatory cell infiltrate (shadowed area). In this situation, the increasing tooth mobility may also be associated with an enhanced loss of connective tissue attachment and further downgrowth of dentogingival epithelium; compare arrows in (c) and (d). Occlusal adjustment will result in a narrowing of the periodontal ligament, less tooth mobility, but no improvement of the attachment level (d). (Source: Lindhe & Ericsson 1982. Reproduced from the American Academy of Periodontology.)

The direction and magnitude of the displacement of the implant as a result of loading could thus be calculated in the sagittal plane.

Following the baseline recordings, springs extending from the anterior to the posterior implant were attached to the power arms buccally and lingually (Fig. 13-10). Total load applied to each implant varied from 100 to 300 cN. One monkey served as a control with the implants in this animal not subjected to any loading.

At the end of the experiment, the monkeys were sacrificed. Subsequently, parallel horizontal tissue sections from the coronal to the apical end of the implants were cut and stained with fast green. A grid consisting of three concentric circular lines was projected onto the sections, with each of these lines intersected by four equidistant radial lines starting at the center of the grid and coinciding with the central axis of the implants. The four radial lines divided the circle into eight areas, two in the direction of the force (A: compression zone), two in the opposite direction (B: tension zone), and four lateral to the implants (C and D: shear zone) (Fig. 13-11).

At a magnification of ×160, the extent of resorption lacunae and the extent of the trabecular bone surfaces covered by osteoid as a fraction of the total were assessed. Also, using morphometry, bone density

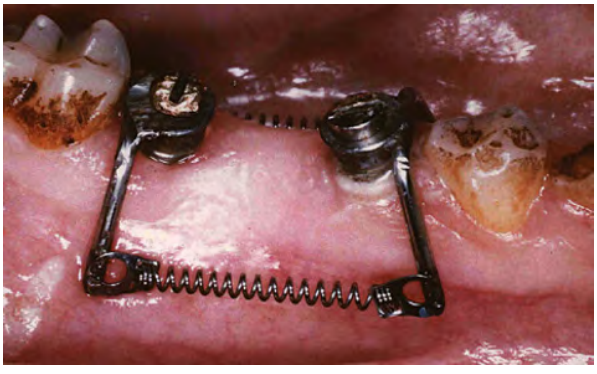

Fig. 13-10 Nickel–titanium coil springs applied for a continuous loading through the center of resistance.

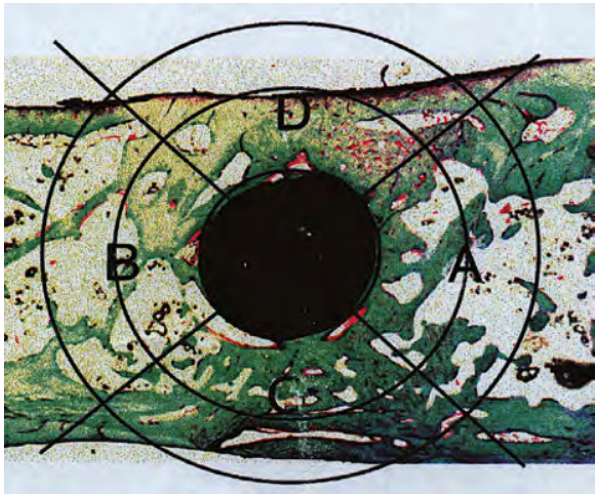

Fig. 13-11 Horizontal section of the implant with the projected grid used for the histomorphometric evaluation of different regions surrounding the implant. Region A is submitted to compression, region B to tension, and regions C and D to shearing forces.

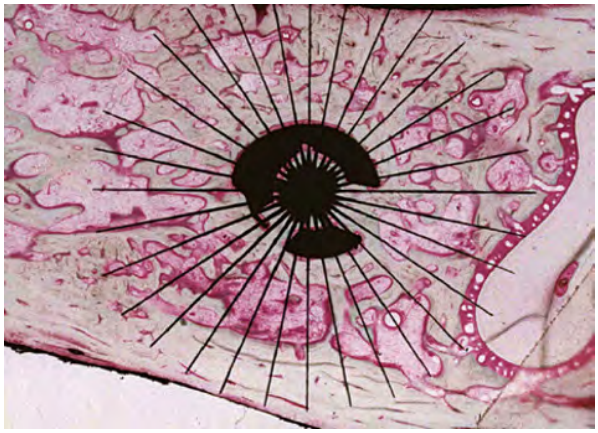

Fig. 13-12 Horizontal section of the implant onto which a grid with 32 radial lines was projected. The evaluation of the osseointegration included the determination of the percentage of direct bone–implant contact (×160).

was evaluated within each quadrant. Furthermore, to measure the amount of osseointegration, the proportion of direct bone–implant contact was calculated by projecting a grid consisting of 32 radial lines extending from the center of the implants onto the section to be analyzed (Fig. 13-12).

None of the implants had lost osseointegration after 11 weeks of orthodontic loading, but loading significantly influenced the turnover of the alveolar bone in the vicinity of the implants. Bone apposition was most frequently found, when the calculated strain varied between 3400 and 6600 μstrain. On the other hand, when the strain exceeded 6700 μstrain, the remodeling of the bone resulted in a net loss of bone density.

This study clearly supports the theory that apposition of bone around an oral implant is the biologic response to a mechanical stress below a certain threshold, whereas loss of marginal bone or complete loss

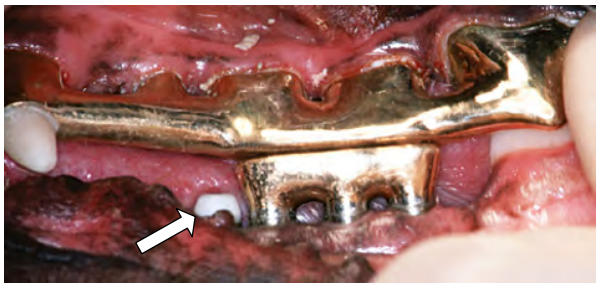

Fig. 13-13 The fixed dental prosthesis (FDP) supported by maxillary canines and premolars. The FDP is installed on implants in the mandible to provide masticatory function. The non-loaded control implant is mesial to the FDP (arrow). (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

of osseointegration may be the result of mechanical stress beyond this threshold. Hence, occlusal forces would have to substantially exceed the physiologic range before occlusal contacts could jeopardize the tissue integrity of an implant.

Several other studies using orthodontic forces have confirmed apposition or increase in bone density surrounding an oral implant, rather than loss of bone (Roberts *et al*. 1984; Wehrbein & Diedrich 1993; Asikainen *et al*. 1997; Akin-Nergiz *et al*. 1998).

Bone reactions to functional loading

A study addressed the reaction of peri-implant bone after longstanding functional loading compared with non-loaded controls (Berglundh *et al*. 2005). After extraction of all mandibular premolars, four implants were placed in one side of the mandible, and four implants were installed in the contralateral side. Three months after abutment connection, fixed dental prostheses (FDPs) were placed on the maxillary canines and premolars (Fig. 13-13). FDPs were also installed on three of the four mandibular implants in both sides. The fourth implant remained unloaded and served as a control (Fig. 13-14). Radiographs were obtained from each site following implant installation, abutment connection, and FDP placement. All radiographs were repeated after 10 months of functional loading. At this time, biopsies were obtained and analyzed histologically.

Radiographic analysis revealed that the largest amount of bone loss occurred following implant installation and abutment connection. However, as a result of functional loading, bone loss was small and did not differ significantly from the unloaded control sites (Fig. 13-15).

Histologic analysis showed that implants exposed to 10 months of functional loading had more direct bone–implant contact than their unloaded counterparts (Fig. 13-16).

Based on the radiographic and histologic results, this study demonstrated that *functional loading of implants may enhance osseointegration* (direct bone–implant contact) rather than induce marginal bone

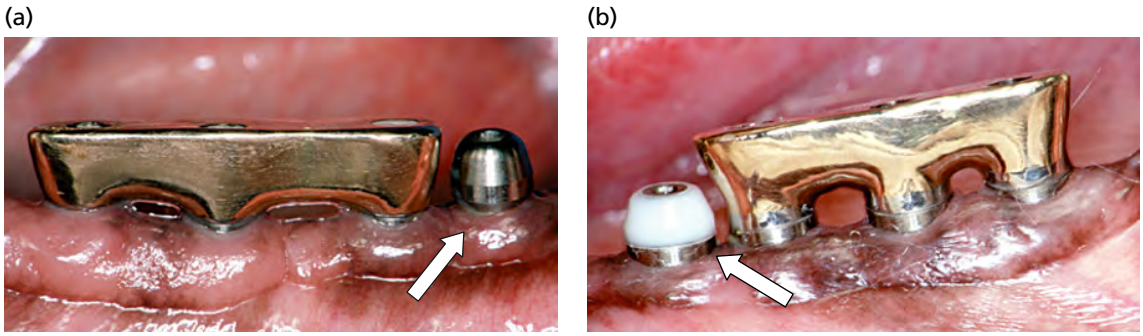

Fig. 13-14 Fixed dental prostheses fabricated of gold and installed on implants for functional loading. Unloaded implant as control (arrows). (a) Right and (b) left side of the mandible. (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

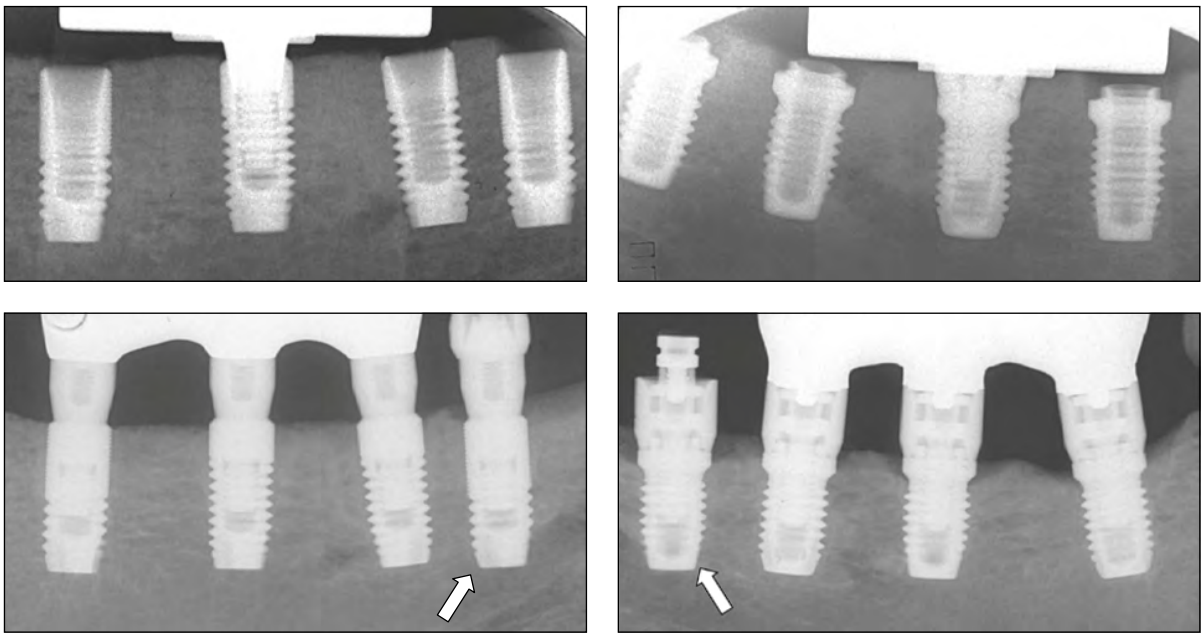

Fig. 13-15 Radiographs obtained from implants on the left and right side immediately after implant installation (top row) and following 10 months of functional loading (bottom row). Unloaded control implants are indicated with arrows.

loss and hence, any bone loss should not be attributed to loading of implants. Whenever marginal bone loss is observed around implants in function, peri-implantitis should be considered (see Chapter 20).

Excessive occlusal load on implants

The effect of *excessive occlusal load* following placement of titanium implants in the presence of healthy peri-implant mucosal tissues was evaluated in an experimental study (Heitz-Mayfield *et al*. 2004). In six dogs, two titanium plasma-sprayed (TPS) implants and two sandblasted, large grit, acid-etched (SLA) implants were placed on each side of the mandible (Fig.13-17a). A total of 45 implants were evaluated. Following 6 months of healing (Fig. 13-17b), gold crowns were placed on implants on the test side of the mandible. The crowns were in supraocclusal contact with the opposing teeth in order to create an excessive occlusal load (Fig. 13-17c). Implants on the control side were not loaded. Plaque control was performed throughout the experimental period. Clinical measurements and standardized radiographs (Fig. 13-17d) were obtained at baseline and 1, 3, and 8 months after loading. At 8 months, all implants were osseointegrated, the dogs were euthanized, and histologic analyses were performed. The mean probing depth was 2.5 ± 0.3 and 2.6 ± 0.3 mm at the unloaded and loaded implants, respectively. Radiographically, the mean distance from the implant shoulder to the marginal bone level was 3.6 ± 0.4 mm in the control group and 3.7 ± 0.2 mm in the test group. There were no statistically significant changes in any of the parameters from baseline to 8 months in the loaded and unloaded implants.

Histologic evaluation (Fig. 13-18) showed a mean mineralized bone–implant contact of 73% in the control implants and 74% in the test implants, with no statistically significant difference between test and control implants.

Table 13-1 shows the level of osseointegration in relation to the total length of the implant after 8 months of excessive loading or non-loading. These values were generally slightly below those of the alveolar bone height (Table 13-2) for all sites and surfaces in both test and control implants. The

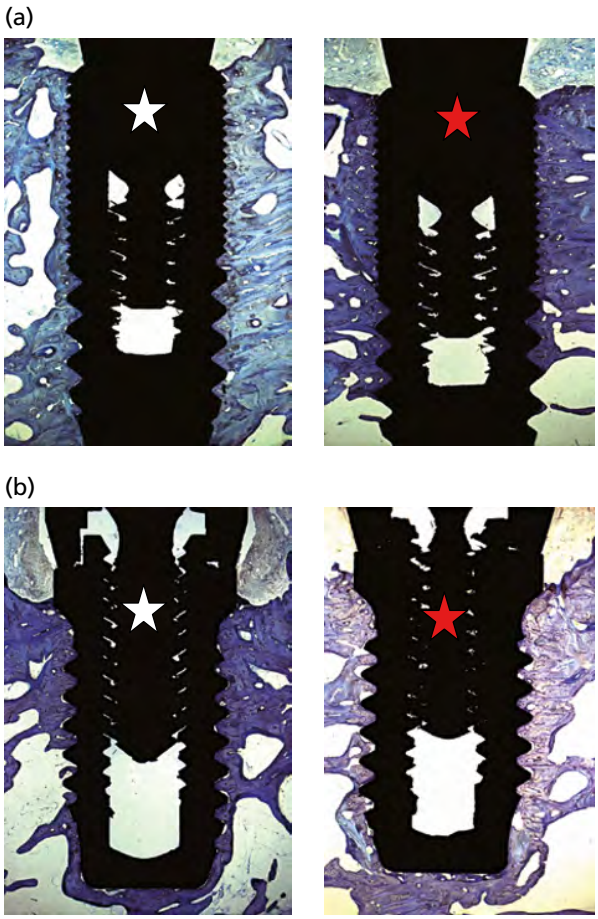

Fig. 13-16 (a) Non-loaded control implant (AstraTech®) after 10 months (white star) and functionally loaded (AstraTech®) implant (red star) after 10 months. (b) Non-loaded control implant (Brånemark®) after 10 months (white star) and functionally loaded (Brånemark®) implant (red star) after 10 months. (Source: Berglundh *et al*. 2005. Reproduced with permission from John Wiley & Sons.)

differences varied between 1.1% and 3.7% and were not statistically significant.

Likewise, there were no statistically significant differences between the excessively loaded and the unloaded implants in terms of peri-implant bone density either at the implant–bone interface or at 1 mm from the implant surface (Fig. 13-18) after 8 months.

Since none of the clinical, radiographic, or histologic parameters yielded statistically significant differences between non-loaded and excessively loaded implants, the study clearly demonstrates that, in the presence of peri-implant mucosal health, a period of 8 months of *excessive occlusal load* on titanium implants does *not* result in loss of osseointegration or marginal bone loss when compared with non-loaded implants.

More recently, implants (with both SLA and SLActive surfaces) that were excessively loaded using cantilever reconstructions were evaluated for stability over a period of 6 months using resonance frequency analysis (RFA) (Lima *et al*. 2019). In five dogs, all mandibular premolars were extracted bilaterally. After 3 months, full thickness flaps were raised, and six implants (three SLA and three SLActive) were installed in a block-randomized split-mouth design (day 0). After 4 weeks, implants were restored on each side of the mandible as follows: one single crown with stable occlusal contacts (SC); one crown and a 13.5-mm cantilever unit with excessive occlusal contacts (OL); and one non-loaded implant (NL) protected by the cantilever unit (Fig. 13-19). The vertical dimension was increased by 3 mm. RFA was evaluated on day 0 and weekly for 2–10 weeks after surgery, and at 12 weeks and 24 weeks after loading.

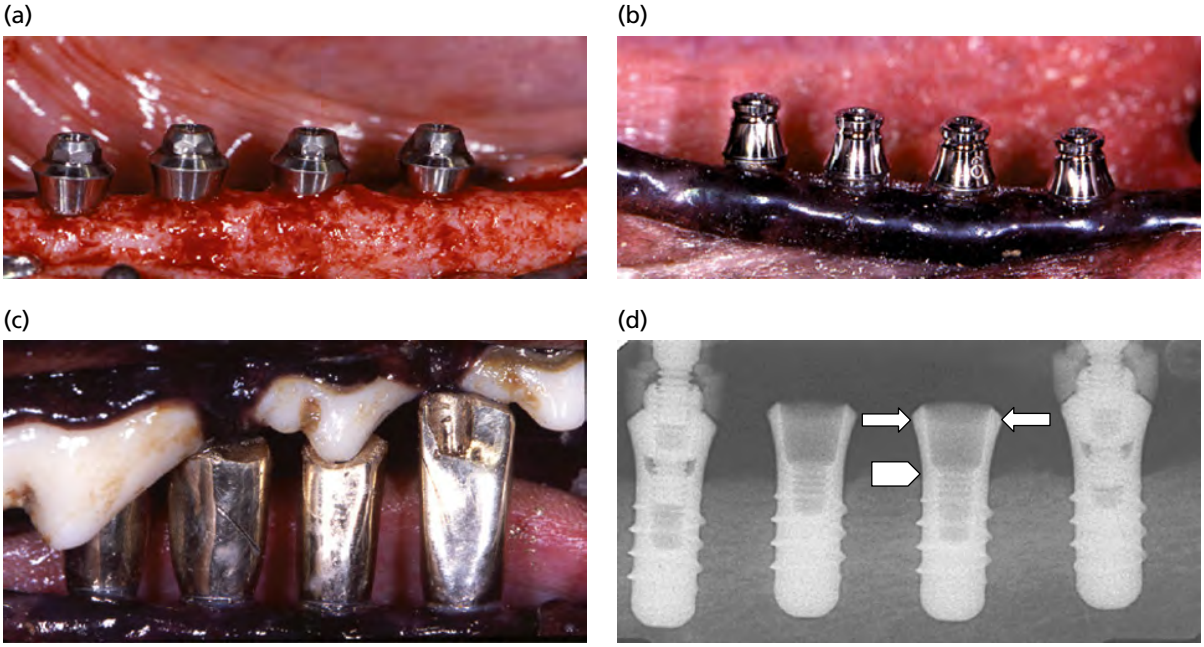

Fig. 13-17 (a) Four implants at the time of placement in one side of the mandible. (b) The implants after 6 months of non-submerged healing. (c) The test side of the mandible in one dog. Note the four single gold crowns in supraocclusal contact with the opposing teeth. (d) Standardized radiograph showing the level of the implant shoulder (arrows), and the first bone–implant contact visible in the radiograph (arrowhead) at the mesial and distal surfaces of the implant.

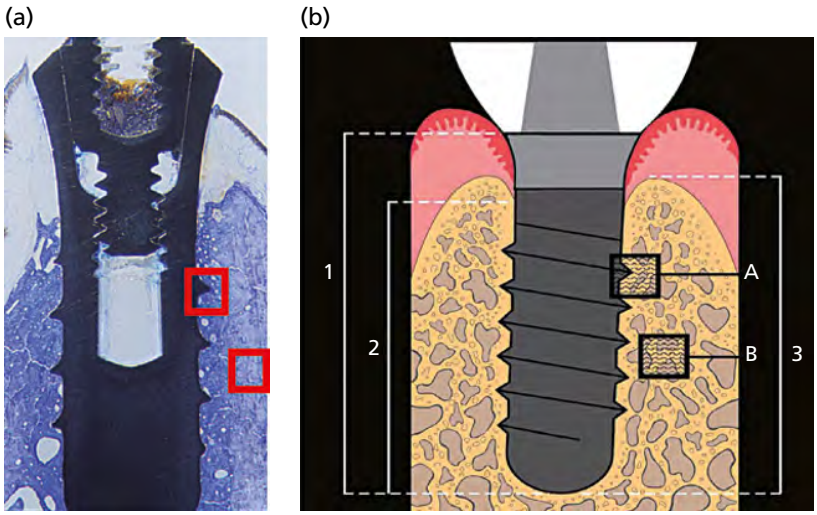

Fig. 13-18 (a) Histologic and (b) schematic representation of the histomorphometric measurements. 1, Implant length = distance from the base of the implant to the implant shoulder; 2, distance from the base of the implant to the most coronal point of bone–implant contact; 3, distance from the base of the implant to the alveolar bone crest. A, Percentage of mineralized bone density adjacent to the implant surface and B, 1 mm distant from the implant surface. Red frames in (a) correspond to zones A and B in (b).

Table 13-1 Buccal and lingual percentages of the level of osseointegration (bone–implant contact) in relation to the total length of the implant for control and test implants with a titanium plasma-sprayed (TPS) or sandblasted, large grit, acid-etched (SLA) surface after 8 months.

	Buccal osseointegration		Lingual osseointegration	
	TPS	SLA	TPS	SLA
Number	12	11	12	11
Control (%)	57.9	60.4	67.5	66.7
Number	10	12	10	12
Test (%)	62.1	59.2	68	68

Table 13-2 Buccal and lingual percentages of alveolar bone height in relation to the total length of the implant for control and test implants with a titanium plasma-sprayed (TPS) or sandblasted, large grit, acid-etched (SLA) surface after 8 months.

	Buccal osseointegration		Lingual osseointegration	
	TPS	SLA	TPS	SLA
Number	12	11	12	11
Control (%)	61.1	63.8	69.5	68.7
Number	10	12	10	12
Test (%)	64.7	60.3	71.4	70.2

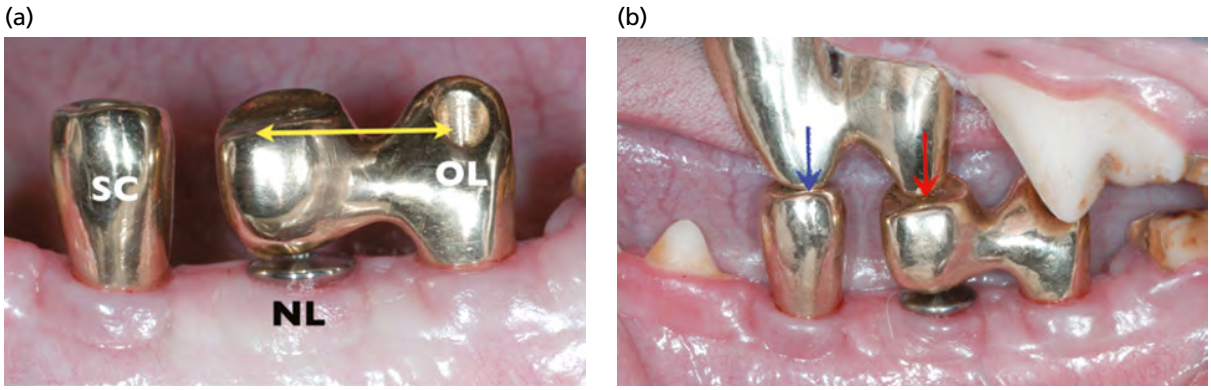

Fig. 13-19 Osseointegrated implants (a) not in occlusal contact and (b) in occlusal contact: a single crown unit with normal occlusal contacts and stable occlusion (SC) (blue arrow); a single non-loaded implant (NL) protected by a cantilever beam of 13.5 mm in length (yellow arrow); and an overloaded abutment (OL) with overt occlusal contacts through the cantilever beam (red arrow).

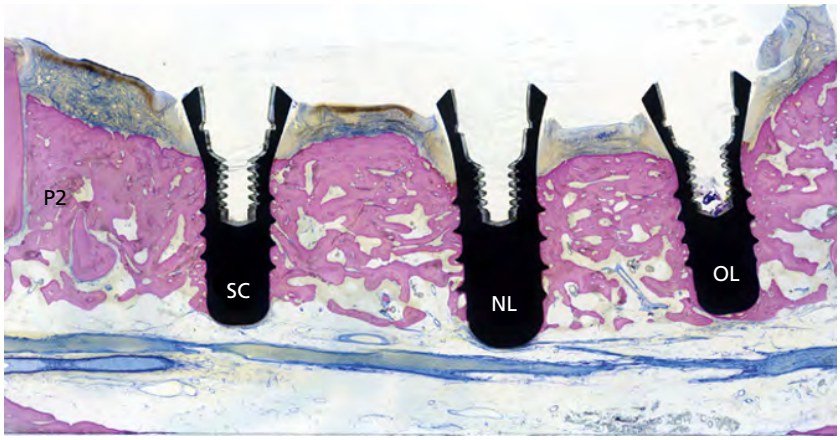

Fig. 13-20 Histological micrograph representing SC (single crown, normally occlusally loaded), NL (non-loaded), and OL (excessively occlusally loaded) implants after 6 months in function. P2, second mandibular premolar. Irrespective of loading conditions, full osseointegration of all units was achieved. Although the junctional epithelium had a normal length and was confined to the smooth surface part of the implants, the coronal-most bone in contact with the implant was on the rough part of the implant surface. Ground section, 80-µm thick. (Source: Lima *et al*. 2019. Reproduced with permission from Wiley.)

The mean implant stability quotient (ISQ) assessed by the RFA ranged from 58 to 67 for implants immediately after placement, and then increased to 74–78 at the time of crown placement 4 weeks later. Six months after loading, ISQ values varied between 74 and 80 with no significant differences between NL, SC, and OL sites. This was confirmed by a subsequent histological analysis of block sections prepared from the three different sites (Fig. 13-20) (Lima *et al*. 2019). This confirms previous results and documents that excessive occlusal load on implants does not affect osseointegration.

Static and cyclic loads on implants

While the study by Berglundh *et al*. (2005) addressed the possible influence of functional loading on the marginal bone levels of implants by applying a flat occlusal plane scheme and physiologic forces, many authors have studied the influence of loading forces exceeding physiologic functional conditions and impacting on the implants in a non-axial direction (Barbier & Schepers 1997; Gotfredsen *et al*. 2001a–c, 2002; Heitz-Mayfield *et al*. 2004).

The bone tissue reaction to axial loading was evaluated using conventional three-unit FDPs in the mandible of dogs, and compared with that to non-axial loading provoked by installing a distal cantilever of two implants (Barbier & Scheppers 1997). Bone remodeling was modest at the implant sites supporting conventional FDPs, while the non-axial load induced by the cantilever FDPs yielded a more pronounced bone response, including a higher activity of osteoclasts in the peri-implant bone. However, bone levels were not affected. This was interpreted as an adaptive phenomenon within the peri-implant bone as a result of non-axial loading.

The bone reactions around osseointegrated implants to static load were analyzed in three studies in dogs (Gotfredsen *et al*. 2001a–c, 2002). In the first study (Gotfredsen *et al*. 2001a), a lateral static load was induced by an orthodontic expansion screw at eight implants with a rough surface (TPS) in each dog. After a loading period of 24 weeks, during which time the screws were activated every 4 weeks from 0.0, 0.2, 0.4, to 0.6 mm, histologic and histometric analysis revealed no marginal bone loss at loaded and unloaded implant sites. Peri-implant bone density and mineralized bone–implant contact was higher at the loaded than the unloaded implant sites. This, again, was interpreted as lateral static load resulting in an *adaptive remodeling of the peri-implant bone*.

In the second study (Gotfredsen *et al*. 2001b), two TPS and two turned, "smooth" surface implants were exposed to the 24-week loading period in each dog using orthodontic expansion screws. These were activated by 0.6 mm every 4 weeks. The histologic and histometric analysis showed higher marginal bone levels around TPS implants than around turned implants. Likewise, the peri-implant bone density and mineralized bone–implant contact was higher around the rough surface than the smooth surface implants. Hence, it was concluded that surface roughness influences the bone reactions to the applied load. This, in turn, indicates that surface roughness may also be a determining factor in the remodeling process triggered by load at the bone–implant interface.

The third study (Gotfredsen *et al*. 2001c) analyzed the dynamics of applying a static load for various durations to implants in three dogs. After 24 weeks, the static load was maximally activated onto the implants of the right mandibular side giving a total loading period of 46 weeks at sacrifice. At 60 weeks, maximal activation of static load was set onto the implants of the left mandibular side, giving a total loading period of 10 weeks at sacrifice.

Fluorochrome labeling was performed at weeks 62, 64, 66, and 68. The dogs were sacrificed at week 70. A similar distribution of bone markers, bone

density, and bone–implant contact was observed at 10 and 46 weeks of static lateral loading. However, higher fluorochrome proportions were seen at 10 weeks compared with 46 weeks of lateral loading, suggesting higher adaptive activity at 10 weeks. Nevertheless, the structural adaptation appeared to be similar at the two observation periods.

In all three studies, greater bone–implant contact was identified at implants exposed to lateral static load application compared with non-loaded implants. Moreover, lateral static load failed to induce peri-implant bone loss or to enhance peri-implant bone loss. Hence, *lateral static load* does *not* appear to be detrimental to implants exhibiting peri-implant mucositis or peri-implantitis (Gotfredsen *et al*. 2001a–c).

In contrast to these findings are those from a study in dogs by Hoshaw *et al*. (1994). In this study, excessive cyclic axial forces were applied to implants (high cyclic [500 cycles/day] axial tension [10–300 N] for 5 consecutive days) placed in the tibiae of 10 animals. Bone loss was observed to occur around the neck of the implants after 1 year. Similar results were reported for a rabbit model (Duyck *et al*. 2001) in which dynamic load on implants resulted in the establishment of marginal crater defects, while no effects on osseointegration could be identified in other parts of the implants.

Load and loss of osseointegration

It has been reported (Isidor 1996, 1997) that excessive occlusal load may–under certain circumstances–lead to loss of osseointegration along the entire length of the implant, resulting in implant mobility. In this study, four monkeys received 18 self-tapping screw implants in the mandible after the first molars (n = 7), premolars (n = 8), and incisors (n = 3) had been extracted. Using an opposing maxillary splint in heavy supraocclusal contacts, *excessive occlusal load*, predominantly in the non-axial (lateral) direction, was applied to eight implants. Furthermore, cotton ligatures for increased plaque retention were placed around another 10 implants, resulting first in mucositis and later in peri-implantitis (Lindhe *et al*. 1992; Lang *et al*. 1993). After 18 months of excessive occlusal loading, two of the eight implants subjected to excessive occlusal load were lost. Two of the 10 implants with the cotton ligatures revealed partial loss of osseointegration as a result of plaque-induced peri-implantitis (Fig. 13-21a). Of the retained six implants subjected to excessive load, two showed complete loss of osseointegration with a connective tissue capsule formed around the entire outline of the implants (Fig. 13-21b). Radiographically, the two implants showing complete loss of osseointegration and clinical mobility showed a peri-implant radiolucency after 18 months of excessive occlusal load. However, no loss of marginal bone height was evident.

Another two excessively loaded implants (in one monkey) showed no loss of osseointegration whatsoever. Instead, an increase in bone density and the highest percentage of bone–implant contact area was seen at these implants compared with the remaining implants. This monkey also did not develop ligature-induced peri-implantitis (at three implants). Two implants under excessive occlusal load revealed a reduced bone–implant contact.

Thus, the study demonstrated that excessive occlusal load can, indeed, result in loss of osseointegration characterized by a fibrous connective tissue capsule around the implant, in contrast to the marginal bone loss encountered at implants with ligature-induced peri-implantitis. It must be noted, however, that the bone trabecular structure around the implant loosing osseointegration as a result of excessive occlusal load (Fig. 13.21b) was much less dense than that of, for example, the implants subjected to experimental peri-implantitis (Fig. 13.21a). Thus, this study does not support the concept that occlusal overload may lead to implant losses. Rather, it supports the fact that marginal bone loss at implants is associated with peri-implant disease.

Masticatory occlusal forces on implants

Closing and occlusal functional force distributions have been studied using one- (Lundgren *et al*. 1987, 1989; Falk *et al*. 1989, 1990) or three-dimensional

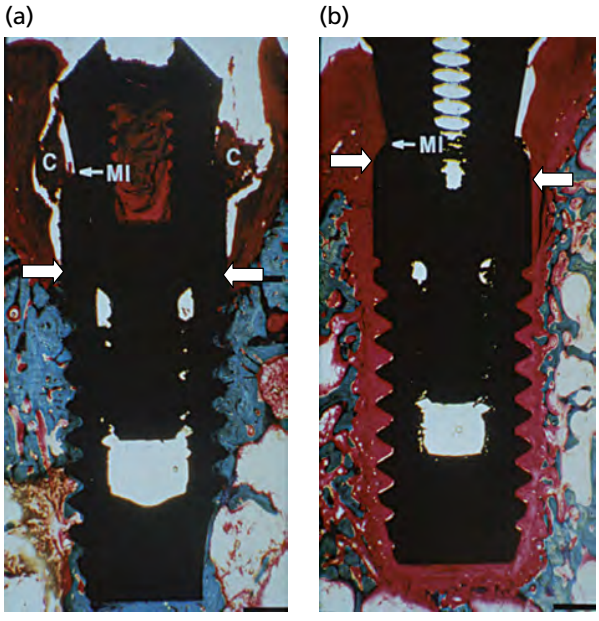

Fig. 13-21 (a) Osseointegrated implant with plaque accumulation. The marginal bone level is located apical to the margin of the implant. (b) Excessively loaded implant with complete loss of osseointegration. The marginal bone level is located near the margin of the implant. Narrow zone of fibrous tissue interposed between implant and bone. MI, margin of implant; C, cotton ligature; arrows, apical extent of epithelium. (Source: Isidor 1997. Reproduced with permission from John Wiley & Sons.)

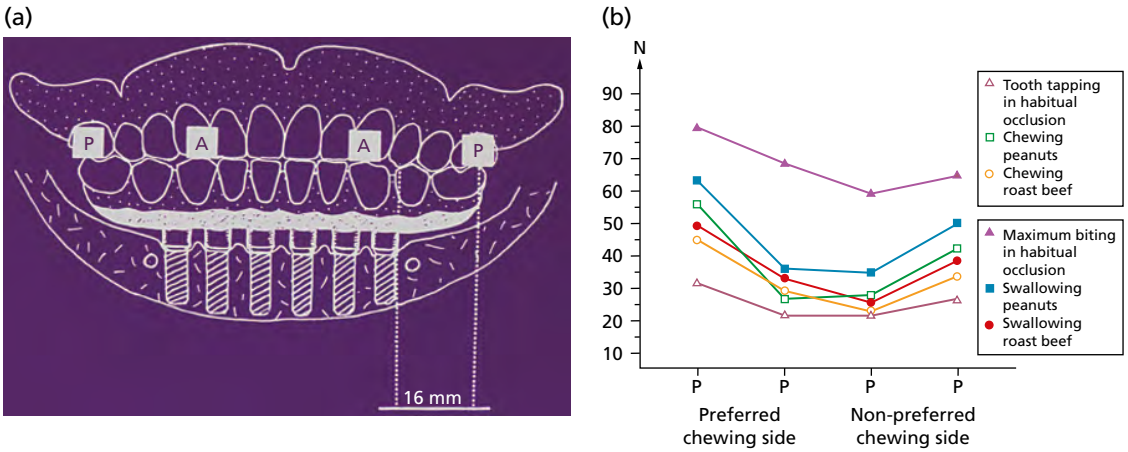

Fig. 13-22 (a) Eight strain gauge transducers placed into a maxillary completely removable prosthesis (A, anterior; P, posterior) and occluding against an implant-supported fixed mandibular dental prosthesis with cantilever beams of 16 mm. (Source: Lundgren *et al*. 1989. Reproduced from Quintessence.) (b) Chewing forces amounting to a maximum biting force of 80 N on the preferred (right) chewing side and 64 N on the non-preferred (left) chewing side (P, posterior; F, Front). While masticating, higher forces are applied to the cantilever beams than to the implant-supported part of the mandibular FDP. (Source: Data from Lundgren *et al*. 1989)

piezoelectric force transducers (Mericske-Stern *et al*. 1996, 2000; Mericske-Stern 1997, 1998).

Eight strain gauge transducers were mounted bilaterally in a maxillary complete denture to occlude with a mandibular implant-supported fixed cantilever prosthesis (Fig. 13-22a) (Lundgren *et al*. 1989). The study demonstrated that closing and chewing forces *increased* distally along the cantilever beams when occluding with complete dentures. Moreover, on both the preferred and non-preferred chewing sides, significantly larger closing and chewing forces were measured over the cantilever segments than over the implant-supported area (Fig. 13-22b). Also, the distally increasing force distribution pattern could be changed to a distally *decreasing* force distribution pattern by infra-occluding the second cantilever unit by as little as 100 µm. Such slight reductions in posterior occlusal contacts on cantilevers may need to be considered whenever the opposing masticatory unit is a complete removable dental prosthesis. However, maximal biting and chewing forces *decreased* distally along the cantilever beams when occluding with tooth-supported FDPs (Fig. 13-23) (Lundgren *et al*. 1987).

From this series of experimental clinical studies it was concluded that forces directed onto the implants *per se* are difficult to evaluate using the transducer methodology. Nevertheless, maximal closing forces were always substantially greater than chewing forces. In addition, each subject in these studies developed a preferred chewing side that was associated with higher chewing forces than the non-preferred chewing side (Lundgren *et al*. 1987, 1989; Falk *et al*. 1989, 1990).

Occlusal force distribution patterns have been studied using three-dimensional piezoelectric transducers for mandibular overdentures that were mounted onto two mandibular implants in the canine region designed to support either a ball joint- or a bar-retained mandibular complete removable prosthesis. Rigid bars provided the best distribution of forces in a vertical direction onto the two mandibular implants (Mericske- Stern *et al*. 1996; Mericske-Stern 1998). Moreover, short distal bar extensions did not negatively influence the force pattern (Mericske-Stern 1997).

When ball joint anchors were used to retain the mandibular overdenture, rather low forces were measured on the implants, particularly in a vertical direction (Mericske-Stern 1998). Vertical forces amounted to 60–140 N, while horizontal forces were much smaller (15–60 N).

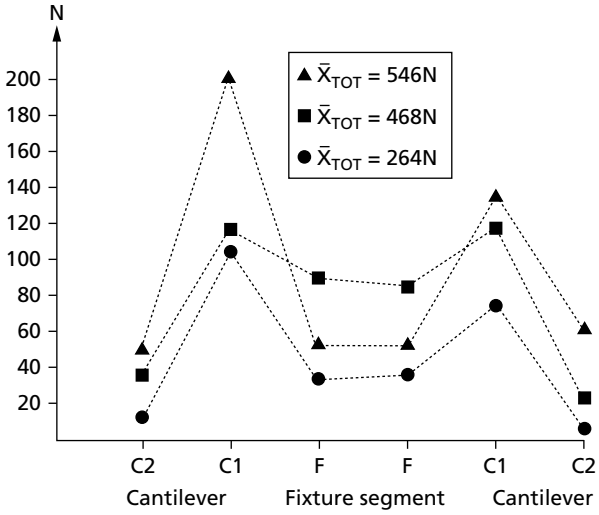

Fig. 13-23 Chewing force patterns in implant-supported fixed dental prosthesis (FDP) with cantilever beams occluding against the tooth-supported FDP. (Source: Lundgren *et al*. 1987. Reproduced with permission from Elsevier.)

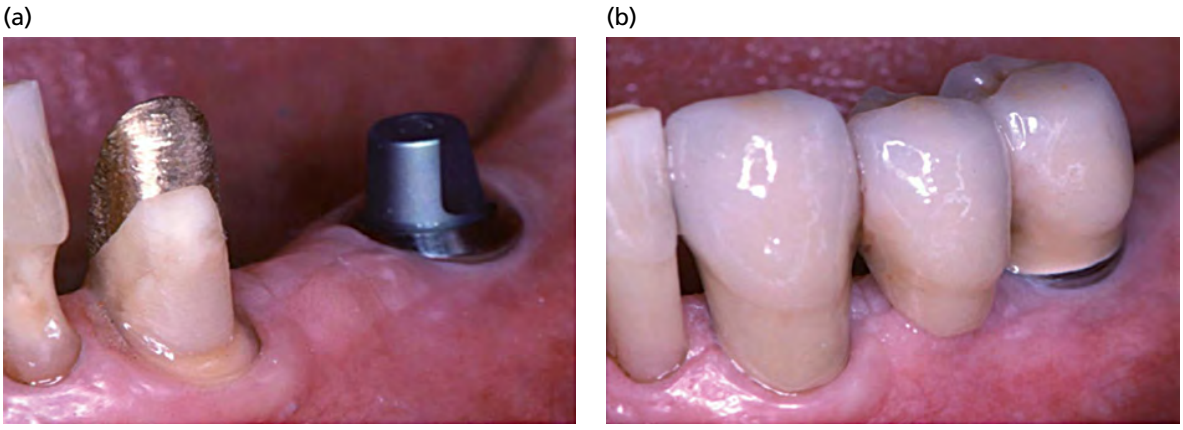

Fig. 13-24 Reconstruction of function in the left side of the mandible using a fixed dental prosthesis (FDP). (a) Prepared abutment tooth 33 after having established adequate abutment height by the installation of a cast post and core prior to seating a three-unit FDP. (b) Tooth-implant supported three-unit FDP 10 years after placement.

Tooth–implant supported reconstructions

In reconstructing patients with inadequate masticatory function, oral implants are often used to increase the patients' chewing comfort (see Chapter 44) and provide additional chewing units in an edentulous posterior region. Occasionally, reconstruction of a chewing side may be contemplated, with the reconstruction supported by both a tooth and an implant (Fig. 13-24). In this way, problems with the location of the mental nerve in an area of a planned implant installation or lack of an adequate bone volume may be overcome.

Combined tooth–implant reconstructions have been associated with numerous clinical problems, including root intrusion as a potential clinical hazard of non-rigid connection. Hence, it has been claimed that natural teeth should not be connected to implants beneath a fixed prosthesis.

However, experimental studies have clearly established that no detrimental effects on the periodontium of abutment teeth can be demonstrated despite the different biomechanical condition mediated by a periodontal ligament as opposed to the ankylotic anchorage of an implant (Biancu *et al*. 1995).

In vivo measurements of vertical forces and bending moments during biting and chewing were carried out on 10 three-unit prostheses in the posterior mandibles of five patients. Each patient had two prostheses, one supported by two implants and the other supported by one implant and one tooth. The results demonstrated no major difference in functional load magnitudes between the support types. Obviously, functional loads were shared between the teeth and the implants (Rangert *et al*. 1991, 1995; Gunne *et al*. 1997).

Further studies using FEA showed no increased risk of stress concentrations at the neck of the implant (Gross & Laufer 1997; Laufer & Gross 1998).

Clinical studies reporting life table statistics in combined implant and tooth restorations do not show adverse effects of splinting teeth to implants. No increased risk of tooth intrusion was reported if the implant was rigidly connected to the tooth (Fugazzotto *et al*. 1999; Lindh *et al*. 2001; Naert *et al*. 2001a, b).

For 843 consecutive patients treated in a private practice set-up (Fugazzotto *et al*. 1999) with 1206 natural tooth–implant supported prostheses utilizing 3096 screw-fixed attachments, after 3–14 years in function, only nine intrusion problems were noted. All problems were associated with fractured or lost screws.

Probably the most relevant clinical study is a 10-year randomized controlled prospective study of 23 patients with residual mandibular anterior teeth (Gunne *et al*. 1999). Each patient received two three-unit FDPs either supported by two implants or, on the contralateral side, by one implant and one tooth, thus permitting intraindividual comparison. The distribution of the two types of FDPs in each jaw was randomized. Implant success rates, marginal bone changes, and mechanical complications were studied. The tooth–implant connection did not demonstrate any negative influences on the overall success rates for the 10-year period when compared with the implant–implant supported FDPs (Fig. 13-25). Hence, it was suggested that a prosthetic construction supported by both a tooth and an implant may be recommended as a predictable and reliable treatment alternative in the posterior mandible (Gunne *et al*. 1999).

Based on the available evidence, it can be stated that a combination of implant and tooth support for FDP is acceptable (Belser *et al*. 2000).

Although a systematic review (Lang *et al*. 2004) indicated that tooth–implant reconstructions have a 5-year survival rate of 94.1%, thus comparing very well with the 5-year survival rate of implant–implant reconstructions of 95.0% (Pjetursson *et al*. 2004), the 10-year survival rate of tooth–implant reconstructions (77.8%) appears to be significantly lower than the 10-year survival of implant–implant reconstructions (86.7%). However, owing to the fact that the former 10-year survival rate was based on only 60

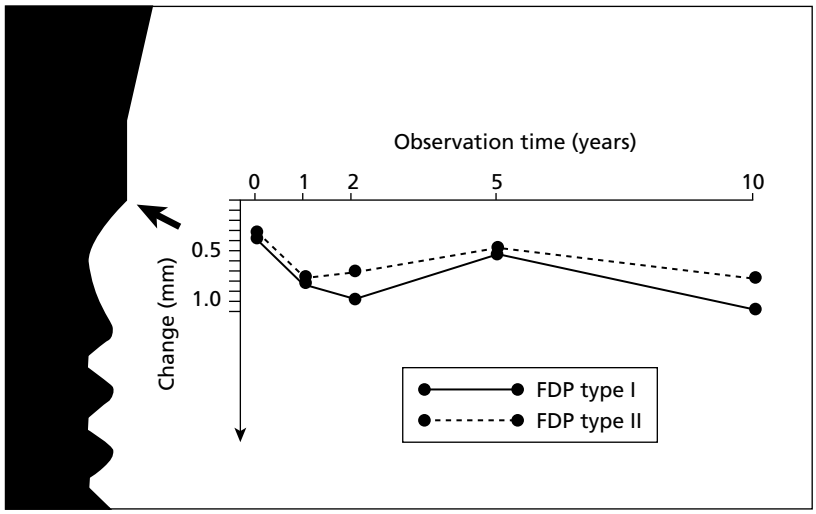

Fig. 13-25 Ten-year randomized controlled clinical trial of three-unit fixed dental prostheses (FDP), either implant–implant (type I) or tooth–implant (type II) supported. No differences in the crestal bone levels after 1, 2, 5, and 10 years in function. (Source: Lundgren *et al*. 1987. Reproduced with permission from Elsevier.)

(I–T) FDPs and the latter on only 219 (I–I) FDPs, the reliability of such 10-year survival rates has to be questioned.

The biomechanical aspects of implant–tooth-supported FDPs have been presented (Lundgren & Laurell 1994). As the implant is rigidly fixed within the alveolus and the tooth is surrounded by a periodontal ligament that allows minute movement, rigid FDP designs have been advocated.

The movement of the natural tooth abutment affects the load-bearing capacity of the FDP whenever a long-span FDP is constructed (e.g. a beam length of 24 mm or two premolar or molar pontics). Before the occlusal load is applied, the FDP acts as a cantilever construction. Upon loading, an angular deflection of the implant–crown unit of approximately 50 µm is noted. Along with bending of the long-span beam, an apical deflection of the tooth of approximately 50 µm is allowed, leading to bilateral (tooth and implant) support for the FDP.

If the tooth and implant only support a short-span FDP (e.g. a beam length of 12 mm or one premolar pontic only), however, the angular deflection of the implant–crown unit of approximately 50 µm and the bending of the short-span beam are insufficient to provide bilateral support for the bridge. Apical deflection of the tooth will not be achieved, and the implant will bear the entire occlusal load applied to the FDP. As indicated above, there is no doubt that osseointegration will cope with such functional loads.

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Part 6: Periodontal Pathology

Chapter 14

Non-Plaque-Induced Gingival Diseases

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Introduction

Gingival inflammation, clinically presenting as gingivitis, is not always due to accumulation of plaque on the tooth surface, and non-plaque-induced inflammatory gingival reactions often present with characteristic clinical features (Holmstrup 1999; Holmstrup *et al*. 2018). They may have several causes, such as specific bacterial, viral, or fungal infection. The non-plaque-induced gingival lesions are often manifestations of systemic conditions but they may also represent pathological changes limited to gingival tissues. Inherited gingival lesions are seen in hereditary gingival fibromatosis, and several mucocutaneous disorders manifest as gingival inflammation. Typical examples of such disorders are lichen planus, pemphigoid, pemphigus vulgaris, and erythema multiforme. Allergic and traumatic lesions are other examples of non-plaque-induced gingival inflammation. Dentists, and especially specialists in periodontology, are the key healthcare providers in the diagnostic unraveling and treatment of patients affected by such lesions.

This chapter focuses on some of the most relevant non-plaque-induced inflammatory diseases of the gingival tissues, either because they have a serious outcome, are common, or because they are important examples for the understanding of the variety of tissue reactions that take place in the periodontium. For further information, the reader is referred to oral medicine textbooks and current reviews.

Although non-plaque-induced gingival diseases are less common than plaque-induced gingival disease it is important to note that they are often of major significance for the patients. A classification of the wide spectrum of lesions based upon their etiology (Box 14-1) was proposed at the 2017 World Workshop on Classification of Periodontal Diseases arranged by American Academy of Periodontology and European

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

Box 14-1 Classification of non-plaque-induced gingival diseases and conditions.

Genetic/developmental disorders
- **Hereditary gingival fibromatosis**

Specific infections
- **Bacterial origin**
  - *Neisseria gonorrhea*
  - *Treponema pallidum*
  - *Mycobacterium tuberculosis* (tuberculosis)
  - *Streptococcus* gingivitis (strains of streptococcus)
- **Viral origin**
  - Coxsackie virus (hand, foot, and mouth disease)
  - Herpes simplex virus types 1 and 2 (primary or recurrent)
  - Varicella zoster virus (chicken pox or shingles affecting V nerve)
  - Molluscum contagiosum
  - Human papilloma virus
    - Squamous cell papilloma
    - Condyloma acuminatum
    - Verruca vulgaris
    - Focal epithelial hyperplasia
- **Fungal origin**
  - Candidosis
  - Other mycoses (e.g. histoplasmosis, aspergillosis)

Inflammatory and immune conditions
- **Hypersensitivity reactions**
  - Contact allergy
  - Plasma cell gingivitis
  - Erythema multiforme
- **Autoimmune diseases of skin and mucous membranes**
  - Pemphigus vulgaris
  - Pemphigoid
  - Lichen planus
  - Lupus erythematosus
- **Granulomatous inflammatory conditions (orofacial granulomatosis)**
  - Crohn's disease
  - Sarcoidosis

Reactive processes
- **Epulides**
  - Fibrous epulis (± calcification)
  - Calcifying fibroblastic granuloma
  - Pyogenic granuloma (vascular epulis)
  - Peripheral giant cell granuloma (or central)

Neoplasms
- **Premalignant (potentially malignant)**
  - Leukoplakia
  - Erythroplakia
- **Malignant**
  - Squamous cell carcinoma
  - Leukemia
  - Lymphoma

Endocrine, nutritional, and metabolic diseases
- **Vitamin deficiencies**
  - Vitamin C deficiency (scurvy)

Traumatic lesions
- **Physical/mechanical insults**
  - Frictional keratosis
  - Mechanically induced gingival ulceration
  - Factitious injury (self-harm)
- **Chemical (toxic) burn**
  - Etching
  - Chlorhexidine
  - Acetylsalicylic acid
  - Cocaine
  - Hydrogen peroxide
  - Dentifrice detergents
  - Paraformaldehyde or calcium hydroxide
- **Thermal insults**
  - Burns to gingival mucosa

Gingival pigmentation
- Melanoplakia
- Smoker's melanosis
- Drug-induced pigmentation (antimalarials; minocycline)
- Amalgam tattoo

Federation of Periodontology (Chapple *et al*. 2018). The content of this chapter is written based on this most recent classification system.

Genetic/developmental disorders

Hereditary gingival fibromatosis

Gingival hyperplasia (synonymous with gingival overgrowth, gingival fibromatosis) may occur as a side effect in response to systemic medications, including phenytoin, cyclosporine, and nifedipine. These lesions are to some extent plaque dependent and they are reviewed in Chapter 15. Gingival hyperplasia may also be of genetic origin. Such lesions are known as hereditary gingival fibromatosis (HGF) (Coletta & Graner 2006; Alminana-Pastor *et al*. 2017), which is an uncommon condition characterized by diffuse gingival enlargement, sometimes covering major parts of or the entire tooth surfaces. The lesions develop irrespective of effective plaque removal.

HGF may be an isolated disease entity or part of a syndrome (Gorlin *et al*. 1990), associated with other clinical manifestations, such as hypertrichosis (Horning *et al*. 1985; Cuestas-Carneiro & Bornancini 1988), mental retardation (Araiche & Brode 1959), epilepsy (Gorlin *et al*. 1990), hearing loss (Hartsfield *et al*. 1985), growth retardation (Bhowmick *et al*. 2001), and abnormalities of the extremities (Nevin *et al*. 1971; Skrinjaric & Baci 1989). Most cases are related to an autosomal dominant mode of inheritance, but cases have been described with an autosomal recessive background (Emerson 1965; Jorgensen & Cocker 1974; Singer *et al*. 1993). The most common syndrome of HGF includes hypertrichosis, epilepsy, and mental retardation; the latter two features, however, are not present in all cases (Gorlin *et al*. 1990).

Typically, HGF presents as large masses of firm, dense, resilient, insensitive fibrous tissue that covers the alveolar ridges (Coletta & Graner 2006) and extends over the teeth, resulting in extensive pseudopockets. The color may be normal or erythematous if inflamed (Figs. 14-1, 14-2). Depending on the extent of the gingival enlargement, patients complain of functional and esthetic problems. The enlargement may result in protrusion of the lips and the patient may chew on a considerable hyperplasia of tissue covering the teeth. HGF is seldom present at birth but may be noted at an early age. If the enlargement is present before tooth eruption, the dense fibrous tissue may interfere with or prevent the eruption (Shafer *et al*. 1983).

Studies have suggested that an important pathogenic mechanism may be enhanced production of transforming growth factor-beta1 (TGF-β1) which reduces the proteolytic activities of HGF fibroblasts, which again favors the accumulation of extracellular matrix (Coletta *et al*. 1999; Han *et al*. 2019). A locus for autosomal dominant HGF has been mapped to a region on chromosome 2 (Hart *et al*. 1998; Xiao *et al*. 2000), although at least two genetically distinct loci seem to be responsible for this type of HGF (Hart *et al*. 2000) and a novel locus for maternally inherited human gingival fibromatosis has been reported at human chromosome 11p15 (Zhu *et al*. 2007). Also, mutations of "Son of Sevenless" genes (*SOS1* and *SOS2*) may account for HGF (Hart *et al*. 2002)

The histologic features of HGF include moderate hyperplasia of a slightly hyperkeratotic epithelium with extended rete pegs. The underlying stroma is almost entirely made up of dense collagen bundles with only a few fibroblasts. Local accumulation of inflammatory cells may be present (Shafer *et al*. 1983). Histologic examination may facilitate the differential diagnosis from other genetically determined gingival enlargements, such as Fabry's disease, characterized by telangiectasia.

The treatment is surgical removal, often in a series of gingivectomies, but relapses are not uncommon. If the volume of the overgrowth is extensive, a repositioned flap to avoid exposure of connective tissue by gingivectomy may better achieve elimination of pseudopockets. Recently, an original approach for screening of optimal miRNAs with antifibrotic functions and pinpoint miR-335-3p has been suggested as a novel potential therapeutic target for HGF (Gao *et al*. 2019).

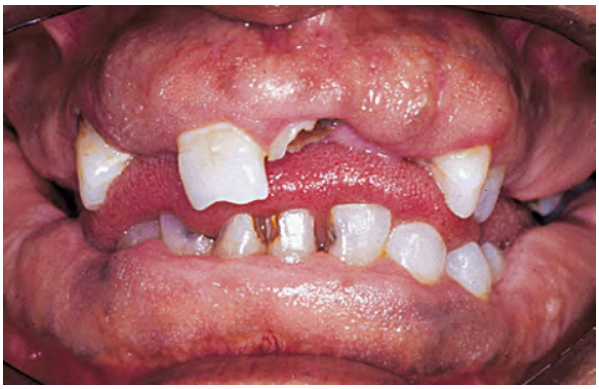


Fig. 14-1 Hereditary gingival fibromatosis. Facial aspect with partial coverage of teeth.

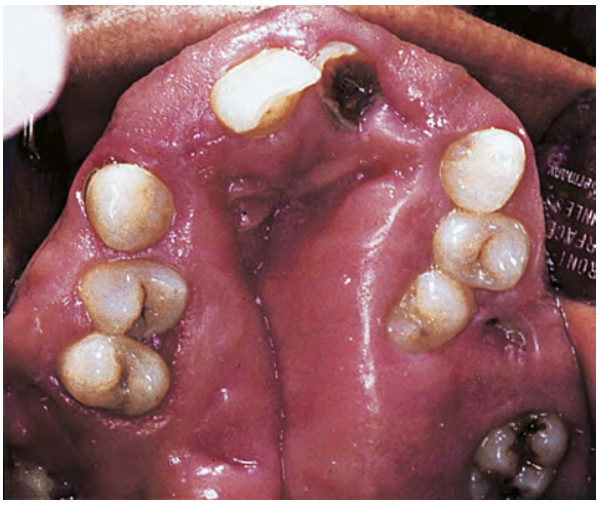


Fig. 14-2 Same patient as shown in Fig. 14-1. The maxillary gingival fibromatosis is severe and has resulted in total disfiguration of the dental arch.

Specific infections

Bacterial origin

Infective gingivitis and stomatitis may occur on rare occasions in both immunocompromised and non-immunocompromised individuals, when the homeostasis between innate host resistance and non-plaque-related pathogens is not maintained (Rivera-Hidalgo & Stanford 1999). The lesions may be due to bacteria and oral lesions may be the primary presentation of the infection. Typical examples of such lesions are due to infections with *Neisseria gonorrhea* (Scully 1995; Siegel 1996), *Treponema pallidum* (Scully 1995; Ramirez-Amador *et al*. 1996; Siegel 1996; Rivera-Hidalgo & Stanford 1999), Streptococci, *Mycobacterium chelonae* (Pedersen & Reibel 1989), *Mycobacterium tuberculosis* (Bansal *et al*. 2015), or other organisms (Blake & Trott 1959; Littner *et al*. 1982). Although oral manifestations of syphilis and gonorrhea are most likely to be observed during secondary disease, all stages of the disease can give rise to oral lesions. The gingival lesions manifest as fiery red edematous painful ulcerations, as asymptomatic chancres or mucous patches, or as atypical non-ulcerated, highly inflamed gingivitis. Biopsy supplemented by microbiologic examination reveals the background of the lesions.

Viral origin

A number of viral infections may manifest in the oral mucosa including gingiva (Clarkson *et al*. 2017).

Coxsackie virus (hand, foot, and mouth disease)

Hand, foot, and mouth disease (HFMD) is a viral illness caused most commonly by coxsackievirus A16 (CVA16) and enterovirus 71 (EV71) (Kimmis *et al*. 2018). It is a mild virus infection that mainly occurs during summer and autumn. The infection usually affects children under 10 years of age and spreads quickly across childcare centers and elementary schools. Adults may also be infected and usually after contact with infected children. The clinical characteristics of the disease is blisters in the oral mucosa, mainly the tongue, buccal mucosa, and the throat. A slight fever may occur. The patient also gets deep-seated blisters on the skin, mainly on the palms and around the fingers and toes. The infection debuts with red, dot-shaped changes that develop into vesicles, which rapidly rupture and become sores (Fig. 14-3).

Herpes simplex type 1 and 2

A number of viral infections are known to cause gingivitis (Scully *et al*. 1998b). The most important are the herpes viruses: herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) and varicella zoster virus. These viruses usually enter the human body in childhood and may give rise to oral mucosal disease followed by periods of latency and sometimes reactivation. HSV-1 usually causes oral manifestations, whereas herpes HSV-2 is mainly involved in anogenital infections and only occasionally is involved in oral infection (Scully 1989; Petti & Lodi 2019).

Primary herpetic gingivostomatitis

HSV infections are among the most common viral infections. HSV is a DNA virus with low infectiosity, which after entering the oral mucosal epithelium, penetrates a neural ending and by retrograde transport through the smooth endoplasmic reticulum (200–300 mm/day) travels to the trigeminal ganglion where it can remain latent for years. The virus has also been isolated in extraneural locations such as the gingiva (Amit *et al*. 1992). Sometimes HSV may also be involved in recurring erythema multiforme. It is presently unknown whether the virus plays a role in other oral diseases, but HSV has been found in gingivitis (Ehrlich *et al*. 1983), acute necrotizing gingivitis (Contreras *et al*. 1997), and periodontitis (Parra & Slots 1996).

When a newborn is infected, sometimes from the parent's recurrent herpes labialis, he/she is often wrongly diagnosed as "teething". With increased hygiene in industrialized societies, more and more primary infections occur at older ages than occur during adolescence or adulthood. It has been estimated in the USA that there is about half a million cases of primary infection per year (Overall 1982). The primary herpetic infection may run an asymptomatic course in early childhood, but may also give rise to severe gingivostomatitis, which occurs mostly before adolescence (Fig. 14-4). This manifestation includes painful severe gingivitis with redness, ulcerations with serofibrinous exudate, and edema accompanied by stomatitis (Figs. 14-5, 14-6). The incubation period is 1 week. A characteristic feature is the formation of vesicles, which rupture, coalesce, and leave fibrin-coated ulcers (Scully *et al*. 1991; Miller & Redding 1992). Fever and lymphadenopathy are other classic features. Healing occurs spontaneously without scarring in 10–14 days (Fig. 14-6). During this period, pain can render eating difficult.

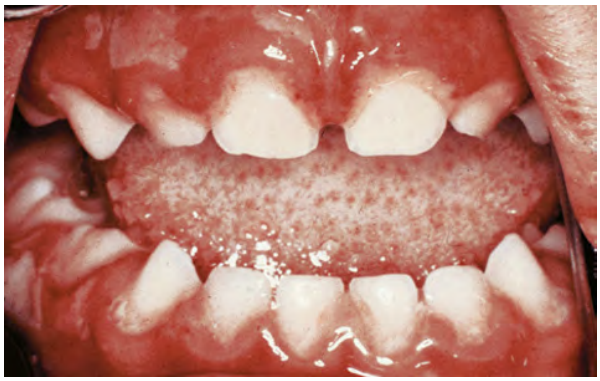


Fig. 14-4 Herpetic gingivostomatitis in a 3-year-old child. Erythematous swelling of attached gingiva with serofibrinous exudate along the gingival margin.

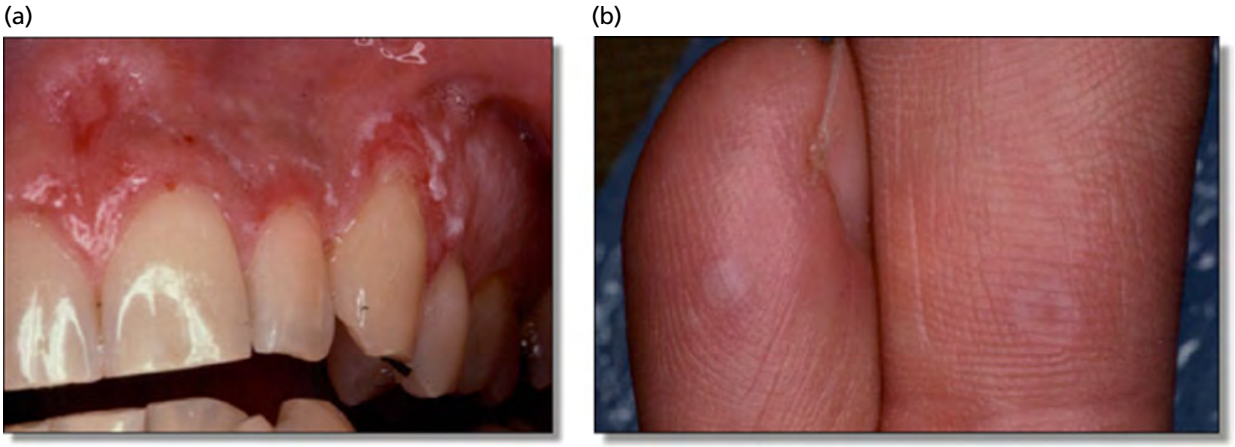


Fig. 14-3 Hand-foot-and-mouth disease. Gingival lesions (a) are rare but common on hands and feet (b).

The virus remains latent in the ganglion cell, probably through integration of its DNA in that of the chromosomal DNA (Overall 1982). Reactivation of the virus occurs in 20–40% of primary infected individuals (Greenberg 1996) and usually presents as herpes labialis, but recurrent intraoral herpes infections are also seen. Herpes labialis occurs in general more than once per year, usually at the same location on the vermilion border and/or the skin adjacent to it, where neural endings are known to cluster. A large variety of factors trigger reactivation of latent virus: trauma, ultraviolet light exposure, fever, menstruation, and others (Scully *et al*. 1998b).

While recurrences at the vermilion border are well recognized, recurrent intraoral herpes lesions often remain undiagnosed because they are considered to be aphthous ulcerations (Lennette & Magoffin 1973; Sciubba 2003), irrespective of the fact that aphthous ulcers do not affect keratinized mucosa. Recurrent intraoral herpes typically presents a less dramatic course than does the primary infection. A characteristic manifestation is a cluster of small painful ulcers in the attached gingiva and hard palate (Yura *et al*. 1986) (Fig. 14-7). The diagnosis can be made on the basis of the patient history and clinical findings supported by isolation of HSV from lesions. The polymerase chain reaction (PCR) has largely superseded most other methods and is a rapid and reliable diagnostic tool providing subtype diagnosis. Laboratory diagnosis may also involve examination of a blood sample for increased antibody titer against HSV. However, this is most relevant in cases of primary infection, because the antibody titer remains elevated for the rest of the individual's lifetime. The histopathologic features of cytologic smears from the gingival lesions are not specific, but the presence of giant cells and intranuclear inclusion bodies may indicate intracellular activity of the virus (Burns 1980).

Immunodeficient patients, such as human immunodeficiency virus (HIV)-infected individuals, are at increased risk of acquiring the infection (Holmstrup & Westergaard 1998). In the immunocompromised

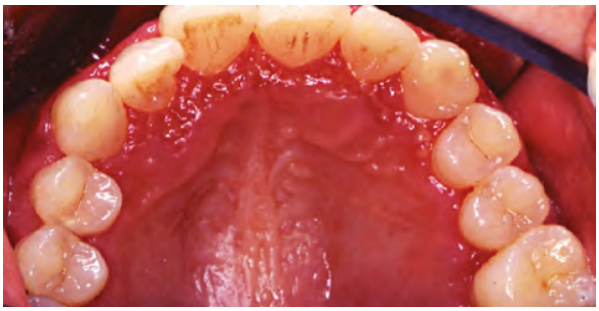


Fig. 14-5 Herpetic gingivostomatitis affecting palatal gingivae. Numerous vesicles and small ulcerations.

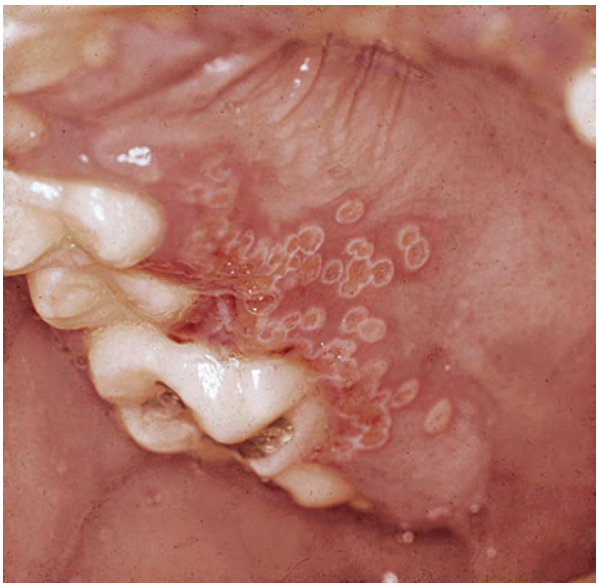
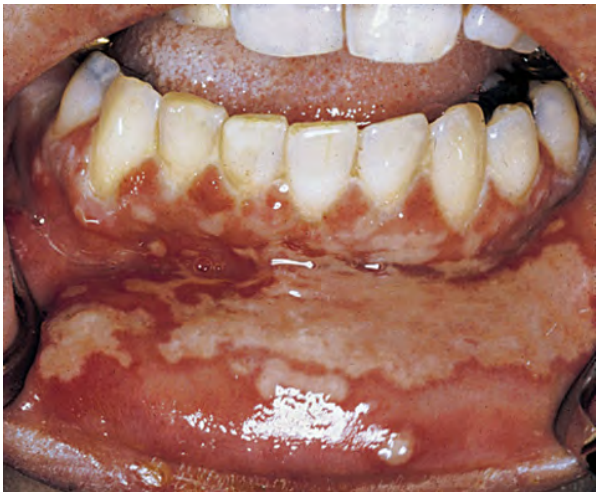


Fig. 14-7 Recurrent intraoral herpes infection. Ruptured vesicles of right palatal gingivae and mucosa.

(a)



(b)

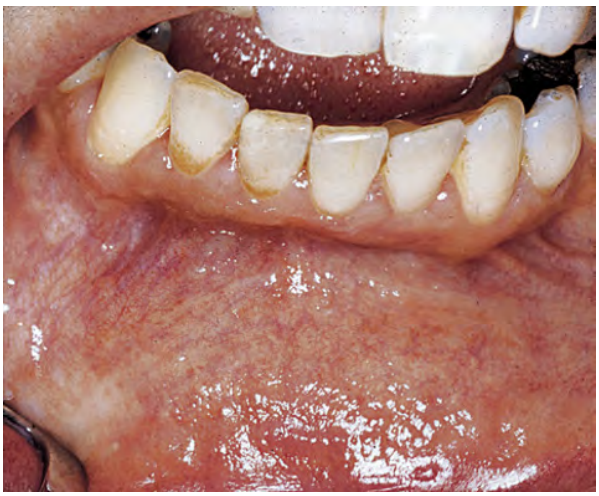


Fig. 14-6 Herpetic gingivostomatitis in a 38-year-old woman. Widespread ulceration of the lower lip mucosa and gingivae (a). Same patient 4 weeks later (b). Healing without loss of tissue or scar formation.

patient the recurrence of herpes infection, either gingival or elsewhere, may be severe and even life threatening.

The treatment of herpetic gingivostomatitis includes careful plaque removal to limit bacterial superinfection of the ulcerations, which delays their healing. In severe cases, including patients with immunodeficiency, the systemic use of antiviral drugs such as acyclovir, valacyclovir, or famciclovir is recommended (O'Brien & Campoli-Richards 1989; Mindel 1991; Arduino & Porter 2006). There is only weak evidence for treating children with acyclovir. However, it may be considered within the first 72 hours of symptom onset, but only if clear symptoms of gingivostomatitis exist and if the patient suffers from substantial pain or dehydration (Goldman 2016). Resistance to acyclovir, especially among immunodeficient patients on long-term therapy, is a growing concern (Westheim *et al*. 1987) and explains why other antiviral drugs may be relevant. Prophylactic antiviral treatment before dental treatment has been recommended for patients at risk of a recurrence, as well as to minimize transmission of the disease (Miller *et al*. 2004).

Varicella zoster virus

Varicella zoster virus causes varicella (chicken pox) as the primary self-limiting infection. It occurs mainly in children and later reactivation of the virus in adults causes herpes zoster (shingles). Both manifestations can involve the gingiva (Straus *et al*. 1988; Scully 1995). Chicken pox is associated with fever, malaise, and a skin rash. The intraoral lesions are small ulcers, usually on the tongue, palate, and gingiva (Miller 1996; Scully *et al*. 1998b). The virus remains latent in the dorsal root ganglion from where it can be reactivated years after the primary infection (Rentier *et al*. 1996). Later reactivation results in herpes zoster, with unilateral lesions following the infected nerve (Miller 1996). The reactivation normally affects the thoracic ganglia in elderly or immunocompromised patients. Reactivation of virus from the trigeminal ganglion occurs in 20% of reported cases (Hudson & Vickers 1971). If the second or third branch of the trigeminal nerve is involved, skin lesions may be associated with intraoral lesions, or intraoral lesions may occur alone (Eisenberg 1978), for instance affecting the palatal gingiva (Fig. 14-8). Initial symptoms are pain and paraesthesia, which may be present before lesions occur (Greenberg 1996). The associated pain is usually severe. The lesions, which often involve the gingiva, start as vesicles. They soon rupture to leave fibrin-coated ulcers, which often coalesce to irregular forms (Millar & Troulis 1994) (Fig. 14-8). In immunocompromised patients, including those infected with HIV, the infection can result in severe tissue destruction with tooth exfoliation and necrosis of alveolar bone and high morbidity (Melbye *et al*. 1987; Schwartz *et al*. 1989). The diagnosis is usually obvious due to the unilateral occurrence of lesions associated with severe pain. Healing of the lesions usually takes place in 1–2 weeks.

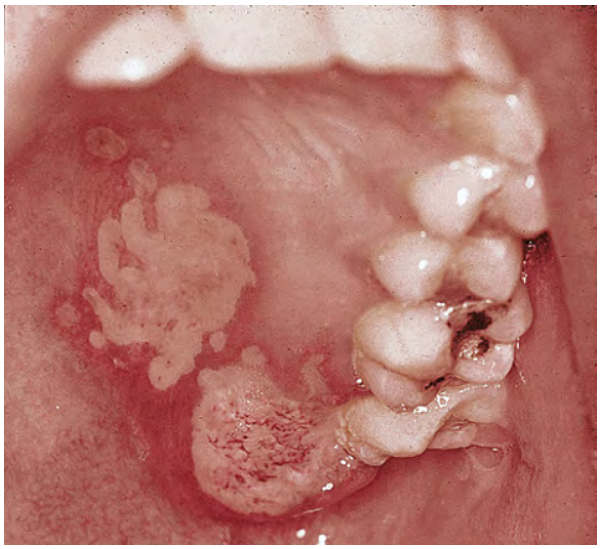


Fig. 14-8 Herpes zoster of left palatal gingiva and mucosa. Irregular fibrin-coated ulcerations with severe pain.

Treatment consists of a soft or liquid diet, rest, atraumatic removal of plaque, and diluted chlorhexidine rinses. This may be supplemented by antiviral drug therapy. Postherpetic neuralgia is a dreaded complication of herpes zoster, which can persist for months to years, potentially resulting in marked debilitation and reduced quality of life. Targeting individuals aged 60 years and above, vaccination appears to be cost-effective (Carpenter *et al*. 2019).

Molluscum contagiosum virus

Molluscum contagiosum is a contagious self-limited viral infection that commonly affects the skin. Involvement of mucous membranes is rare. The disease can affect individuals of any age, but its prevalence is higher among infants (2–5 years), sexually active adults, and immunocompromised individuals (de Carvalho *et al*. 2012). It is caused by a member of a DNA pox virus, and it has an incubation period of 2–7 weeks. It is characterized by a single/multiple, round/dome-shaped, pink waxy papule ranging from 1 mm to 5 mm on face, eyelids, neck, axilla, and thigh (Fornatora *et al*. 2001). Gingival affection has been reported but is extremely rare. The histopathological features are characteristic, and the presence of Molluscum bodies is diagnostic.

Human papillomavirus

Close to 200 genotypes or strains of human papillomavirus (HPV) have been identified. Viruses selectively infect mucous membranes and skin squamous epithelium. However, only very few of the genotypes are associated with infections in the oral mucosa (Syrjänen 2018). Unlike herpes infections,

HPV infections are more chronic and rarely cause any symptoms. Up to 80% of the population of the western world are infected at a specific time-point. Oral sex behaviors and open-mouthed kissing are probably reasons for oral HPV infection, but it remains unclear whether other pathways of infection exist (Jiang & Dong 2017). The infections are associated with several tumor-like conditions, benign as well as malignant. There are 15 subtypes of HPV that are associated with high risk of malignant change. Of these, HPV type 16 and 18 are the most common causes of HPV-associated cancer. As the gingival pocket is the only site in the oral mucosa in which basal cells, the known targets of HPV at other mucosal sites, are normally exposed to the environment, it has been hypothesized that this could be the site of a latent HPV infection in oral mucosa. Different treatment strategies are available for papillomas/condylomas, verrucas, and focal epithelial hyperplasia such as cryotherapy, electrosurgery, surgical removal, laser therapy, and trichloroacetic acid. An increased awareness of HPV-positive squamous cell carcinomas is the background of increasing utilization of HPV vaccines, and there is some epidemiological evidence that HPV vaccine may provide a possible solution for preventing oral HPV infection. Biological and epidemiological data regarding the link between sexual behavior and HPV-associated cancers indicate a connection, but definitive data are lacking.

Squamous cell papilloma and verruca vulgaris

Squamous cell papilloma and verruca vulgaris are the most common clinical types of intraoral HPV infections. Papillomas are probably caused by HPV types 6 and 11, while verruca vulgaris is associated with HPV types 2, 4, and 57. Clinically, there is no clear dividing line between the two changes. They can be manifested as small white icicle-like projections (Fig. 14-9), but the lesions can also have a more cauliflower-like appearance and, if so, they are usually the same color as the surrounding mucosa. The size rarely exceeds 10 mm. The patient may be aware of the infections, but they rarely give rise to any symptoms.

Condyloma acuminatum

Condyloma acuminatum (Fig 14-10) has been reported to affect the mucosa of the gingiva, cheeks, lips, and hard palate. This HPV infection was previously considered as a completely separate entity, but since condylomas are associated with the same subtypes as papillomas, it now seems questionable whether the two clinical types should be separated. There are no clear differences with regard to the clinical characteristics.

Focal epithelial hyperplasia

Focal epithelial hyperplasia (FEH) is an intraoral HPV infection which is strongly associated with subtypes 13 and 32. The infection is a benign familial disorder with autosomal-recessive inheritance. FEH is most prevalent among Native American and Mexican Indians, Indigenous peoples of South America, and Eskimos. Clinically, this HPV infection differs from the others in that it exhibits multiple warty circular swellings of the mucosa. The size may vary, but rarely exceeds 5 mm. FEH has the same color as the healthy oral mucosa. Sometimes the changes may coalesce into larger lesions.

Fungal origin

Fungal infection of the oral mucosa includes a range of diseases such as aspergillosis, blastomycosis, candidosis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, and paracoccidioidomycosis infections (Scully *et al*. 1998b), but some of the infections are very uncommon and not all of them manifest as gingivitis. This section focuses on candidosis and histoplasmosis, both of which may cause gingival infection.

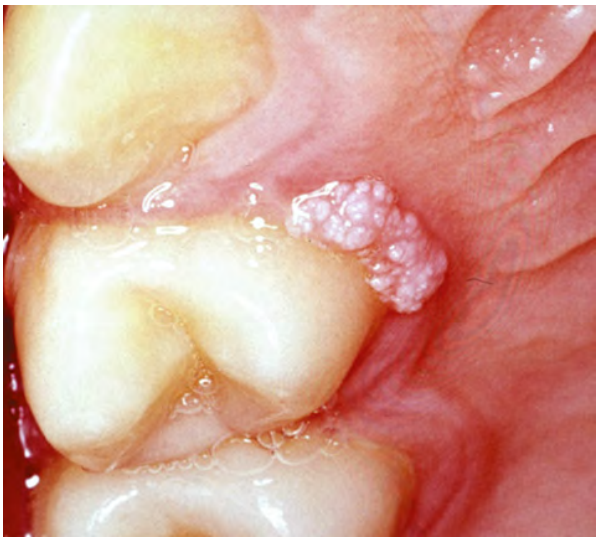


Fig. 14-9 Squamous cell papilloma of palatal gingiva.

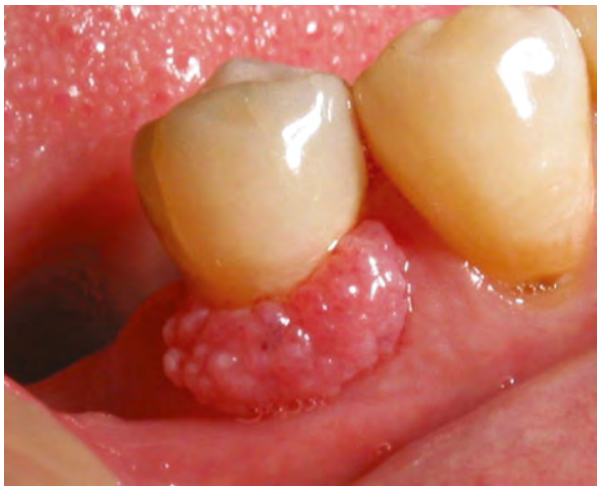


Fig. 14-10 Gingival condyloma acuminatum.

Candidosis

Various *Candida* species are recovered from the mouth of humans, including *C. albicans, C. glabrata, C. krusei, C. tropicalis, C. parapsilosis,* and *C. guillermondii* (Cannon *et al*. 1995). The most common fungal infection of the oral mucosa is candidosis, mainly caused by the organism *C. albicans* (Scully *et al*. 1998b). *C. albicans* is a normal commensal of the oral cavity but also an opportunistic pathogen (Lewis & Williams 2017). The prevalence of oral carriage of *C. albicans* in healthy adults ranges from 3% to 48% (Scully 1995), the large variation being due to differences in examined populations and the procedures used. The proportion of *C. albicans* in the total oral yeast population can reach about 50–80% (Wright *et al*. 1985). The proteinase-positive strains of *C. albicans* are associated with disease (Negi *et al*. 1984; Odds 1985) and invasion of keratinized epithelia such as that of the gingiva. Invasion and increased desquamation is due to hyaluronidase production. Infection by *C. albicans* usually occurs as a consequence of reduced host defense (Holmstrup & Johnson 1997), including immunodeficiency (Holmstrup & Samaranayake 1990) (Figs. 14-11, 14-12, 14-13), reduced saliva secretion, smoking, and treatment with corticosteroids, but may be due to a wide range of predisposing factors. The occurrence of oral candidosis may act as a predictor of immune and virologic failure in HIV-infected patients treated with antiviral drugs (Miziara & Weber 2006). Disturbances in the oral microbial flora, such as after therapy with broad-spectrum antibiotics, may also lead to oral candidosis. The predisposing factors are, however, often difficult to identify. Based on their site, infections may be defined as superficial or systemic. Candidal infection of the oral mucosa is usually a superficial infection, but systemic infections are not uncommon in debilitated patients.

In otherwise healthy individuals, oral candidosis rarely manifests in the gingiva. This is surprising when considering the fact that *C. albicans* is frequently isolated from the subgingival flora of patients with severe periodontitis (Slots *et al*. 1988). The most common clinical characteristic of gingival candidal infections is redness of the attached gingiva, often associated with a granular surface (Fig. 14-12).

Various types of oral mucosal manifestations are pseudomembranous candidosis (also known as thrush in neonates), erythematous candidosis, plaque-type candidosis, and nodular candidosis (Holmstrup & Axell 1990). Pseudomembranous candidosis shows whitish patches (Fig. 14-11), which can be wiped off the mucosa with an instrument or gauze to leave a slightly bleeding surface. The pseudomembranous type usually has no major symptoms. Erythematous lesions can be found anywhere in the oral mucosa (Fig. 14-13). The intensely red lesions are usually associated with pain, which is sometimes severe. The plaque type of oral candidosis usually affects smokers and presents with a whitish plaque, which cannot be removed. There are usually no symptoms and the lesion is clinically indistinguishable from oral leukoplakia. Nodular candidal lesions are infrequent in the gingiva. Slightly elevated nodules of a white or reddish color characterize them (Holmstrup & Axell 1990).

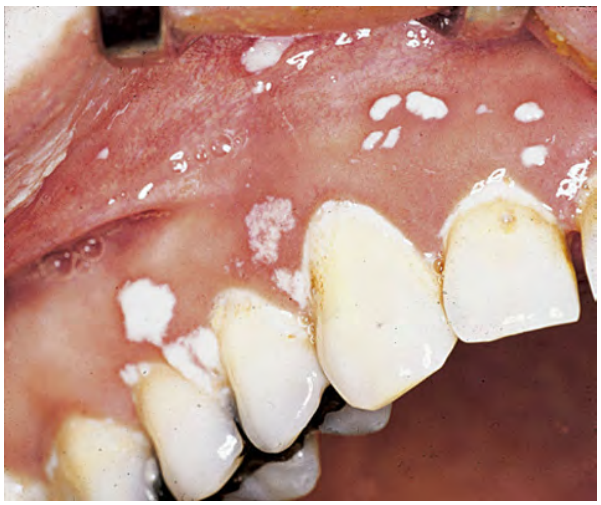
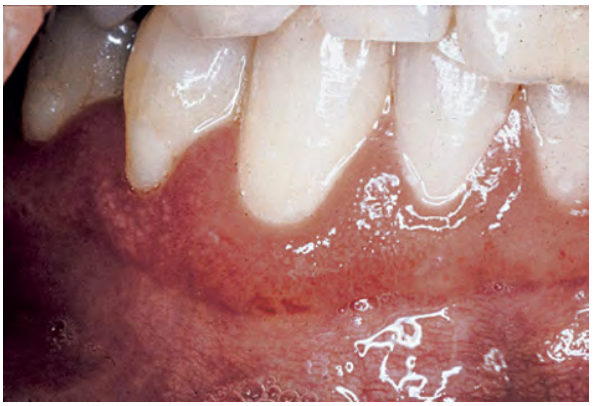


Fig. 14-11 Pseudomembranous candidosis of maxillary gingiva and mucosa in an HIV-seropositive patient. The lesions can be scraped off, leaving a slightly bleeding surface.

(a)



(b)

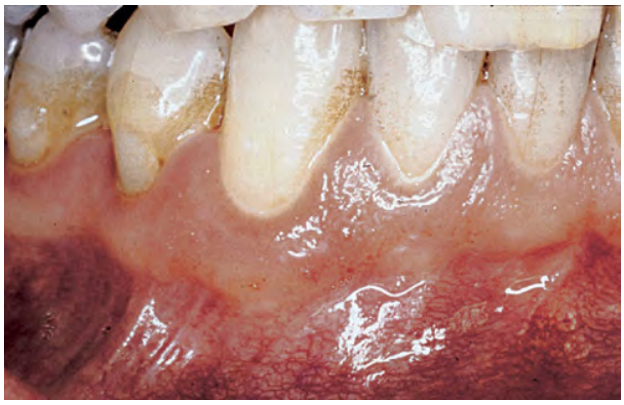


Fig. 14-12 Erythematous candidosis of attached mandibular gingiva in an HIV-seropositive patient. The mucogingival junction is not visible (a). Same patient as (a) after topical antimycotic therapy (b). The mucogingival junction is visible.

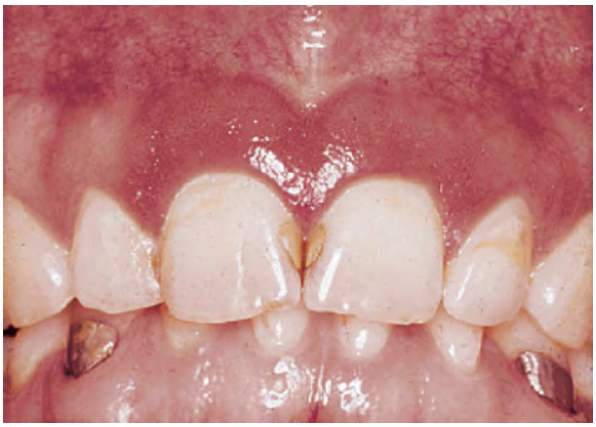


Fig. 14-13 Chronic erythematous candidosis of maxillary attached gingiva of the incisor region.

A diagnosis of candidal infection can be accomplished on the basis of culture, smear, and biopsy. Definitive identification of *Candida* can be made through a variety of supplemental tests usually involving evaluation of morphological and physiological characteristics of an isolate. Increasingly, molecular-based methods are being employed with a number of species-specific PCR approaches for *Candida* being used (Williams & Lewis 2000). A culture on Nickerson's medium at room temperature is easily handled in the dental office. Microscopic examination of smears from suspected lesions is another easy diagnostic procedure, either performed as direct examination by phase-contrast microscopy or as light microscopic examination of periodic acid–Schiff-stained or Gram-stained smears. Mycelium-forming cells in the form of hyphae or pseudohyphae and blastospores are seen in great numbers among masses of desquamated cells. Since oral carriage of *C. albicans* is common among healthy individuals, positive culture and smear does not necessarily imply candidal infection (Rindum *et al*. 1994). Quantitative assessment of the mycologic findings and the presence of clinical changes compatible with the above types of lesions are necessary for a reliable diagnosis, which can also be obtained on the basis of identification of hyphae or pseudohyphae in biopsies from the lesions.

Topical treatment involves application of antifungals, such as nystatin, amphotericin B, or miconazole. Nystatin may be used as an oral suspension. Because it is not resorbed, it can be used in pregnant or lactating women. Miconazole exists as an oral gel. It should not be given during pregnancy and it can interact with anticoagulants and phenytoin. The treatment of severe or generalized forms also involves systemic antifungals such as fluconazole. It should be emphasized that fluconazole has several pharmacokinetic drug–drug interactions (Niwa *et al*. 2014).

There are indications that candidal infection is the background of cases of gingival inflammation sometimes denoted linear gingival erythema (Fig. 14-14) (Winkler *et al*. 1988; Robinson *et al*. 1994), but studies have revealed a microflora comprising both *C. albicans* and a number of periopathogenic bacteria

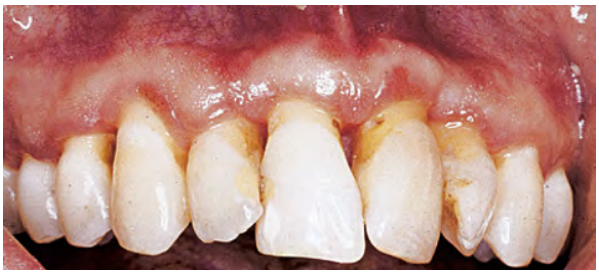


Fig. 14-14 Candidal infection of maxillary gingiva, sometimes denoted linear gingival erythema in an HIV-infected patient. Red banding along the gingival margin, which does not respond to conventional therapy.

consistent with those seen in conventional periodontitis, that is *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Campylobacter rectus* (Murray *et al*. 1988, 1989, 1991).

Histoplasmosis

Histoplasmosis is a granulomatous disease caused by *Histoplasma capsulatum*, a soil saprophyte found mainly in feces from birds and cats. The infection occurs in the North-Eastern, South-Eastern, mid Atlantic, and central states of the USA. It is also found in Central and South America, India, East Asia, and Australia. Histoplasmosis is the most frequent systemic mycosis in the USA. Airborne spores from the mycelial form of the organism mediate it (Rajah & Essa 1993). In the normal host, the course of the infection is subclinical (Anaissie *et al*. 1986). The clinical manifestations include acute and chronic pulmonary histoplasmosis, and a disseminated form, mainly occurring in immunocompromised patients (Cobb *et al*. 1989). Oral lesions have been seen in 30% of patients with pulmonary histoplasmosis and in 66% of patients with the disseminated form (Weed & Parkhill 1948; Loh *et al*. 1989). The oral lesions may affect any area of the oral mucosa (Chinn *et al*. 1995), including the gingiva, which appears to be one of the most frequent sites affected (Hernandez *et al*. 2004). The lesions start as nodular or papillary, and later may become ulcerative with loss of gingival tissue and pain (Figs. 14-15, 14-16). They are sometimes granulomatous and the clinical appearance may resemble a malignant tumor (Boutros *et al*. 1995). The diagnosis is based on clinical appearance and histopathology and/or culture, and the treatment consists of systemic antifungal therapy.

Inflammatory and immune conditions

Hypersensitivity reactions

Contact allergy

Allergic manifestations in the oral mucosa are uncommon. Several mechanisms may be involved in allergy, which is an exaggerated immune reaction. Oral

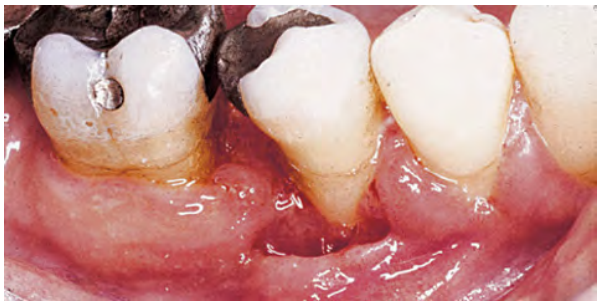


Fig. 14-15 Gingival histoplasmosis with loss of periodontal tissue around the lower right second premolar.

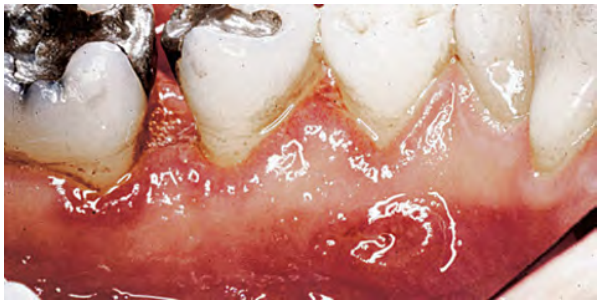


Fig. 14-16 Same patient as shown in Fig. 14-15. Lingual aspect with ulceration in the deeper part of the crater-like lesion.

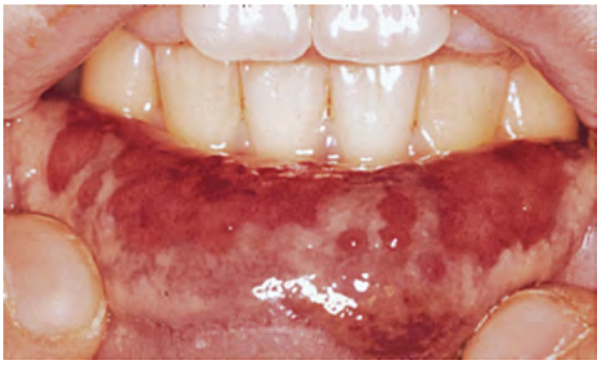


Fig. 14-17 Drug-induced erythema multiforme sometimes involves the gingiva. This is a mucosal lesion due to azathioprine, which is an antimetabolite used for immunosuppression.

mucosal reactions may be type I reactions (immediate type), which are mediated by IgE, or more often they are type IV reactions (delayed type) mediated by T cells. The rare intraoral occurrence may be due to the fact that much higher concentrations of allergen are required for an allergic reaction to occur in the oral mucosa than in skin and other surfaces (Amlot *et al*. 1985; Luders 1987; Holmstrup 1999). This section covers allergies to dental restorative materials, toothpastes, mouthwashes, chewing gum, and food.

The clinical manifestation of type IV allergy (contact allergy) occurs after a period of 12–48 hours following contact with the allergen. The effects on oral mucosa have been denoted contact lesions and prior contact with the allergen resulting in sensitization is a prerequisite for these reactions to occur (Holmstrup 1991). Oral mucosal reactions to restorative materials include reactions to mercury, nickel, gold, zinc, chromium, palladium, and acrylics (Ovrutsky and Ulyanow 1976; Zaun 1977; Bergman *et al*. 1980; Council on Dental Materials Instruments and Equipment Workshop. Biocompatibility of metals in dentistry – Recommendations for Clinical Implementation 1984; Fisher 1987). The lesions, which may infrequently affect the gingiva, have clinical similarities with those for oral lichen planus, which is why they are denoted oral lichenoid lesions (see later in this chapter) or oral leukoplakia (Fig. 14-17). They are reddish or whitish, sometimes ulcerated lesions, but one of the crucial diagnostic observations is that the lesions resolve after removal of the offending material (Feller *et al*. 2017). Additional patch testing to identify the exact allergen gives supplementary information (Larsen *et al*. 2017), but for dental amalgam it has been shown that there is no obvious correlation between the result of an epicutaneous patch test and the clinical result after removal of the fillings (Skoglund 1994). A clinical manifestation confined to the area of contact with the offending restorative material and the result after replacing this material indicate the diagnosis (Bolewska *et al*. 1990).

Contact allergy rarely occurs after the use of toothpastes (Sainio & Kanerva 1995; Skaare *et al*. 1997) and oral rinses (Sainio & Kanerva 1995; Larsen *et al*. 2017). The constituents responsible for the allergic reactions may be flavor additives, for instance carvone and cinnamon (Drake & Maibach 1976) or preservatives (Duffin & Cowan 1985). These flavoring additives may be used also in chewing gum and result in similar forms of gingivostomatitis (Kerr *et al*. 1971). The clinical manifestations of allergy include a diffuse, fiery red edematous gingivitis, sometimes with ulcerations or whitening (Fig. 14-18). The labial, buccal, and tongue mucosa may be similarly affected, and

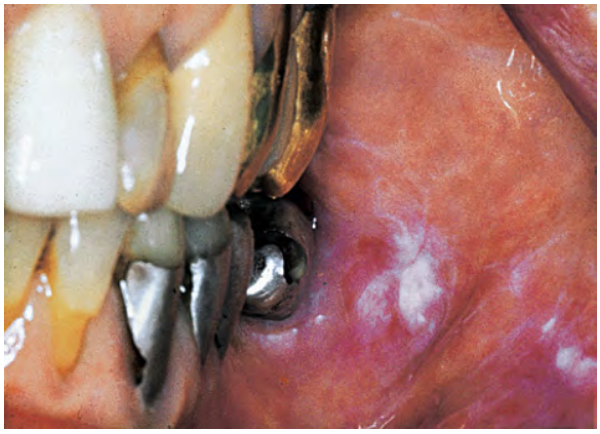


Fig. 14-18 Lichenoid contact lesion of the left buccal mucosa due to type IV hypersensitivity to mercury. The lesion is confined to the zone of contact with the amalgam fillings. These lesions usually recover after replacement of the mercury-containing fillings with composites or other materials devoid of allergy-provoking components.

cheilitis may also be seen. These characteristic clinical manifestations form the basis of the diagnosis, which may be supported by resolution of the lesions after stopping use of the allergen-containing agent.

The gastrointestinal tract is the largest immunologic organ in the body. It is constantly bombarded by a myriad of dietary proteins. Despite the extent of protein exposure, very few patients develop food allergies due to development of oral tolerance to these antigens (Chehade & Mayer 2005). Allergic reactions attributable to food may manifest both as type I and type IV reactions. Type I reaction with severe swelling has been described after intake of food components such as peanuts or pumpkin seeds. Birch pollen allergy is associated with some types of oral mucosal allergy, and >20% of patients with oral allergy may be hypersensitive to kiwi, peach, apple, chestnut, and salami (Yamamoto *et al*. 1995; Antico 1996; Asero *et al*. 1996; Liccardi *et al*. 1996,; Rossi *et al*. 1996; Helbling 1997; Wuthrich 1997). Another food allergen that can result in gingivitis or gingivostomatitis is red pepper (Serio *et al*. 1991; Hedin *et al*. 1994). Unless it has been demonstrated that the lesions resolve after removal of the allergen, the diagnosis is difficult to establish.

Plasma cell gingivitis

Plasma cell gingivitis (PCG) is an unusual benign inflammatory condition of unclear etiology (Jadwat *et al*. 2008), although it is thought to be a hypersensitive reaction to an allergen. PCG is most often encountered in young people (Hedin *et al*. 1994). It is often observed in the anterior part of the gingiva and often extending to the mucogingival junction. The lesion is generally asymptomatic and it is characterized by macular lesions that are bright red, velvety, sharply circumscribed, and flat to slightly elevated (Fig 14-19). Histopathologically, PCG is defined mainly by a dense, bandlike infiltrate of plasma cells in the lamina propria. The diagnosis is not well defined and different gingival conditions where plasma cells dominate have been classified as PCG. Supported by debridement, the condition usually heals spontaneously, although it may take years before it disappears.

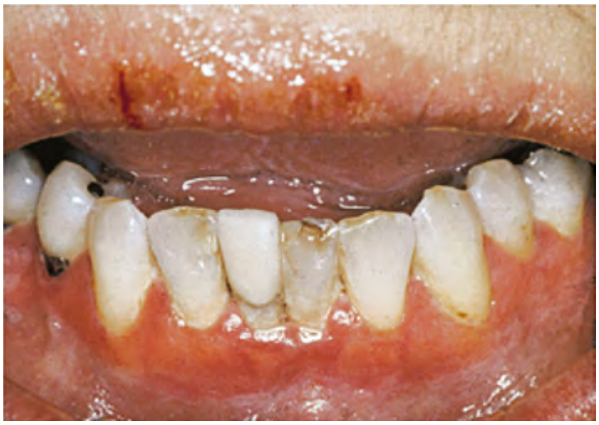


Fig. 14-19 Diffuse gingivitis and cheilitis due to contact allergy to a flavor additive in toothpaste.

Erythema multiforme

Erythema multiforme (EM) is a reactive acute, sometimes recurrent, vesiculobullous disease affecting mucous membranes and skin. A general malaise often precedes the lesions. The spectrum of the disease is from a self-limited, mild, exanthematic, cutaneous variant with minimal oral involvement to a progressive, fulminating, severe variant with extensive mucocutaneous epithelial necrosis. The latter form of the disease has been described as Stevens–Johnson syndrome, with widespread mucous membrane lesions, that is oral, ocular, and genital, in addition to skin lesions (Lozada-Nur *et al*. 1989; Assier *et al*. 1995; Bystryn 1996; Ayangco & Rogers 2003). The multilocular entity has to be differentiated from other disorders such as Reiter's and Behçet's syndromes, which also affect the eyes, the oral mucosa, and often the genitalia. The pathogenesis of EM remains unknown, but the disease appears to be a cytotoxic immune reaction against keratinocytes (Ayangco & Rogers 2003) precipitated by a wide range of factors, including HSV (Lozada & Silverman 1978; Nesbit & Gobetti 1986; Ruokonen *et al*. 1988; Miura *et al*. 1992; Aurelian *et al*. 1998; Lucchese 2018), *Mycoplasma* pneumonia (McKellar & Reade 1986; Stutman 1987), and various drugs (Bottiger *et al*. 1975; Gebel & Hornstein 1984; Kauppinen & Stubb 1984; Celentano *et al*. 2015) (Fig. 14-20).

EM may occur at any age but most frequently affects young individuals. It may or may not involve the oral mucosa, but oral involvement occurs in as many as 25–60% of cases (Huff *et al*. 1983); sometimes it is the only involved site. The characteristic oral lesions comprise swollen lips often with extensive crust formation of the vermilion border (Fig. 14-21). The basic lesions, however, are bullae that rupture and leave extensive ulcers, usually covered by heavy yellowish fibrinous exudates sometimes described as pseudomembranes (Fig. 14-22). Such lesions may also involve the buccal mucosa and gingiva (Huff *et al*. 1983; Lozada-Nur *et al*. 1989; Scully *et al*. 1991; Barrett *et al*. 1993). The skin lesions are characteristic

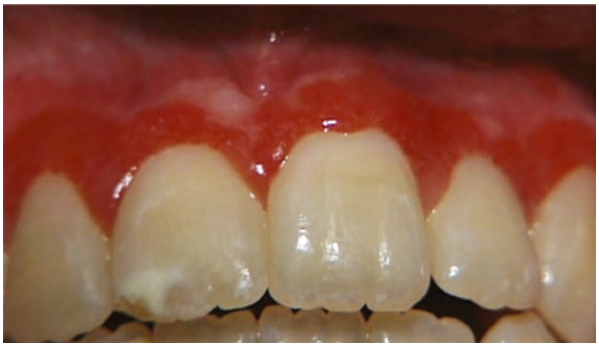


Fig. 14-20 Plasma cell gingivitis.

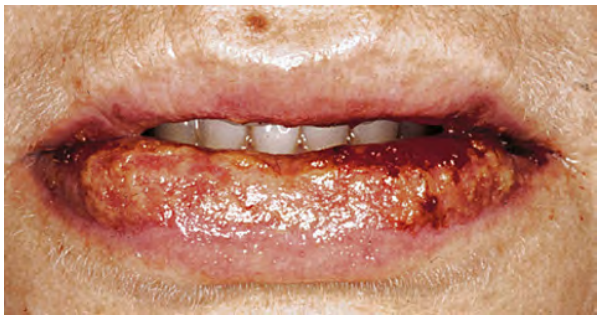


Fig. 14-21 Erythema multiforme with crust formation of the vermilion border of the lower lip.

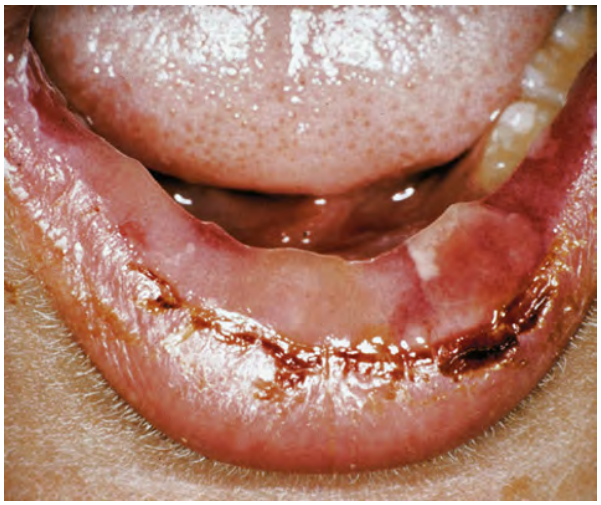


Fig. 14-22 Erythema multiforme with ulceration covered by heavy fibrin exudate.

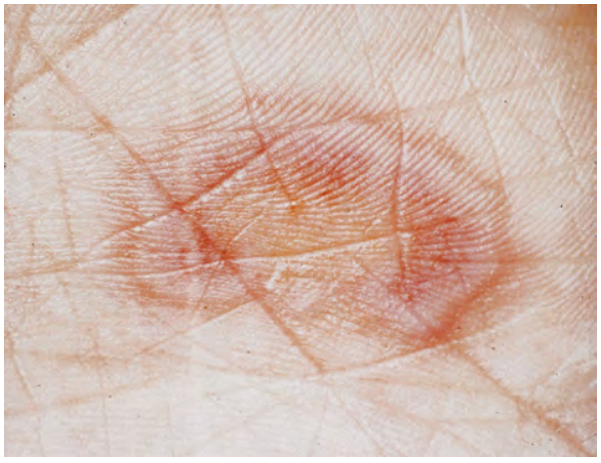


Fig. 14-23 Erythema multiforme. Skin lesion with characteristic iris appearance. A central bulla is surrounded by a blanched halo within an erythematous zone.

due to the iris appearance with a central bulla surrounded by a blanched halo within an erythematous zone (Fig. 14-23). Similar intraoral lesions do occur but they are infrequent. The disease is usually self-limiting but recurrences are common. Healing of the lesions may take several weeks (Fabbri & Panconesi 1993).

The histopathology of EM shows intra- or subepithelial separation of the epithelium from connective tissue with perivascular inflammation (Reed 1985). Immunohistochemical findings are non-specific and in most instances the diagnosis relies on the clinical findings. Although periodontal lesions are not the most frequent intraoral manifestation, they can sometimes pose a differential diagnostic problem. The typical crusty ulcerations of the vermilion border and the heavy fibrin exudates covering intraoral lesions are indicative of EM, and therefore are sometimes denoted erythema multiforme exudativum. The mucosal ulcerations may take weeks to heal and they are painful (Lozada-Nur *et al*. 1989).

As for any intraoral ulcerations, gentle plaque control and professional cleaning are mandatory. The treatment often involves systemic corticosteroids, but topical treatment may be effective in cases with minor lesions. Cases of recurrent EM caused by herpes infection may require prophylactic use of 400 mg acyclovir twice daily.

Autoimmune diseases of skin and mucous membranes

A variety of mucocutaneous disorders present gingival manifestations, sometimes in the form of desquamative lesions or ulceration of the gingiva. The most important of these diseases are lichen planus, pemphigoid, pemphigus vulgaris, erythema multiforme, and lupus erythematosus.

Pemphigus vulgaris

Pemphigus is a group of autoimmune diseases characterized by formation of intraepithelial bullae in skin and mucous membranes (McMillan *et al*. 2015). The group comprises several variants of which pemphigus vulgaris (PV) is the most common and most serious (Barth & Venning 1987).

Individuals of a Jewish or Mediterranean background are more often affected by PV than others. This is an indication of a strong genetic background to the disease (Pisanti *et al*. 1974). The disease may occur at any age but is typically seen in the middle-aged or elderly. It presents with widespread bulla formation, often including large areas of skin, and if left untreated the disease is life threatening. Intraoral onset of the disease with bulla formation is very common and lesions of the oral mucosa, including the gingiva, are frequently seen. Early lesions may resemble aphthous ulcers (Fig. 14-24), but widespread erosions are common at later stages (Fig. 14-25). Gingival involvement may present as painful desquamative lesions or as erosions or ulcerations, which are the remains of ruptured bullae. Such lesions may be indistinguishable from benign mucous membrane pemphigoid (Zegarelli & Zegarelli 1977; Sciubba 1996) (Fig. 14-26). Since the bulla formation is located in the

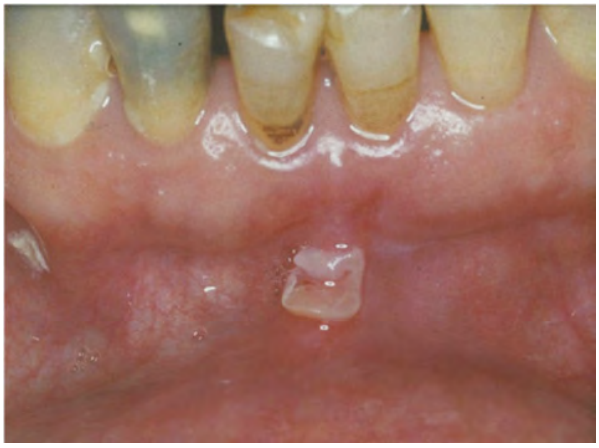


Fig. 14-24 Pemphigus vulgaris. Initial lesion resembling recurrent aphthous stomatitis.

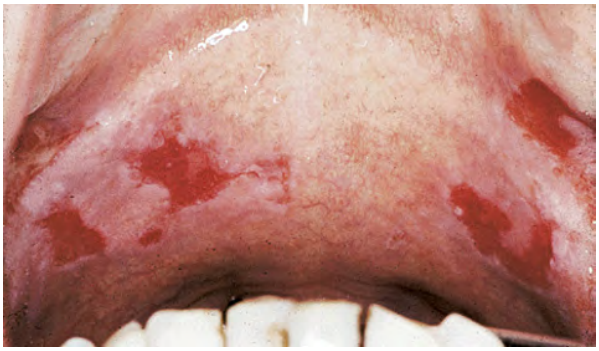


Fig. 14-25 Pemphigus vulgaris. Erosions of soft palatal mucosa. The erosive lesions are due to loss of the superficial part of the epithelium, leaving the connective tissue covered only by the basal cell layers.

spinous cell layer, the chance of seeing an intact bulla is even more reduced than in benign mucous membrane pemphigoid. Involvement of other mucous membranes is common (Laskaris *et al*. 1982). The ulcers heal slowly, usually without scar formation, and the disease runs a chronic course with recurring bulla formation (Zegarelli & Zegarelli 1977).

Diagnosis of PV is based on the characteristic histologic feature of intraepithelial bulla formation due to destruction of desmosomes resulting in acantholysis. The bullae contain non-adhering free epithelial cells, denoted Tzank cells, which have lost their intercellular bridges (Coscia-Porrazzi *et al*. 1985; Nishikawa *et al*. 1996). Mononuclear cells and neutrophils dominate the associated inflammatory reaction. Immunohistochemistry reveals pericellular epithelial deposits of IgG and C3. Circulating autoantibodies against interepithelial adhesion molecules are detectable in serum samples of most patients, but at the initial stage of the intraoral disease, antiepithelial antibody may not be elevated (Melbye *et al*. 1987; Manton & Scully 1988; Lamey *et al*. 1992; Lever & Schaumburg-Lever 1997). The background to bulla formation in PV is damage to the intercellular adhesion caused by autoantibodies to cadherin-type epithelial cell adhesion molecules (desmoglein 1 and 3) (Nousari & Anhalt 1995; Nishikawa *et al*. 1996; Lanza *et al*. 2006). The mechanism by which these molecules trigger the formation of autoantibodies has not yet been established.

Immediate referral of patients with PV to a dermatologist or internal medicine specialist is important because when recognized late (Daltaban *et al*. 2020), the disease can be fatal, although systemic corticosteroid therapy can presently treat most cases. Supplementary local treatment consists of gentle plaque control and professional cleaning, as mentioned for the chronic inflammatory oral mucosal diseases earlier. Sometimes, additional topical corticosteroid application is needed to control the intraoral disease activity

Pemphigoid

Pemphigoid is a group of disorders in which autoantibodies towards components of the basement membrane result in detachment of the epithelium from the connective tissue. Bullous pemphigoid predominantly affects the skin, but oral mucosal involvement may occur (Brooke 1973; Hodge *et al*. 1981). If only mucous membranes are affected, the term benign mucous membrane pemphigoid (BMMP) is often used. The term cicatricial pemphigoid is also used to describe subepithelial bullous disease limited to the mouth or eyes and infrequently other mucosal areas. This term is problematic for the oral lesions, because usually oral lesions do not result in scarring, whereas this is an important concern for ocular lesions. It is now evident that BMMP comprises a group of disease entities characterized by an immune reaction involving autoantibodies directed against various basement membrane zone antigens (Scully & Laskaris 1998). These antigens have been identified as hemidesmosome or lamina lucida components (Leonard *et al*. 1982; Leonard *et al*. 1984; Manton & Scully 1988; Domloge-Hultsch *et al*. 1992; Domloge-Hultsch *et al*. 1994), and sera from patients with oral lesions have been shown to recognize the alpha-6 integrin subunit (Rashid *et al*. 2006). In addition, complement-mediated cell destructive processes may be involved in the pathogenesis of the disease (Eversole 1994). The trigger mechanisms behind these reactions, however, have not yet been revealed.

The majority of affected patients are female with a mean age at onset of 50 years or older (Shklar & McCarthy 1971). Oral involvement in BMMP is almost inevitable and usually the oral cavity is the first site of disease activity (Silverman *et al*. 1986; Gallagher & Shklar 1987). Any area of the oral mucosa may be involved in BMMP, but the main manifestation is desquamative lesions of the gingiva presenting as intensely erythematous attached gingiva (Laskaris *et al*. 1982; Silverman *et al*. 1986; Gallagher & Shklar 1987) (Fig. 14-26). The inflammatory changes, as always when not caused by plaque, may extend

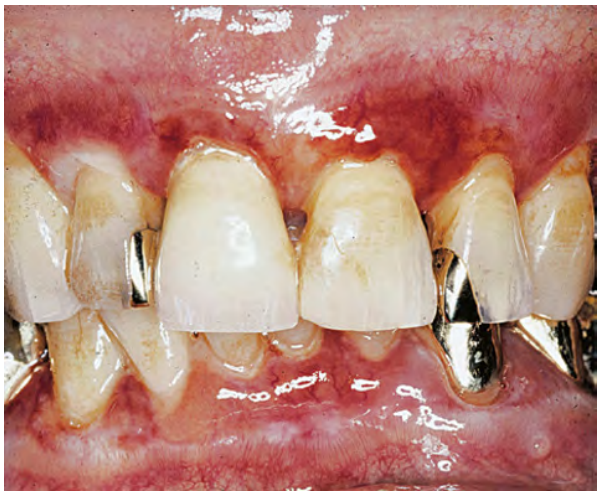


Fig. 14-26 Mucous membrane pemphigoid affecting the attached gingiva of both jaws. The lesions are erythematous and resemble erythematous lichen planus lesions. They result in pain associated with oral procedures, including eating and oral hygiene procedures.

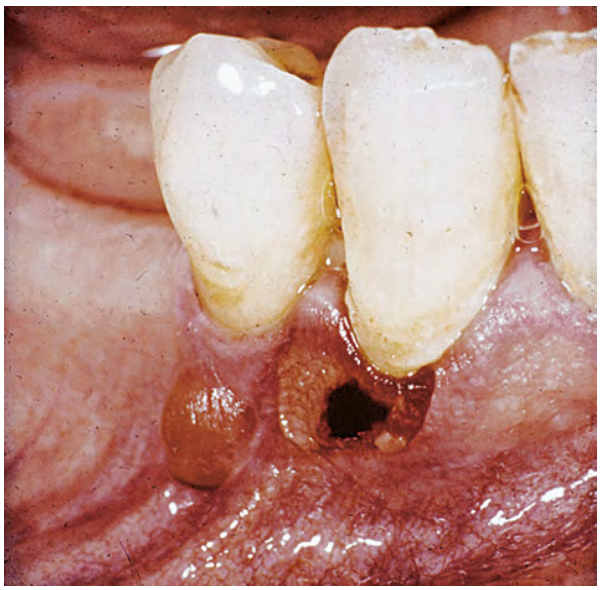


Fig. 14-27 Mucous membrane pemphigoid with intact and ruptured gingival bulla.

over the entire gingival width and even over the mucogingival junction. Rubbing the gingiva may precipitate bulla formation (Dahl & Cook 1979). This is denoted a positive Nicholsky sign and is caused by the destroyed adhesion of the epithelium to the connective tissue. The intact bullae are often clear to yellowish or they may be hemorrhagic (Figs. 14-27, 14-28). This, again, is due to the separation of epithelium from connective tissue at the junction, resulting in exposed vessels inside the bullae. Usually, the bullae rupture rapidly leaving fibrin-coated ulcers. Sometimes, tags of loose epithelium can be found due to rupture of bullae. Other mucosal surfaces may be involved in some patients. Ocular lesions are particularly important because scar formation can result in blindness (Williams *et al*. 1984) (Fig. 14-29).

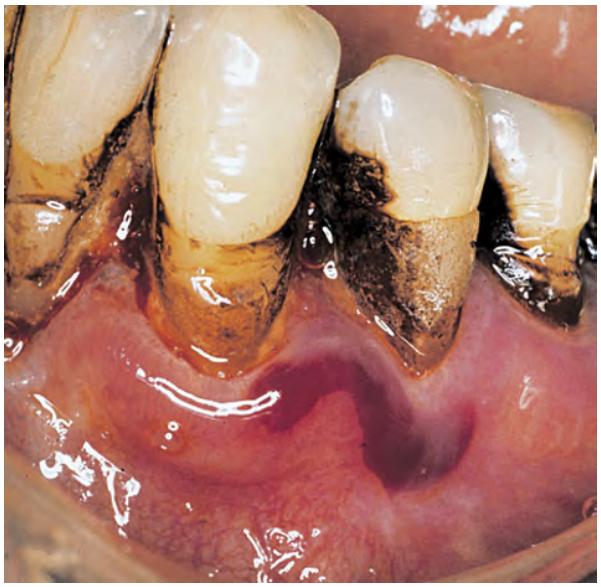


Fig. 14-28 Mucous membrane pemphigoid with hemorrhagic gingival bulla. The patient uses chlorhexidine for daily plaque reduction.

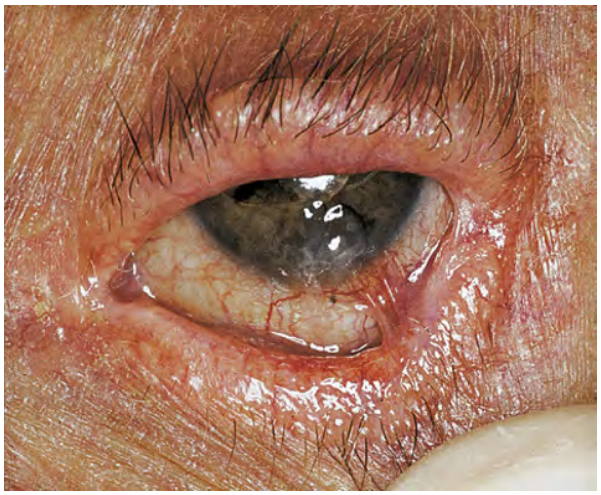


Fig. 14-29 Mucous membrane pemphigoid. Eye lesion with scar formation due to coalescence of palpebral and conjunctival mucosa.

The separation of epithelium from connective tissue at the basement membrane area is the main diagnostic feature of BMMP. A non-specific inflammatory reaction is a secondary histologic finding. In addition, immunohistochemical examination can help distinguish BMMP from other vesiculobullous diseases, in particular pemphigus, which is life threatening. Deposits of C3, IgG, and sometimes other immunoglobulins as well as fibrin are found at the basement membrane zone in the vast majority of cases (Laskaris & Nicolis 1980; Daniels & Quadra-White 1981; Manton & Scully 1988). It is important to involve perilesional tissue in the biopsy because the characteristic features may have been lost within lesional tissue (Ullman 1988). Circulating immunoglobulins are not always found in BMMP by indirect immunofluorescence (Laskaris & Angelopoulos 1981).

However, a study has shown that 75% of 20 patients with oral pemphigoid phenotype without scarring possessed circulating autoantibodies against the BP180 molecule, indicating a prominent role for this protein as a target antigen in this type of pemphigoid with only oral lesions (Calabresi *et al*. 2007).

Therapy consists of professional atraumatic plaque removal and individual instruction in gentle, but careful, daily plaque control, eventually supplemented with daily use of chlorhexidine and/or topical corticosteroid application if necessary. As for all the chronic inflammatory oral mucosal diseases, oral hygiene procedures are very important and controlling the infection from plaque bacteria may result in a considerable reduction of disease activity and symptoms. It is also important to prevent the development of attachment loss due to periodontitis in those patients with difficulties in maintaining oral hygiene (Tricamo *et al*. 2006). However, the disease is chronic in nature and formation of new bullae is inevitable in most patients. Topical corticosteroids, preferably applied as a paste at night, temper the inflammatory reaction. A systematic review has preliminarily suggested that patients with oral PV or BMMP appear somewhat more susceptible to periodontitis, which in turn may potentially trigger the bullous disorders. Obviously, these patients should be encouraged by dermatologists to pursue collaborative professional periodontal follow-up by dentists (Jascholt *et al*. 2017).

Lichen planus

Lichen planus is the most common mucocutaneous disease manifesting on the gingiva. The disease may affect the skin and oral as well as other mucosal membranes in some patients, while others may present with either skin or oral mucosal involvement alone. Oral involvement alone is common and concomitant skin lesions in patients with oral lesions have been found in 5–44% of cases (Andreasen 1968; Axell & Rundquist 1987). The disease may be associated with severe discomfort and since it has been shown to possess a premalignant potential (Holmstrup 1992), it is important to diagnose and treat the patients and to follow them at the regular oral examinations (Holmstrup *et al*. 1988; Mattson *et al*. 2002; Mignogna *et al*. 2007).

The prevalence of oral lichen planus (OLP) in various populations has been found to be 0.1–4% (Scully *et al*. 1998a). The disease may afflict patients at any age, although it is seldom observed in childhood (Scully *et al*. 1994).

Skin lesions are characterized by papules with white striae (Wickham striae) (Fig. 14-30). Itching is a common symptom, and the most frequent locations are the flexor aspects of the arms, thighs, and neck. In the vast majority of cases, the skin lesions disappear spontaneously after a few months, which is in sharp contrast to the oral lesions, which usually persist for many years (Thorn *et al*. 1988).

A variety of clinical appearances is characteristic of OLP. These include:

- Papular (Fig. 14-31)
- Reticular (Figs. 14-32, 14-33, 14-40)
- Plaque-type (Fig. 14-34)
- Erythematous (atrophic) (Figs. 14-35, 14-36, 14-37, 14-38, 14-39)
- Ulcerative (Figs. 14-36, 14-41)
- Bullous (Fig. 14-43).

The simultaneous presence of more than one type of lesion is common (Thorn *et al*. 1988). The most characteristic clinical manifestations of the disease and the basis of the clinical diagnosis are white papules (Fig. 14-31)

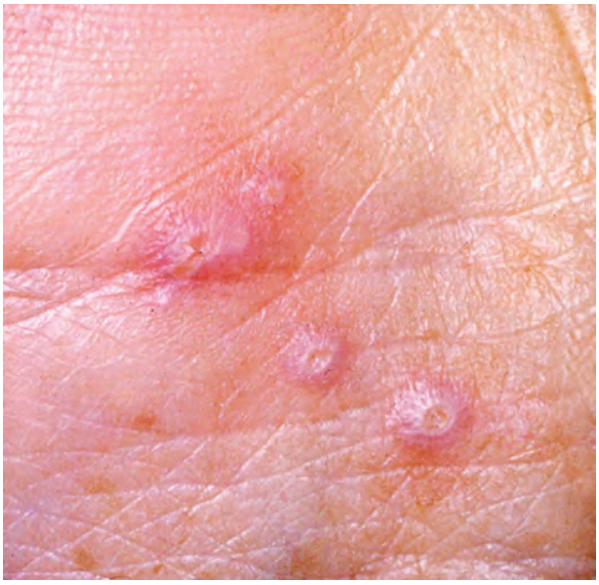


Fig. 14-30 Skin lesions of lichen planus. Papules with delicate white striations.

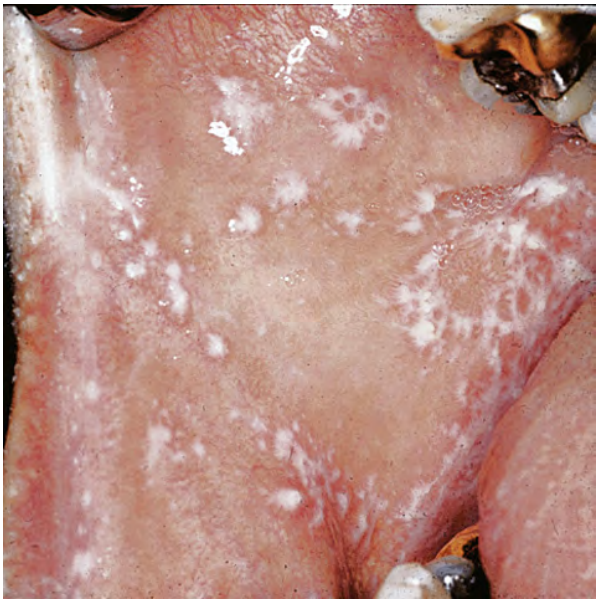


Fig. 14-31 Oral lichen planus. Papular lesion of right buccal mucosa.

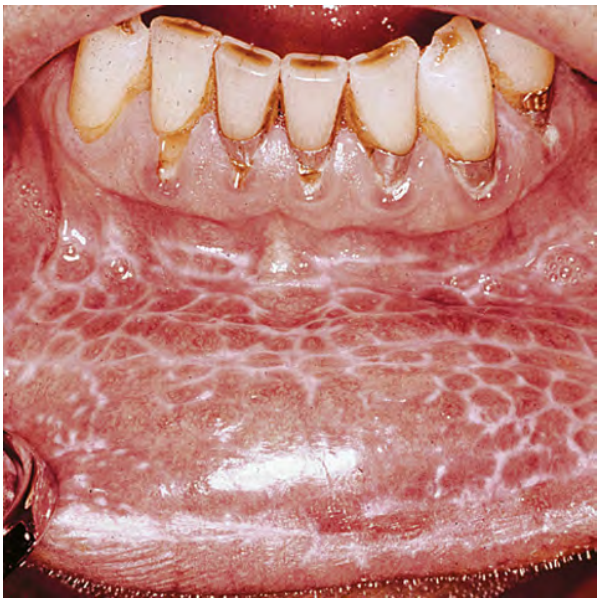


Fig. 14-32 Oral lichen planus. Reticular lesion of lower lip mucosa. The white striations are denoted Wickham's striae.

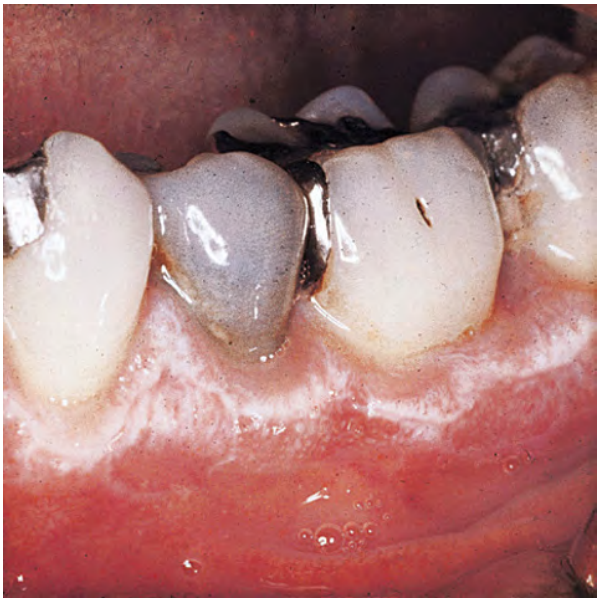


Fig. 14-33 Oral lichen planus. Reticular lesions of gingivae in the lower left premolar and molar region.

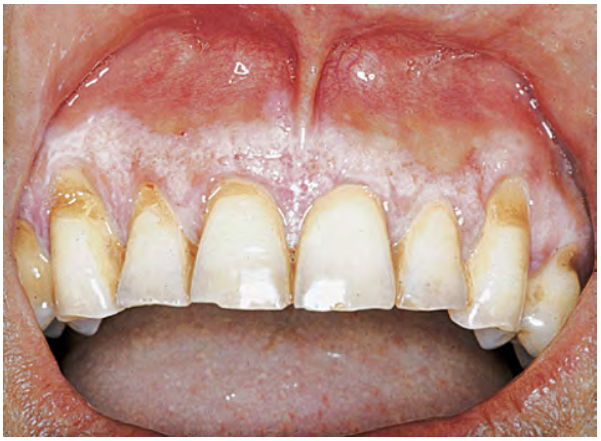


Fig. 14-34 Oral lichen planus. Plaque-type lesion of maxillary gingivae.

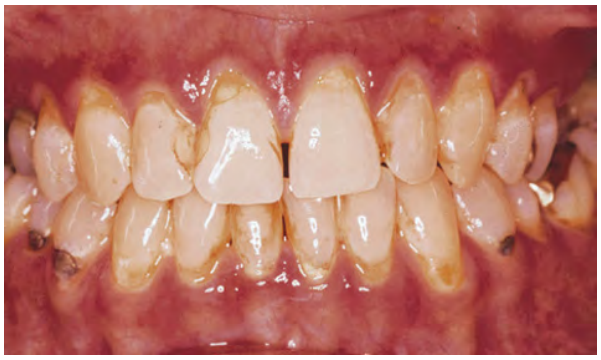


Fig. 14-35 Oral lichen planus. Erythematous lesions of facial maxillary and mandibular gingiva. Such lesions were previously termed desquamative gingivitis. Note that the margin of the gingiva has a normal color in the upper incisor region, which distinguishes the lesions from plaque-induced gingivitis.

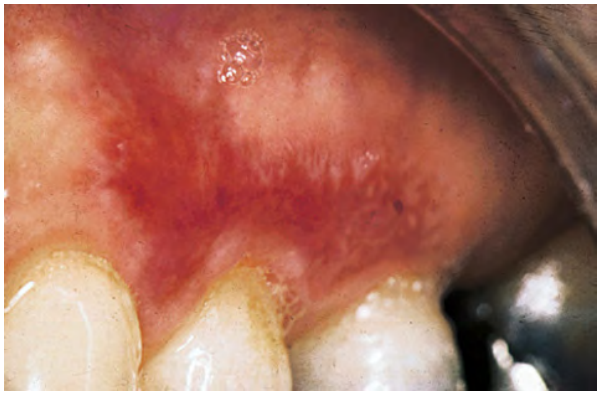


Fig. 14-36 Oral lichen planus. Erythematous and ulcerative lesion of the maxillary gingivae.

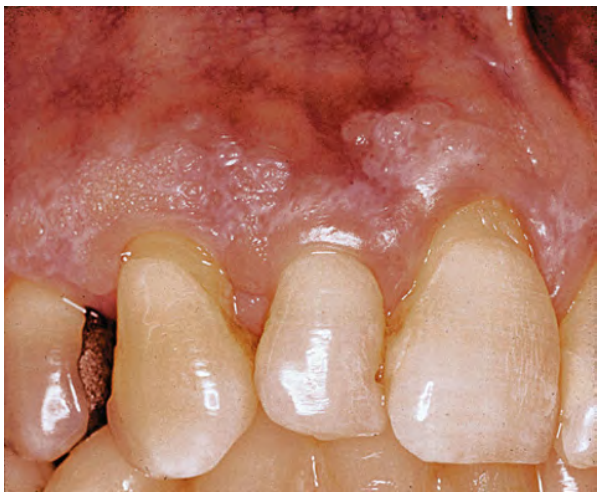


Fig. 14-37 Oral lichen planus. Erythematous and reticular lesion of maxillary gingivae. Several types of lesions are often present simultaneously.

and white striations (Figs. 14-32, 14-33, 14-40), which often form reticular patterns (Thorn *et al*. 1988), usually bilaterally (Ingafou *et al*. 2006). Sometimes erythematous and ulcerative lesions are referred to as erosive (Rees 1989). Papular, reticular, and plaque-type lesions

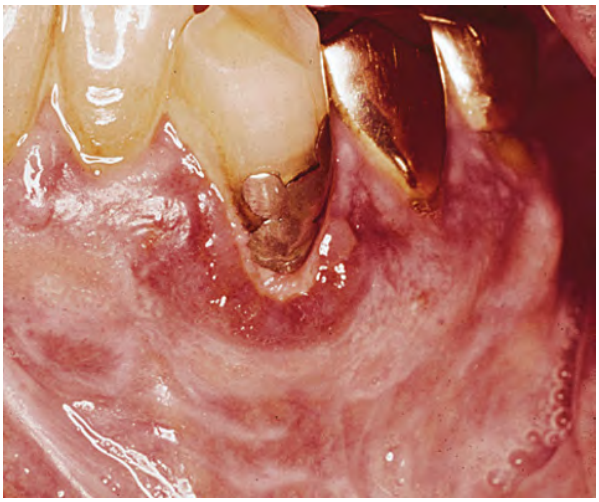


Fig. 14-38 Oral lichen planus. Erythematous and reticular lesion of the lower left canine region. Plaque accumulation results in exacerbation of oral lichen planus, and erythematous lesions compromise oral hygiene procedures. This may lead to a vicious circle that the dentist can help in breaking.

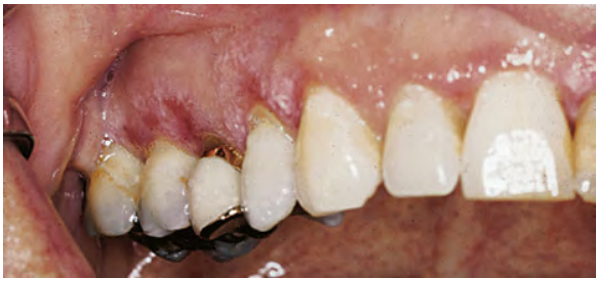


Fig. 14-39 Oral lichen planus. Erythematous and reticular lesion of right maxillary gingiva in a patient using an electric toothbrush, which is traumatic to the marginal gingiva. The physical trauma results in exacerbation of the lesion with erythematous characteristics and pain.

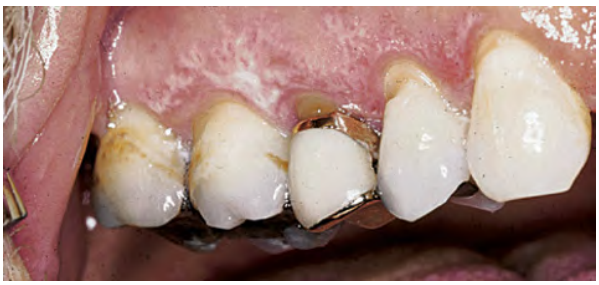


Fig. 14-40 Same patient as shown in Fig. 14-39 after modified toothbrushing instructions with no traumatic action on the marginal gingiva. Pain is no longer noted by the patient.

usually do not give rise to significant symptoms, whereas erythematous and ulcerative lesions are associated with moderate-to-severe pain, especially in relation to oral hygiene procedures and eating. Any area of the oral mucosa may be affected by OLP, but the lesions often change in clinical type and extent over the years. Such changes may imply the development of plaque-type lesions, which are clinically indistinguishable from oral leukoplakia. This may give rise to a diagnostic problem if other lesions more characteristic of OLP have disappeared (Thorn *et al*. 1988).

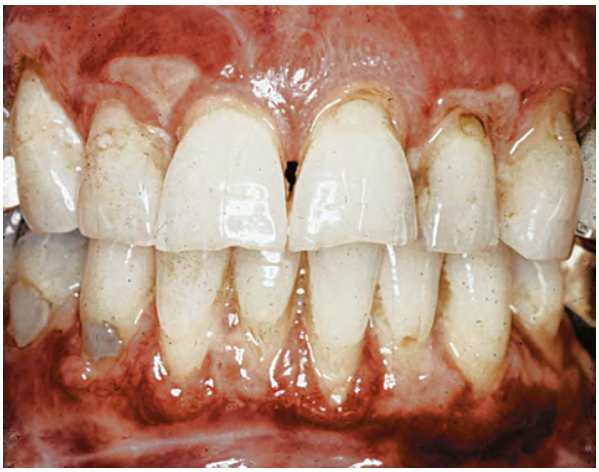


Fig. 14-41 Oral lichen planus. Erythematous and ulcerative/reticular lesions of the maxillary and mandibular incisor regions. This 48-year-old woman suffered from severe discomfort when eating, drinking, and toothbrushing.

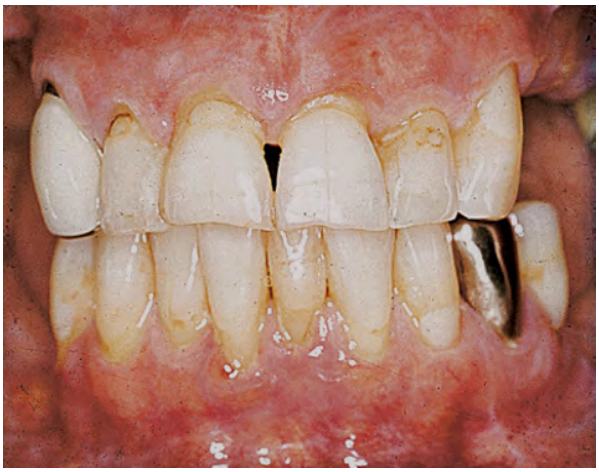


Fig. 14-42 Same patient as shown in Fig. 14-41 after periodontal treatment and extraction of teeth with deep pockets. An individual oral hygiene program, which ensured gentle, meticulous plaque removal, has been used by the patient for 3 months. The erythematous/ulcerative lesions are now healed and there are no longer any symptoms.

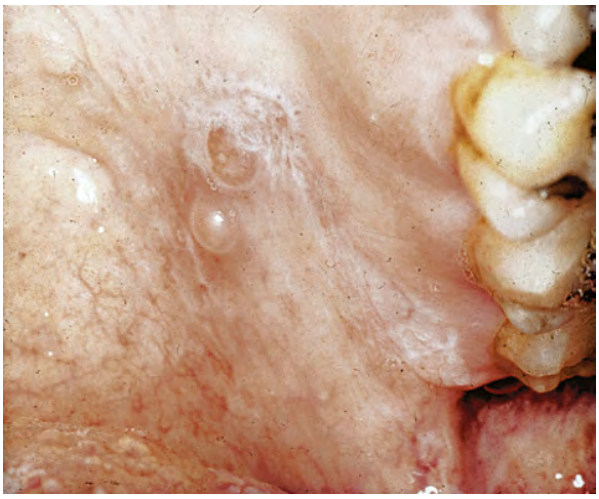


Fig. 14-43 Oral lichen planus. Bullous/reticular lesion of the left palatal mucosa.

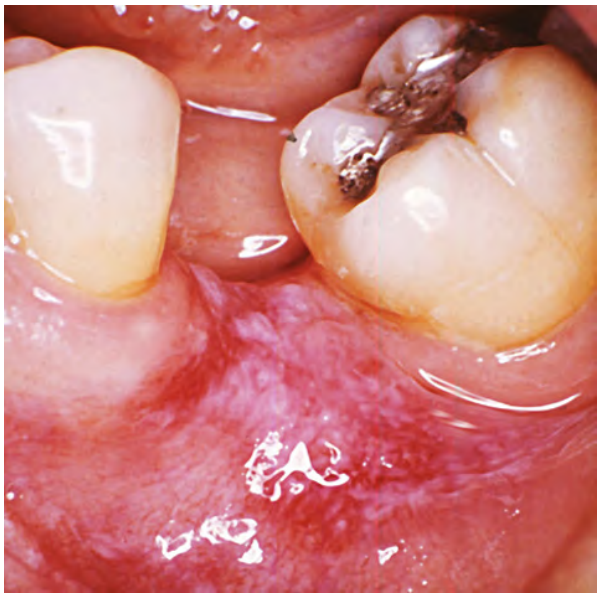


Fig. 14-44 Gingival discoid lupus erythematosus lesion. A central erythematous area with small white dots is surrounded by delicate white striae.

A characteristic histopathologic feature in OLP is a subepithelial, band-like accumulation of lymphocytes and macrophages characteristic of a type IV hypersensitivity reaction (Eversole *et al*. 1994). The epithelium shows hyperortho- or hyperparakeratinization and basal cell disruption with transmigration of lymphocytes into the basal and parabasal cell layers (Eversole 1995). The infiltrating lymphocytes have been identified as CD4- and CD8-positive cells (Buechner 1984; Walsh *et al*. 1990; Eversole *et al*. 1994). Other characteristic features are Civatte bodies, which are dyskeratotic basal cells. Common immunohistochemical findings of OLP lesions are fibrin in the basement membrane zone, and deposits of IgM, C3, C4, and C5 may also be found. None of these findings is specific for OLP (Schiodt *et al*. 1981; Kilpi *et al*. 1988; Eversole *et al*. 1994).

The subepithelial inflammatory reaction in OLP lesions is presumably due to an unidentified antigen in the junctional zone between the epithelium and connective tissue or to components of basal epithelial cells (Holmstrup and Dabelsteen 1979; Walsh *et al*. 1990; Sugerman *et al*. 1994). A lichen planus-specific antigen in the stratum spinosum of skin lesions has been described (Camisa *et al*. 1986), but does not appear to play a significant role in oral lesions since it is rarely identified there. It is still an open question whether OLP is a multivariate group of etiologically diverse diseases with common clinical and histopathologic features or a disease entity characterized by a type IV hypersensitivity reaction to an antigen in the basement membrane area. The clinical diagnosis is based on the presence of papular or reticular lesions. The diagnosis may be supported by histopathologic findings of hyperkeratosis, degenerative changes of basal cells, and subepithelial inflammation dominated by lymphocytes and macrophages (Holmstrup 1999).

The uncertain background of OLP results in several border zone cases of so-called oral lichenoid lesions (OLLs), a final diagnosis for which is difficult to establish (Thornhill *et al*. 2006). The most common OLLs are probably lesions in contact with dental restorations (Holmstrup 1991) (see later in this chapter). Other types of OLL are associated with various types of medications, including antimalarials, quinine, quinidine, non-steroidal anti-inflammatory drugs, thiazides, diuretics, gold salts, penicillamine, and beta-blockers (Scully *et al*. 1998a). Graft-versus-host reactions are also characterized by a lichenoid appearance (Fujii *et al*. 1988) and a group of OLLs is associated with systemic diseases including liver disease (Fortune & Buchanan 1993; Bagan *et al*. 1994; Carrozzo *et al*. 1996). This appears to be particularly evident in Southern Europe and Japan where hepatitis C has been found in 20–60% of OLL cases (Bagan *et al*. 1994; Gandolfo *et al*. 1994; Nagao *et al*. 1995).

Several follow-up studies have demonstrated that OLP is associated with increased development of oral cancer, the frequency of cancer development being in the range of 0.5–2% (Holmstrup *et al*. 1988; Mattson *et al*. 2002; Rodstrom *et al*. 2004; Ingafou *et al*. 2006; Mignogna *et al*. 2007).

When gingiva is involved, the most important part of the therapeutic regimen is atraumatic meticulous plaque control, which results in significant improvement in many patients (Holmstrup *et al*. 1990) (Figs. 14-39, 14-40, 14-41, 14-42). Individual oral hygiene procedures with the purpose of effective plaque removal without traumatic influence on the gingival tissue should be established for all patients with symptoms. In cases of persistent pain, typically associated with atrophic and ulcerative lesions, antifungal treatment may be necessary if the lesions host yeast, which is the case in 37% of OLP cases (Krogh *et al*. 1987). In painful cases, who have not responded to the treatment above, the use of therapeutic agents may be considered, and several agents have been investigated. Among these are corticosteroids, retinoids, cyclosporine, and phototherapy, in addition to other treatment modalities. A systematic review of clinical trials (Al-Hashimi *et al*. 2007) showed that topical corticosteroids particularly are often effective, preferably in a paste or an ointment to be used three times daily for a number of weeks. However, in such cases, relapses are very common, which is why intermittent periods of treatment may be needed over an extended period of time. Aloe vera shows promising results especially with no adverse effects compared with various adverse effects of corticosteroids (Ali & Wahbi 2017). It appears that topical tacrolimus is an effective alternative to topical clobetasol and may be considered as a first-line therapy in the management of painful OLP (Chamani *et al*. 2015).

Lupus erythematosus

Lupus erythematosus (LE) is a group of autoimmune connective tissue disorders in which autoantibodies

form to various cellular constituents, including nucleus and cytoplasmic membrane. All parts of the body may be affected, and the disease is much more prevalent among women than among men. The etiology of LE remains unknown, but deposits of antigen–antibody complexes appear to play a role in the tissue damage characteristic of the disease (Schrieber & Maini 1984). The prevalence of LE has been estimated at 0.05% (Condemi 1987).

There are two major traditional forms: discoid LE (DLE) and systemic LE (SLE), which may involve a range of organ systems, including the kidney, heart, central nervous system, vascular system, and bone marrow. Two additional forms, acute and subacute cutaneous LE, have more recently been added to the classification, and represent different degrees of disease activity and increased risk of development of SLE (Wouters *et al*. 2004).

DLE is a mild chronic form, which involves skin and mucous membranes, sometimes including the gingiva as well as other parts of the oral mucosa (Schiodt 1984; Schiodt & Pindborg 1984). The typical lesion presents as a central atrophic area with small white dots surrounded by irradiating fine white striae with a periphery of erythema (Fig. 14-44). The lesions can be ulcerated or clinically indistinguishable from leukoplakia or erythematous OLP (Fig. 14-45) (Schiodt 1984). Sometimes patients present with brownish gingival lesions, which are a side effect of antimalarial drugs prescribed to these patients as part of their treatment (Fig. 14-46). Eight percent of patients with DLE develop SLE, and ulcerations may be a sign of SLE (Rodsaward *et al*. 2017), which has a 25–40% prevalence of oral lesions (Schiodt & Pindborg 1984; Pisetsky 1986; Jonsson *et al*. 1988). The characteristic Bordeaux-colored "butterfly" skin lesions are photosensitive, scaly, erythematous macules located on the bridge of the nose and the cheeks (Standefer & Mattox 1986). The systemic type, which can still be fatal because of nephrologic and hematologic complications, also shows skin lesions on the face, but they tend to spread over the entire body.

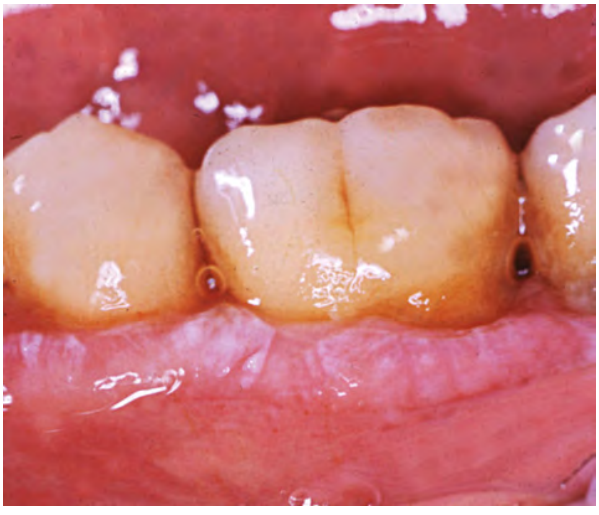


Fig. 14-45 Gingival plaque-type discoid lupus erythematosus lesion resembling frictional keratosis and leukoplakia.

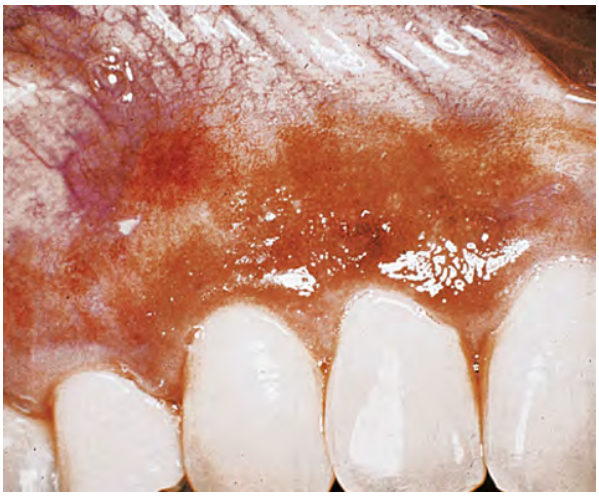


Fig. 14-46 Antimalarial drugs may result in brownish gingival discoloration. This is a patient with discoid lupus erythematosus receiving an antimalarial drug, chloroquine, as part of the treatment regimen.

Diagnosis is based on clinical and histopathologic findings. The epithelial changes, characteristic of oral LE lesions, are hyperkeratosis, keratin plugging, and variation in epithelial thickness, as well as liquefaction degeneration of basal cells and increased width of the basement membrane. The subepithelial connective tissue harbors inflammation, sometimes resembling OLP, but often with a less distinct band-shaped pattern (Schiodt & Pindborg 1984). Immunohistochemical investigation reveals deposits of various immunoglobulins, C3, and fibrin along the basement membrane (Reibel & Schiodt 1986).

Systemic corticosteroid and other anti-inflammatory treatment regimens are required for SLE. Additional topical treatment is sometimes needed for the resolution of symptomatic intraoral lesions.

Granulomatous inflammatory lesions (orofacial granulomatosis)

Crohn's disease

Crohn's disease (CD) is characterized by chronic granulomatous infiltrates of the wall of the last ileal loops, but any part of the gastrointestinal tract can be affected. As the oral cavity is part of the gastrointestinal tract, it is not surprising that CD can occur from the rectum to the lips. When the oral mucosa is involved as part of CD, the oral component is classified as oral Crohn´s disease. Orofacial granulomatosis (OFG) is a rare chronic inflammatory disorder confined to lips, gingivae, buccal mucosa and floor of the mouth. The exact relationship between OFG and oral Crohn´s disease remains unknown, but at present the two diseases are considered as separate entities (Sanderson *et al*. 2005; Zbar *et al*. 2012; Gale *et al*. 2016).

The number of reports of lesions involving the periodontium is limited (van Steenberghe *et al*. 1976), which is probably related to a tradition by many clinicians of using the term aphthous lesions for any ulcerative disease of the oral mucosa. The oral lesions have striking similarity to those of the intestinal tract, that is, irregular long ulcerations with elevated borders with a cobblestone appearance. Usually, the periodontal lesions appear after the diagnosis has been established based on the intestinal involvement, but sometimes the oral lesions are the first findings that lead to diagnosis. Characteristic clinical findings are mucosal foldings of the buccal or labial sulcus (Fig. 14-47) and in the gingiva an erythematous cobblestone or granulomatous appearance may be observed (Fig. 14-48, 14-49). Exacerbations of the oral lesions appear in parallel with those of the intestine. An increased risk of periodontal destruction has been reported to be associated with a defective neutrophil function (Lamster *et al*. 1982).

Sarcoidosis

Granulomatous inflammatory conditions have been used as a collective term for CD, OFG, and sarcoidosis, because these diseases show the same histopathologic features: non-caseating, epithelioid cell granulomas in the affected tissue. Rarely, all three diseases may present with gingival lesions, characterized by swellings (Pindborg 1992; Mignogna *et al*. 2001) and sarcoidosis, which is sometimes present as a fiery red granular gingival overgrowth (Fig. 14-50). Of 45 cases of oral sarcoidosis, 13% had gingival lesions (Blinder *et al*. 1997). A study of 35 patients with OFG demonstrated ileal and colonic abnormalities in 54%, and granulomas were revealed in gut biopsies of 64% of the patients. Intestinal abnormality was significantly more likely if the age of onset was <30 years (Sanderson *et al*. 2005).

Local treatment of disconfiguring lip swelling as part of oral granulomatous inflammatory conditions consists of intralesional steroid injection (El-Hakim

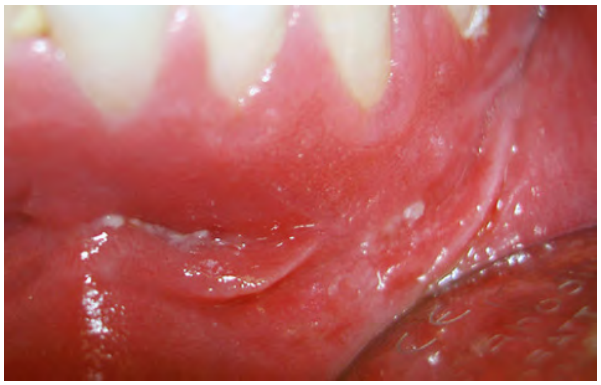


Fig. 14-47 A frequent oral finding in patients with Crohn´s disease is mucosal foldings, usually located in the buccal or labial sulcus. Such lesions may be the first clinical finding that leads to the diagnosis of the disease. Histopathologic examination of biopsies from these foldings reveals epithelioid cell granulomas. The foldings are also characteristic for the other types of orofacial granulomatosis.

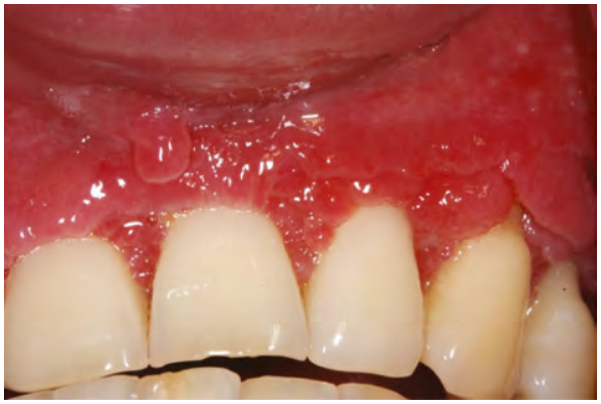


Fig. 14-48 Gingival lesion in a Crohn's patient. Cobblestoning may be seen in the gingiva. Histopathologic examination of biopsies from this type of lesion very often contain granulomas. Thus, if such a lesion is present, a biopsy should be taken from this location.

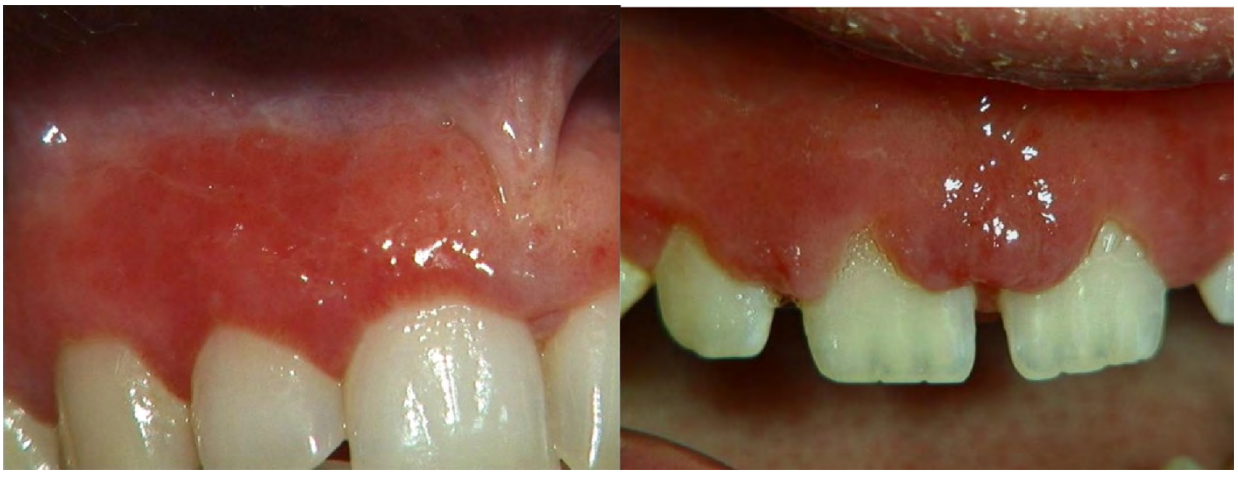


Fig. 14-49 Gingival lesion in a Crohn's patient. Erythema and swelling with a granular surface.

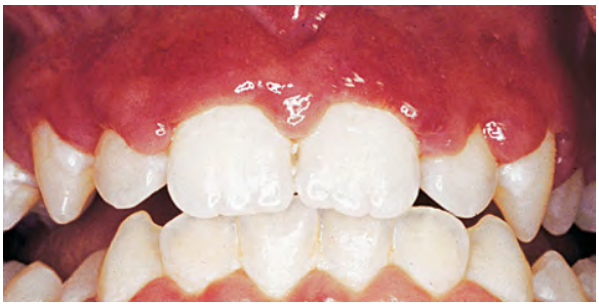


Fig. 14-50 Granulomatous gingival hyperplasia may be due to sarcoidosis, which is one of the orofacial granulomatoses; others are Crohn's disease and Melkersson–Rosenthal syndrome.

and Chauvin 2004; Mignogna *et al*. 2004) or paste application daily or twice daily during painful exacerbations, and meticulous oral hygiene to reduce additional inflammation of the oral cavity. Treatment of any inflammatory condition in the oral region, including periodontitis, periapical inflammation, and even mucosal lesions due to hypersensitivity to restorative dental materials, is important for resolution in some cases (Guttman-Yassky *et al*. 2003). An important differential diagnosis is a gingival lesion presumably associated with mouth breathing. This type of lesion, which may resemble those of OFG, is confined to the area between the maxillary canine teeth. The erythematous surface has a dry and shiny appearance, and the lesion is primarily seen in patients with impaired lip closure. Deposition of bacteria on the facial side of the front teeth and the gingiva, facilitated by mouth breathing, may play a role in the development of this type of gingival lesion, which may also be seen in conjunction with lichenoid lesions of the mucosal side of the upper lip (Backman & Jontell 2007).

Reactive processes

Epulis

Epulis is a localized tumor of the gingiva. Most of these gingival lesions are reactive processes with a presumed exogenic origin, such as trauma, calculus, etc. This is in contrast to epulides, which are true neoplasms, characterized by genetic loss of its proliferative regulation. The most common reactive processes in the gingiva are:

- Fibrous epulis (Fig. 14-51)
- Calcifying fibroblastic granuloma (Fig. 14-52)
- Pyogenic granuloma (vascular epulis) (Fig. 14-53, 14-54)
- Peripheral giant cell granuloma (or central) (Fig. 14-55)

Fibrous epulis

A fibrous epulis (focal fibrous hyperplasia, fibroepithelial hyperplasia) is a reactive process often

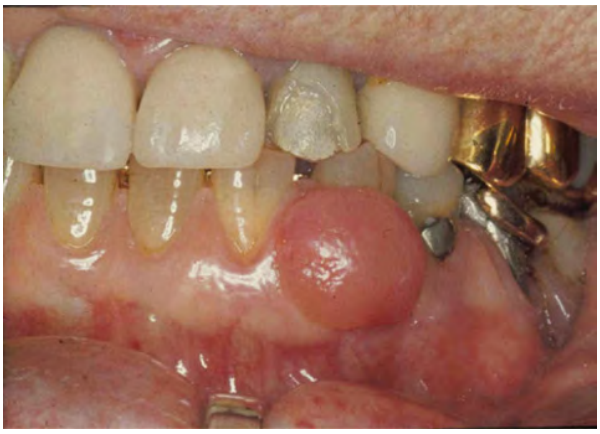


Fig. 14-51 Fibrous epulis.

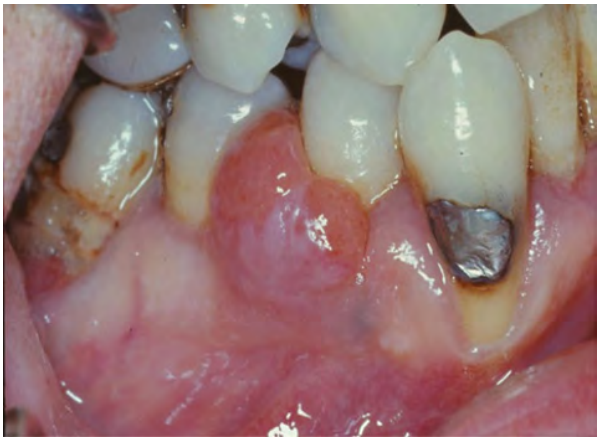


Fig. 14-52 Calcifying fibroblastic granuloma of the lower right premolar region.

covered by a normal epithelium and are usually the same color as the surrounding oral mucosa. Proliferation of the subepithelial connective tissue is induced by chronic trauma or other local factors. By definition, an epulis is confined to the gingiva, but the same type of lesion is often observed in buccal mucosa as a result of a tooth gap. It should be distinguished from fibroma, which is a true neoplasm (Babu & Hallikeri 2017).

Calcifying fibroblastic granuloma

Calcifying fibroblastic granuloma (CFG) is a true epulis, as it can only affect the gingiva (Fig. 14-52). Clinically, it is difficult to discriminate between CFG and a fibrous epulis, and the diagnosis is established by histopathology where calcifying tissues are seen as part of the connective tissue (Andersen *et al*. 1973). The CFG derives from the undifferentiated mesenchymal cells of the periodontal ligament and are induced by local irritants.

Pyogenic granuloma

Pyogenic granuloma (PG) may occur at any site of the oral mucosa. As an epulis, it is often clinically

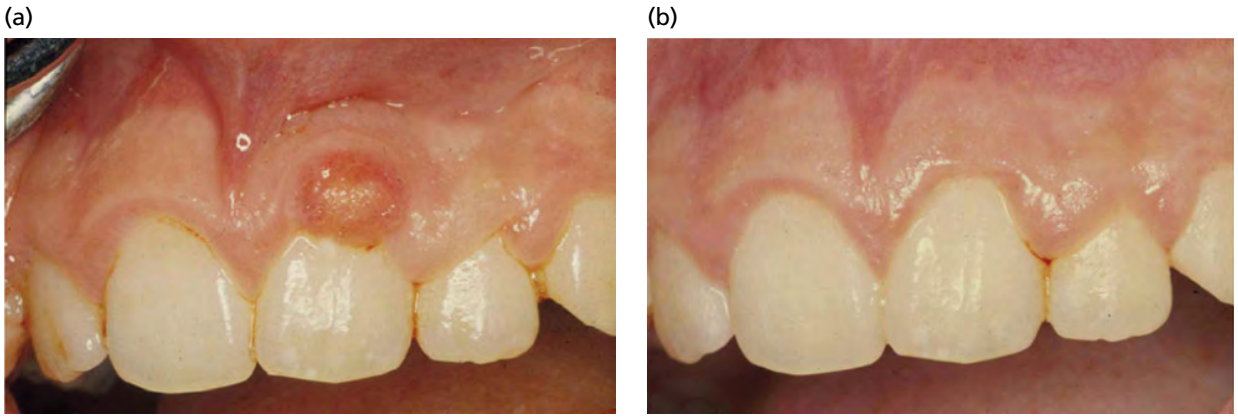


Fig. 14-53 Pyogenic granuloma of upper incisor region before (a) and after treatment (b).

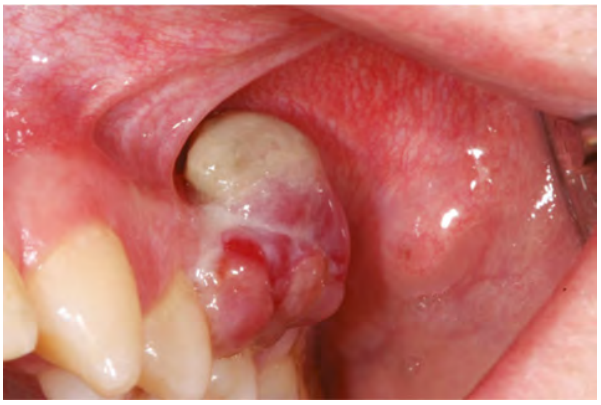


Fig. 14-54 Large pyogenic granuloma of the maxillary premolar/molar region.

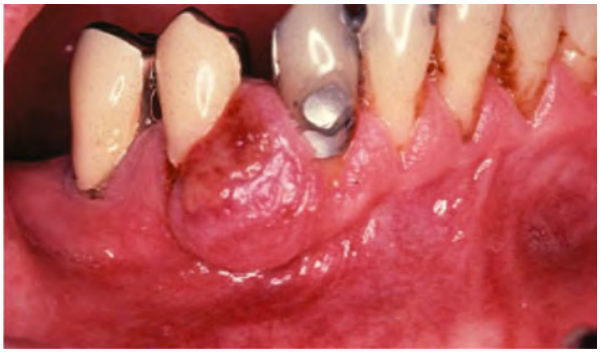


Fig. 14-55 Peripheral giant cell granuloma of the mandibular canine/premolar region.

distinguishable from fibrous epulis and CFG. A variety of blood vessels can be seen in the connective tissue, giving PG a complex coloration, with both red and yellowish ulcerated elements. The size of the lesion, which may be large, is also a distinguishing factor (Fig. 14-53, 14-54). The main contributing factors to PG are the presence of plaque and calculus. A definite correlation has been observed between serum estrogen, progesterone hormone, and PG during pregnancy (Daley *et al*. 1991).

Peripheral giant cell granuloma

Peripheral giant cell granuloma (PGCG) is characterized by numerous multinucleated giant cells and a fibrocellular stroma. The origin of the giant cells is not known, but most likely they relate to osteoclasts and endothelial cells. As a true epulis, PGCG is often observed as a tumor located in the interdental papilla, edentulous alveolar margin, or at the marginal gingival level, emanating from the periodontal ligament and periosteum. The color of a PGCG often ranges from dark red to purple or blue (Fig. 14-55). As surgical excision alone shows a considerable recurrence rate, excision followed by an additional therapy, either curettage or peripheral osteotomy, should be the first choice of treatment for PGCG (Chrcanovic *et al*. 2018).

Neoplasms

Premalignant (potentially malignant)

Leukoplakia

Leukoplakia, which is still a challenging condition (Villa & Sonis 2018), is a clinical diagnosis of a predominantly white lesion of the oral mucosa that cannot be diagnosed as any other lesion. The prevalence of leukoplakia has been estimated at around 4% in Sweden (Axell 1976), but differs dependent on lifestyle. Leukoplakias, which are usually asymptomatic, occur most frequently on the mandibular gingiva, buccal mucosa, tongue, and the floor of the mouth. Homogenous leukoplakia is characterized by a whitish color with a more or less corrugated surface (Fig. 14-56), while non-homogenous leukoplakia is characterized by a whitish-reddish color (Fig. 14-57a). Verrucous leukoplakia is characterized by white papillary lesions. Lesions exhibiting exophytic growth and invasion of the surrounding tissues are referred to as proliferative verrucous leukoplakia (Fig. 14-58), a high-risk subtype of non-homogenous leukoplakia (van der Waal & Reichart 2008). The significance of leukoplakia relies on the fact that they are premalignant with an annual rate of malignant transformation

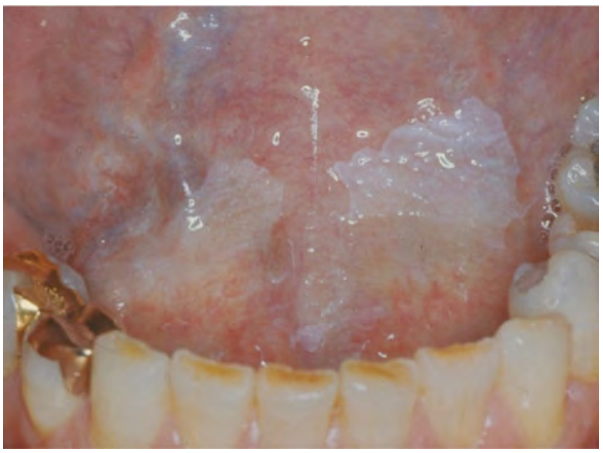


Fig. 14-56 Homogenous leukoplakia of the sublingual area.

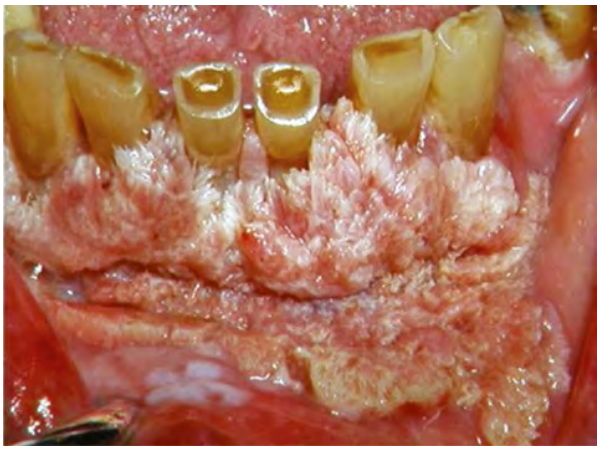
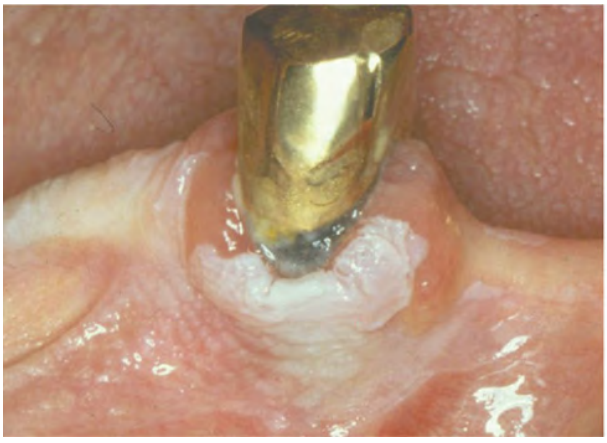


Fig. 14-58 Proliferative verrucous leukoplakia with exophytic growth and invasion of the surrounding tissues.

(a)



(b)

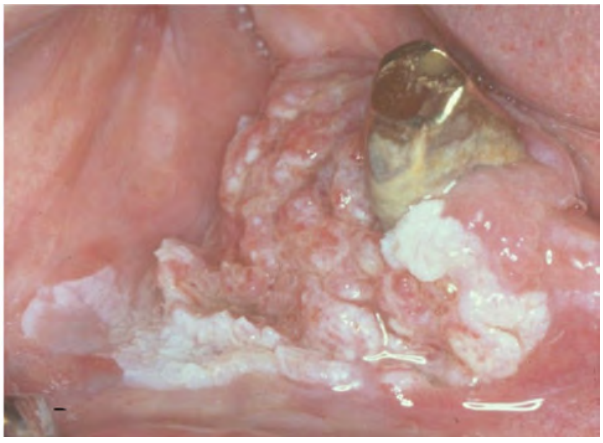


Fig. 14-57 (a) The combined red and white areas is characteristic of this non-homogenous gingival leukoplakia of the lower right molar region. (b) The lesion developed into a carcinoma after a 2 year follow-up. (Source: Courtesy of Dr. Henrik Nielsen.)

of 2–3% (van der Waal 2014). The lesions may demonstrate some degree of epithelial dysplasia or frank carcinoma upon biopsy and several oral cancers are preceded by a long-standing area of leukoplakia. While the prognosis of leukoplakia has been shown to depend on homogenous or non-homogenous appearance and size, the significance of epithelial dysplasia as a prognostic marker has been questioned (Holmstrup *et al*. 2006; Brouns *et al*. 2014) as has the reliability of a biopsy of the lesions (Holmstrup *et al*. 2007).

The basic concept of handling oral premalignant lesions is to prevent malignant transformation, but no universally approved standard therapy regimen has yet been developed (Holmstrup & Dabelsteen 2016), and surgical removal does not appear to reduce malignant development in long-term follow-up studies (Holmstrup *et al*. 2006; Balasundaram *et al*. 2014). This is why continuous follow-up of patients is important, whether or not the lesions are surgically removed.

Erythroplakia

Erythroplakia is an uncommon lesion, which cannot be diagnosed as any other disease. It is the red counterpart of leukoplakia, characterized by a fiery, sharply demarcated red area situated slightly below the surrounding mucosa (Holmstrup 2018). This is in contrast to other red lesions, which are usually diffusely demarcated. Erythroplakia appears to have a higher premalignant potential than leukoplakia (Dionne *et al*. 2015). The lesions may uncommonly affect the gingiva (Fig. 14-59).

Malignancy

Squamous cell carcinoma

The WHO has estimated that 657 000 cases of cancers of the oral cavity and oropharynx occur worldwide each year, and more than 330 000 deaths. When detected early, oral cancers can have an 80–90% survival rate. At more advanced stages, the death rate

decreases to about 40% at 5 years from diagnosis. These figures emphasize that physical examination of the oral mucosa is important, but, unfortunately, it too often receives minimal attention in routine practice. Oral squamous cell carcinoma (OSCC) is by far the most common cancer in the oral cavity, representing more than 90% of all oral cancer forms (Johnson *et al*. 2011). There is substantial evidence that lifestyle factors, including use of tobacco, alcohol, and betel quid will cause the vast majority of instances of OSCC (Johnson *et al*. 2011; Mortazavi *et al*. 2017).

The 5-year survival rate is more than 90% for those with an early diagnosed OSCC, but only around 20% for patients with stages 3 and 4. Unfortunately, in the majority of cases, the cancer is diagnosed in these advanced stages with lymph node metastasis. One reason is that OSCC does not often give rise to any significant symptoms, which avert the patient from seeking healthcare.

As early detection is critical for a successful outcome, it is important to be able to recognize how OSCC may present itself at an initial stage. Although OSCC is often described as an ulcer that will not heal (Fig. 14-60), the primary stage is in fact not always an ulcer but characterized as a proliferation of epithelial cells reflected clinically by small nodules (Fig. 14-61). The nodular appearance of the tumor surface is a characteristic of OSCC (Fig. 14-62). An OSCC can develop within a few of months, from clinically being a relatively innocent lesion (Fig. 14-61) to an advanced tumor with ulcerations and tissue necrosis (Fig. 14-57b). Thus, this is also a reason why immediate diagnosis and treatment is necessary to improve the prognosis. A rare variant is the verrucous carcinoma, which sometimes affects the gingiva. This tumor is characterized by a slightly exophytic projection of the surface (Fig. 14-63).

Leukemia

Leukemia is a malignant hematologic disorder with abnormal proliferation and development of leukocytes and their precursors in blood and bone marrow. It can involve any of the subsets of leukocytes, polymorphonuclear leukocytes, lymphocytes, or monocytes. Normal hematopoiesis is suppressed and, in most cases of leukemia, the white blood cells appear in the circulating blood in immature forms.

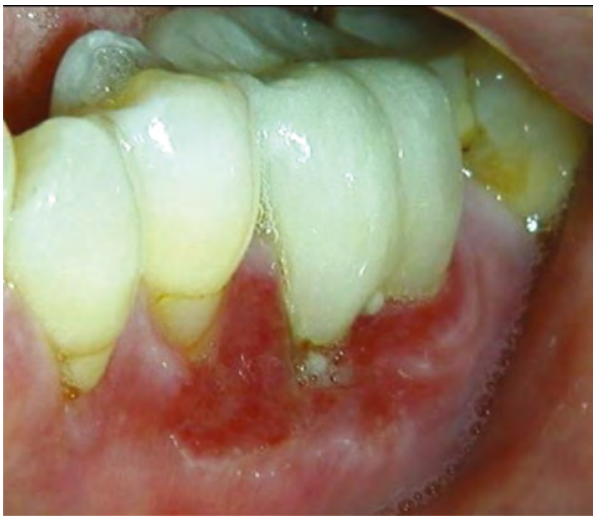


Fig. 14-59 Gingival erythroplakia of the lower left premolar/molar region.

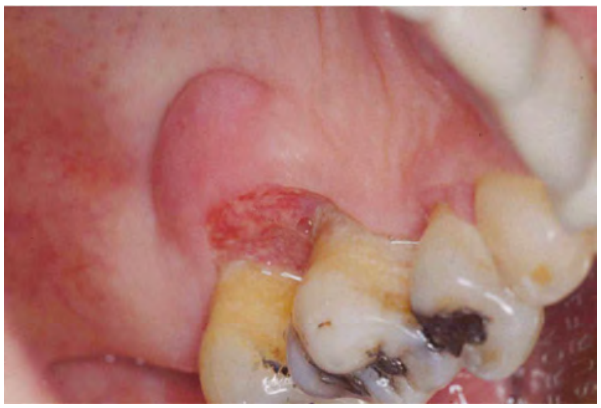


Fig. 14-60 Gingival cancer characterized by a persisting ulcer.

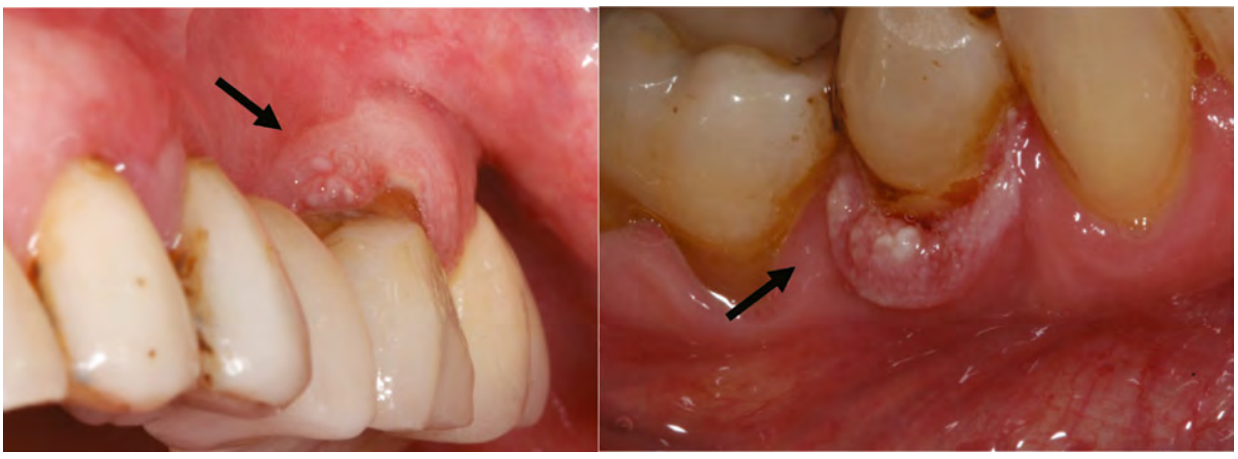


Fig. 14-61 Early squamous cell carcinomas clinically demonstrating small nodules (arrows).

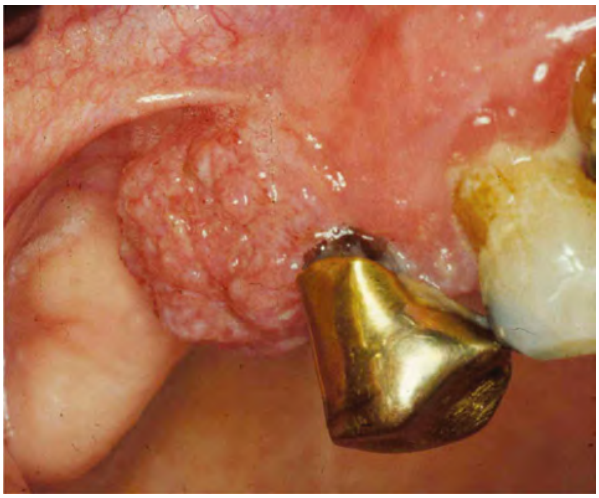


Fig. 14-62 Gingival cancer characterized by proliferating small nodules on the surface.

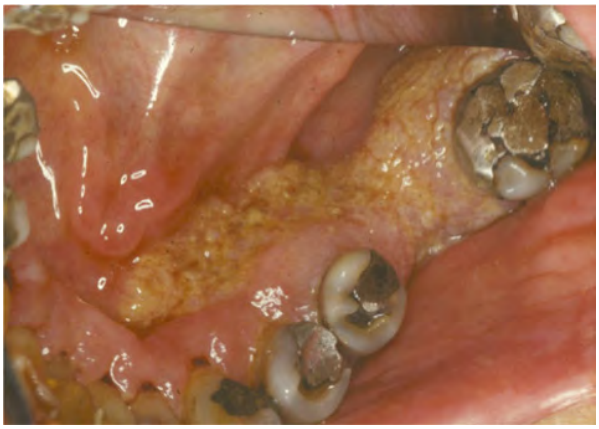


Fig. 14-63 Verrucous carcinoma of the mandibular lingual gingivae.

As a consequence of the inability to produce sufficient functional white blood cells and platelets, death may result from infection or bleeding associated with neutropenia and thrombocytopenia, respectively.

The classification of leukemia is based on its course, acute or chronic, and origin of the cells involved. The basic forms are: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). Acute leukemias have an aggressive course, resulting in death within 6 months if untreated. They are rather rare and patients are usually either under 20 or over 60 years of age. Chronic leukemias, of which the lymphocytic form is the most common, have less pronounced bone marrow failure and a more indolent course, usually lasting several years. They occur during adulthood and normally after the age of 40 years. Whereas the peripheral granulocyte count is markedly elevated in chronic leukemia, it may be elevated, decreased, or normal in acute leukemia (McKenna 2000).

Gingival manifestations in leukemia, which include extensive swelling (Fig. 14-64), ulceration (Fig. 14-65), petechiae (Fig. 14-66), and erythema, are much more common in acute than in chronic forms. Sometimes, the oral manifestations lead to the diagnosis of leukemia; 69% of patients with acute leukemia had oral signs of leukemia on examination and 33% of the patients had gingival swelling (Pindborg 1992). In another study, gingival swelling was observed in 21% of AML patients, but in no patients with ALL (Meyer *et al*. 2000). The pronounced gingival swelling seen

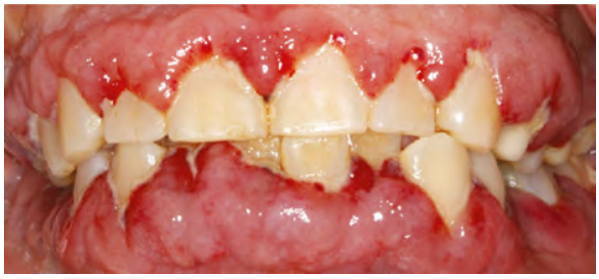


Fig. 14-64 Acute myelogenous leukemia with extensive swelling of the gingivae

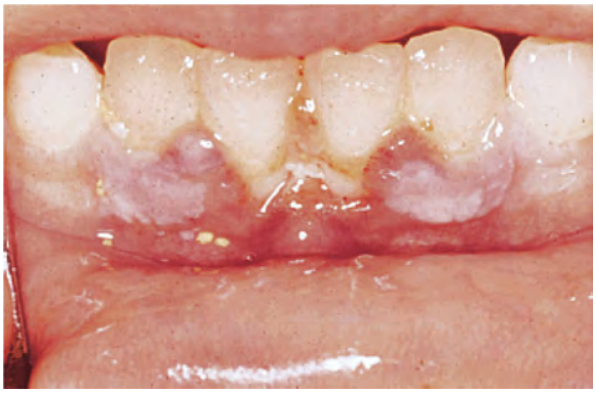


Fig. 14-65 Acute lymphocytic leukemia with gingival ulceration in a child.

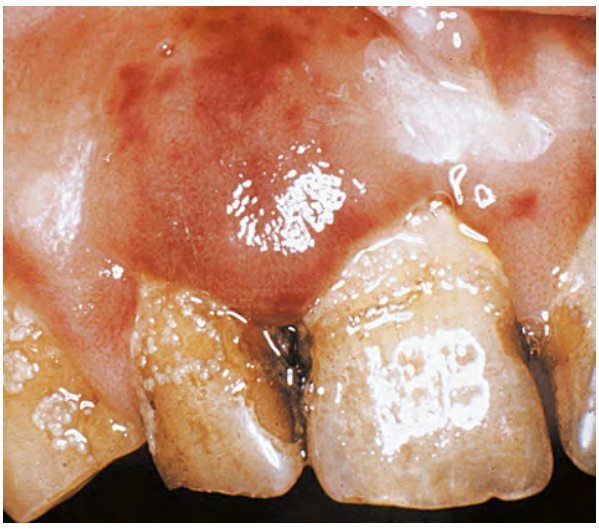


Fig. 14-66 Acute myelogenous leukemia with petechiae and swelling of the gingiva. This patient had several episodes of spontaneous bleeding from the gingiva, which prevented oral hygiene procedures from being undertaken.

in patients with leukemia is mostly due to plaque-induced inflammation, since stringent plaque control appears to resolve the swelling (Barrett 1984); it may also be due to the presence of leukemic infiltrates, although this has been reported to be an uncommon feature of patients with leukemia (Barrett 1984). Gingival bleeding, which may be a major problem, due to secondary thrombocytopenia, is a common sign in patients with leukemia. It has been reported as the initial sign in 17.7% of patients with acute leukemias and in 4.4% of patients with chronic forms (Lynch & Ship 1967).

In general, the periodontal treatment of patients with leukemia is important; it aims to reduce plaque as a source of bacteremia and damage to the periodontal tissues, both during the disease course and during periods of chemotherapy. In such periods, potentially pathogenic bacteria occur in plaque simultaneously with granulocytopenia (Peterson *et al*. 1990). The reduction of periodontal inflammation may also prevent episodes of gingival bleeding. As with many other patients, chemical plaque control in combination with mechanical debridement appears to be most effective and is the preferred method of periodontal therapy in patients with leukemia (Holmstrup & Glick 2002). However, the increased tendency to bleeding in many of these patients may necessitate the use of alternative methods to toothbrushing. A study of professional plaque removal preceding mouth rinsing with 0.1% chlorhexidine in patients with AML showed that the additional initial removal of plaque and calculus was more effective in reducing gingival inflammation than mouth rinsing with chlorhexidine alone (Bergmann *et al*. 1992). A 1-day antibiotic prophylaxis regimen with a combination of piperacillin and netilmicin was given prior to and after the mechanical debridement. Periodontal treatment always involves a close cooperation with the medical department or specialist responsible for coordination of the patient's treatment.

Lymphoma

Next to malignant salivary gland tumors, oral lymphomas represent the third most common malignancy in the oral cavity. Lymphoma is a general term for tumors of the lymphoid system and lymphoma represents the most common hematologic malignancy. Lymphoma may originate from B-lymphocytes and T-lymphocytes cell lines. There are two main types of lymphoma: Hodgkin's lymphoma and non-Hodgkin's lymphoma, the former being one-sixth as common as non-Hodgkin's lymphoma. In contrast to non-Hodgkin's lymphoma, oral manifestations of Hodgkin's lymphoma are extremely rare (Fornatora *et al*. 2004; Gowda *et al*. 2013; Valera *et al*. 2015). It may mimic abscesses emanating from a tooth, and therefore lymphomas may be an optional diagnosis when a process is not responding as expected after endodontic or periodontal treatment (Fig. 14-67). Clinically, it can be observed as discrete swelling of the mucosa including the gingiva and the patient is usually unaware of the tumor until its later stages.

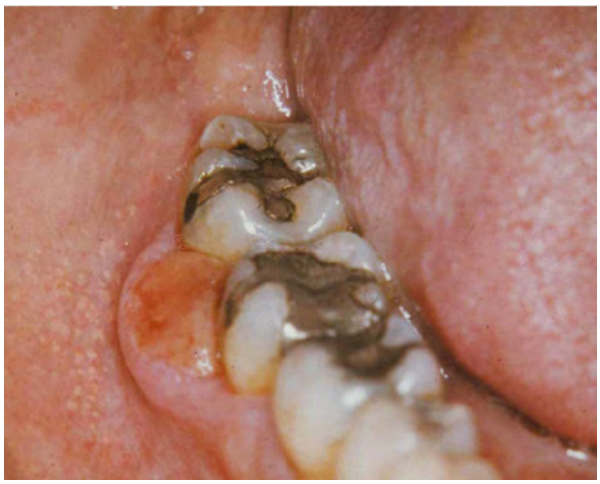


Fig. 14-67 Gingival non-Hodgkin's lymphoma of the mandibular molar region.

Endocrine, nutritional, and metabolic diseases

Vitamin deficiencies

Vitamin C deficiency (scurvy)

Ascorbic acid (vitamin C) is necessary for various metabolic processes in the connective tissue as well as in the formation of catecholamines. Acting as an antioxidant against reactive oxygen species ascorbic acid is of crucial importance in the maintenance of periodontal tissue homeostasis (Chapple & Matthews 2007). Ascorbic acid deficiency ("scurvy") has been a severe burden on humans, and even in the nineteenth century an epidemic of scurvy occurred in central Europe. Characteristic clinical findings in scurvy are gingival bleeding and sore gums as well as a depressed immune response. Interestingly, the concentration of ascorbic acid in gingival crevicular fluid in gingival health is higher than in plasma (Meyle & Kapitza 1990), and there appears to be an inverse relationship between plasma ascorbic acid concentration and the severity of periodontitis (Pussinen *et al*. 2003; Kuzmanova *et al*. 2012).

Traumatic lesions

Traumatic lesions of the gingiva are very common and may be caused by a wide range of physical, chemical, and thermal incidents. The background to traumatic lesions of the oral tissues may be self-inflicted, iatrogenic, or accidental (Armitage 1999).

Physical/mechanical trauma

Frictional keratosis

Oral hygiene agents, including toothbrushes, and inexpedient procedures can be injurious to the gingival tissues. If physical trauma is limited, the gingival response is hyperkeratosis, resulting in a white leukoplakia-like, frictional keratosis (Almazyad *et al*. 2020) (Fig. 14-68).

Mechanically induced gingival ulceration

In cases of more aggressive soft tissue trauma, the damage varies from superficial gingival laceration to major loss of tissue resulting in gingival recession (Axell & Koch 1982; Smukler & Landsberg 1984). Abrasiveness of toothpaste, strong brushing force, and horizontal movement of the toothbrush contribute to the gingival injury even in young patients. Characteristic findings in these patients are extremely good oral hygiene, cervical tooth abrasion, and unaffected tops of the interdental papillae at the site of injury (Figs. 14-69, 14-70, 14-71, 14-72). The condition has been termed traumatic ulcerative gingival lesion (Axell & Koch 1982). Dental flossing may also cause gingival ulceration and inflammation primarily affecting the top of the interdental papillae (Fig. 14-73). The prevalence of such findings is unknown (Gillette & Van House 1980). Diagnosis of physical injuries is based on the clinical findings. An important differential diagnosis is necrotizing gingivitis (Blasberg *et al*. 1981) (see Chapter 19). The latter normally reveals itself as a necrotic gingival margin and interdental papillae, while brushing trauma leads to ulceration of a few millimeters of the gingival margin.

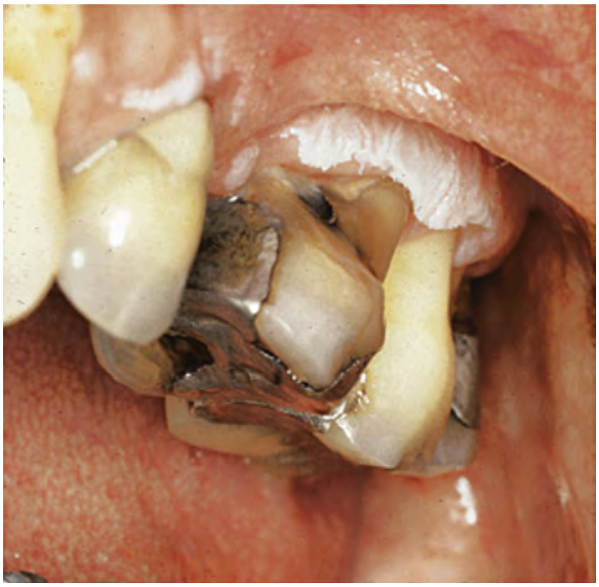


Fig. 14-68 Frictional keratosis due to an aggressive tooth brushing habit. Note the cervical abrasion of adjacent teeth.

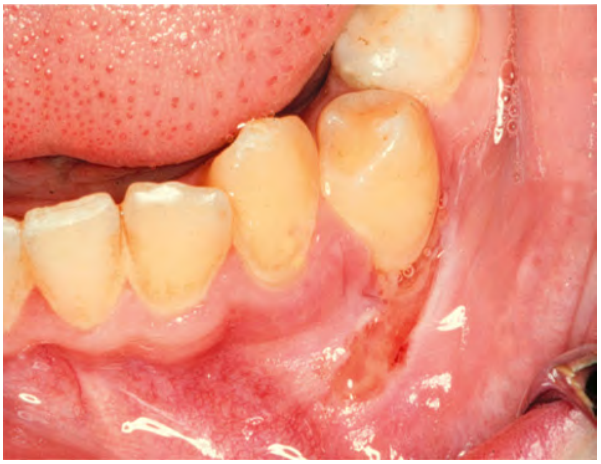


Fig. 14-69 Gingival wounding due to improper toothbrushing. Note the characteristic horizontal extension of the lesion, affecting the most prominent part of the tooth arch.

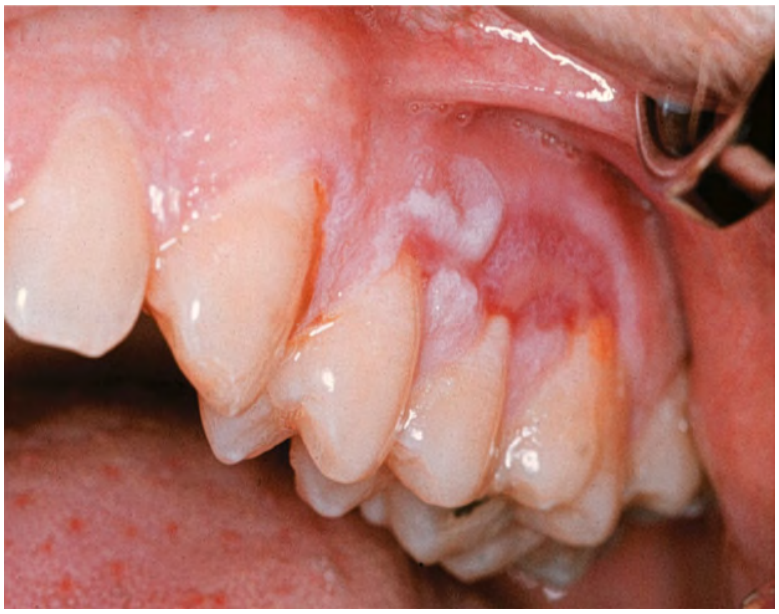


Fig. 14-70 Gingival wounding due to improper toothbrushing. Note the characteristic horizontal extension of the lesion and the uninflamed, unaffected interdental papillae.

Factitious injury (self-harm)

Self-inflicted physical injury to the gingival tissues can occur; sometimes these lesions are termed gingivitis artefacta. The lesions often show ulceration of the gingival margin and this is often associated with recession. Such lesions are most common in children and young adults and two-thirds appear to occur in female patients. The lesions, which may be hemorrhagic, are usually produced by picking at or scratching the gingiva with a finger or a fingernail (Fig. 14-74). Sometimes the lesions are made by instruments (Pattison 1983). The correct diagnosis is often difficult to establish based on clinical findings, and identification of the cause may be impossible.

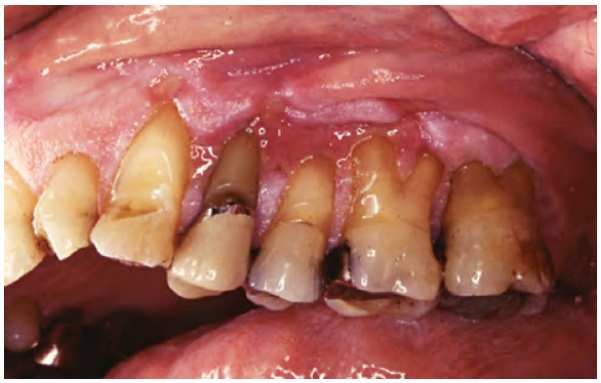


Fig. 14-71 Severe gingival recession and wounding due to improper toothbrushing technique. Note the unaffected interdental papillae.

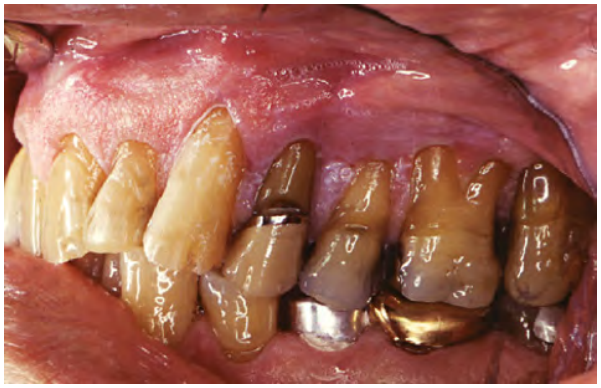


Fig. 14-72 Healing of the lesion shown in Fig. 14-71. The damage to the periodontal tissues is severe, leaving extensive gingival recession.

Chemical (toxic) burn

Surface etching by various chemical products with toxic properties may result in mucosal reactions, including reactions of the gingiva. These lesions are usually reversible and resolve after removing the toxic influence. In most instances, the diagnosis is obvious from the combination of clinical findings and patient history. Chlorhexidine-induced mucosal desquamation (Flotra *et al*. 1971; Almqvist & Luthman 1988) (Fig. 14-75), acetylsalicylic acid burn (Najjar 1977), cocaine burn (Dello Russo & Temple 1982), hydrogen peroxide (Rees & Orth 1986; Rostami & Brooks 2011), and slough due to toothpaste detergents are examples of such reactions (Muhler 1970). Chemical injury to the gingival tissue may be caused by incorrect use of caustics by dentists. Paraformaldehyde used for pulp mummification may give rise to inflammation and necrosis of the gingival tissue if the cavity sealing is insufficient (Di Felice & Lombardi 1998).

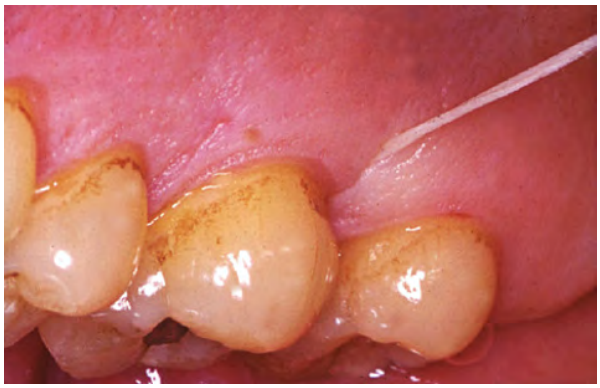


Fig. 14-73 Lesions after dental flossing are common and sometimes result in permanent fissuring of the gingival tissue.

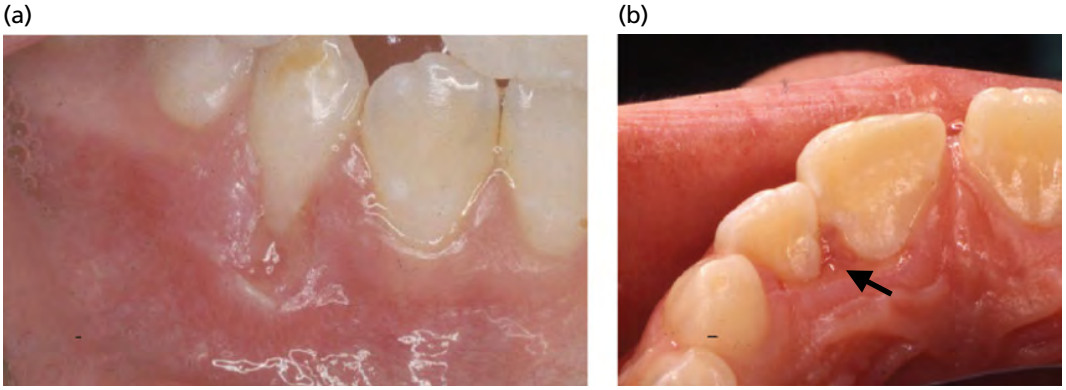


Fig. 14-74 (a) Self-inflicted gingival recession with an ulcerated margin in a 7-year-old boy because of fingernail scratching. (b) Gingival ulceration (arrow) of the palatal gingiva of the upper right incisor region in the same boy as shown in (a). This lesion was also caused by fingernail scratching.

Thermal insults

Extensive thermal burns of the oral mucosa are very rare, but minor burns particularly from hot beverages, are seen occasionally. Their site of predilection is the palatal and labial mucosa, but any part of the oral mucosa can be involved, including the gingiva (Colby *et al*. 1961). The area involved is painful and erythematous, and may slough a coagulated surface. Vesicles may also occur (Laskaris 1994) and sometimes the lesions present as ulceration, petechiae, or erosion (Fig. 14-76). Obviously, the history is important for reaching the correct diagnosis. Common causes are hot coffee, pizza, or melted cheese, but dental treatments involving improper handling of hot hydrocolloid impression material, hot wax, or cautery instruments are other causes (Colby *et al*. 1961).

Gingival pigmentation

Melanoplakia

Oral pigmentation in the form of melanoplakia may be associated with a broad variety of exogenous and endogenous circumstances previously mentioned (Holmstrup *et al*. 2018). These include genetics, endocrine disturbances (Addison's disease), syndromes (Albright syndrome, Peutz-Jegher syndrome (Fig. 14-77)), and postinflammatory reactions (Hassona *et al*. 2016). Physiologic pigmentation is usually symmetrical occurring on the gingiva, buccal mucosa, hard palate, lips, and tongue (Hedin & Larsson 1978).

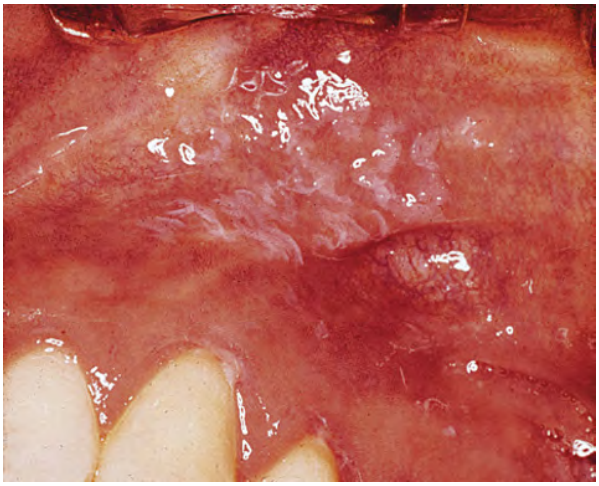


Fig. 14-75 Chlorhexidine-induced mucosal desquamation. This is a reversible type of lesion, which is completely normalized after stopping chlorhexidine use.

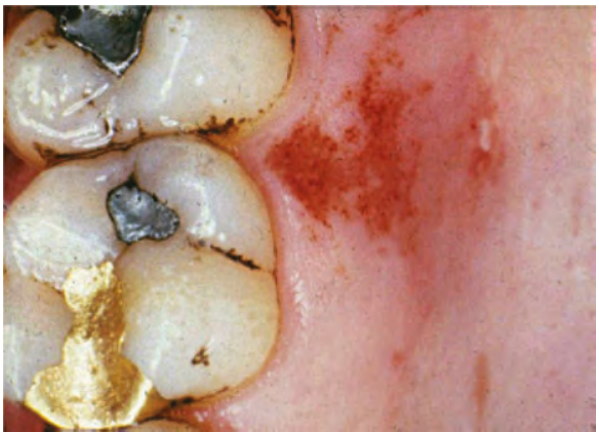


Fig. 14-76 Thermal burn with slight erosion and petechiae of palatal gingiva due to hot coffee intake.

Smoker's melanosis

A common cause of melanocytic pigmentation of the oral mucosa is cigarette smoking. Smoker's melanosis occurs most frequently on the mandibular anterior facial gingiva (Hedin 1977; Sarswathi *et al*. 2003; Nwhator *et al*. 2007) (Fig. 14-78). The pigmentation may gradually improve or completely resolve upon smoking cessation.

Drug-induced pigmentation

Drug-induced pigmentation (DIP) may be caused by the accumulation of melanin, deposits of drug or drug metabolites, synthesis of pigments under the influence of a drug, or deposition of iron as a consequence of damage to the vessels.

Quinine derivatives such as quinolone (Fig. 14-46), hydroxyquinolone, and amodiaquine are antimalarial

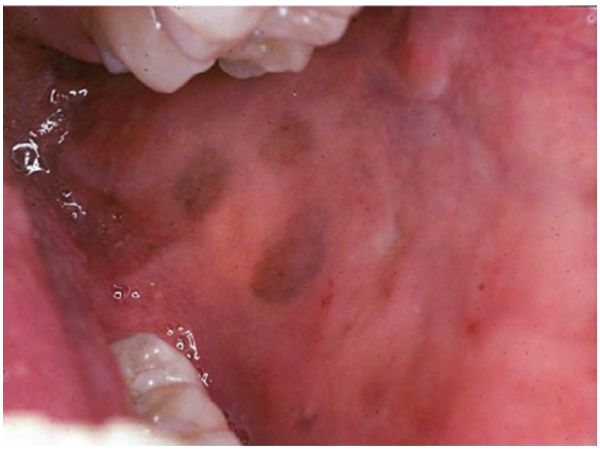


Fig. 14-77 Pigmentation in left buccal mucosa in a patient with Peutz-Jegher syndrome

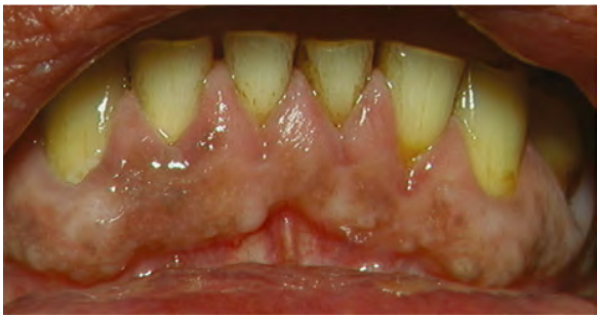


Fig. 14-78 Smoker's melanosis of mandibular anterior gingiva.

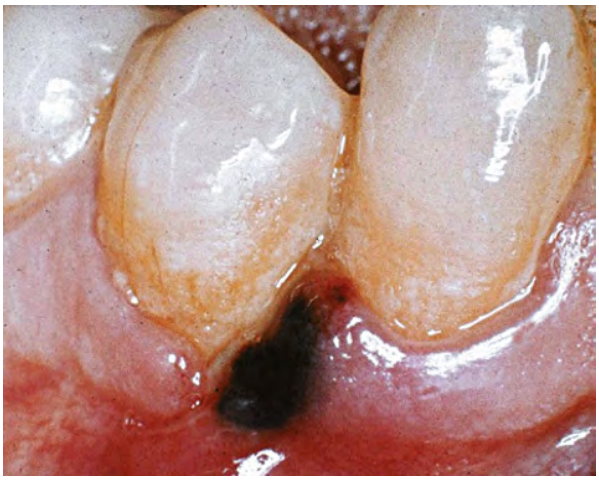


Fig. 14-79 Amalgam tattoo of the attached gingiva.

drugs causing bluish grey or black mucosal pigmentation most frequently seen on the hard palate including the palatal gingiva (Kleinegger *et al*. 2000; de Andrade *et al*. 2013).

Long-term use of minocycline may be associated with pigmentation of the alveolar bone and teeth. When such changes in bone are viewed through a thin overlying mucosa, the gingiva may appear grey. This is seen primarily in the maxillary anterior region. Minocycline-induced soft tissue pigmentation is much less common and occurs primarily on the tongue, lip, buccal mucosa, and gingiva (Treister *et al*. 2004; LaPorta *et al*. 2005).

Amalgam tattoo

Another type of tissue reaction is established through epithelial ulceration allowing entry of foreign material into the gingival connective tissue. This can happen via abrasion or cutting (Gordon & Daley 1997b), a route of tissue injury, which is best exemplified by the amalgam tattoo (Buchner & Hansen 1980) (Fig. 14-79). Gingival inflammation associated with foreign bodies has been termed foreign body gingivitis. A clinical study of this condition has shown that it often presents as a red or combined red–white painful chronic lesion which is frequently misdiagnosed as lichen planus (Gordon & Daley 1997a). An X-ray microanalysis of foreign body gingivitis showed that most of the identified foreign bodies were of dental material origin, usually abrasives (Gordon & Daley 1997b). Another way in which foreign substances can enter the tissues is self-inflicted injury, for instance due to chewing on sticks or self-induced tattooing (Gazi 1986). It is uncertain whether the inflammatory reaction in such cases is due to a toxic or an allergic reaction.

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Chapter 15

Plaque-Induced Gingivitis

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Clinical features of plaque-induced gingivitis

Plaque-induced gingivitis is defined at the site level as "an inflammatory lesion resulting from interactions between the dental plaque biofilm and the host's immune-inflammatory response, which remains contained within the gingiva and does not extend to the periodontal attachment (cementum, periodontal ligament, and alveolar bone). Such inflammation remains confined to the gingiva and does not extend beyond the mucogingival junction and is reversible by reducing levels of dental plaque at and apical to the gingival margin" (Chapple *et al*. 2018).

Plaque-induced gingival inflammation begins at the gingival margin and can spread throughout the remaining gingival unit (Table 15-1). The features of a gingivitis lesion include clinical signs of inflammation that are confined to the gingiva, presence of bacteria-laden plaque to initiate and/or exacerbate the severity of the lesion, and reversibility of the disease by removal of etiology(ies). The gingivitis lesion may be either associated with an intact periodontium (which exhibits no loss of periodontal attachment or alveolar bone) or a reduced periodontium. The clinical findings for plaque-induced gingivitis on a reduced periodontium are similar to those for plaque-induced gingivitis in an intact periodontium, except for the presence of pre-existing attachment/bone loss (Trombelli *et al*. 2018).

A site showing a clinically manifest plaque-induced gingivitis usually presents (Chapple *et al*. 2018) (Fig. 15-1):

- swelling, seen as loss of knife-edged gingival margin and blunting of papillae
- bleeding on gentle probing
- redness
- discomfort on gentle probing.

The symptoms a patient may report include:

- bleeding gums (metallic/altered taste)
- pain (soreness)
- halitosis
- difficulty eating
- appearance (swollen red gums).

The intensity of the clinical signs and symptoms of gingivitis varies between individuals even when there appears to be no quantitative nor qualitative difference in plaque accumulation (Abbas *et al*. 1986; Trombelli *et al*. 2004a; Nascimento *et al*. 2019). In a clinical study on systemically healthy young adults,

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Table 15-1 Common clinical changes from gingival health to gingivitis.

Parameter	Normal gingiva	Gingivitis
Color	Coral pink (correlated to mucocutaneous pigmentation)	Red/bluish-red hue
Contour	Scalloped outline that envelops teeth Papillary gingiva fills interdental space while marginal gingival forms a knife-edged appearance with tooth surface	Edema blunts marginal tissues leading to loss of knife edge adaptation to tooth and produces bulbous papillary tissues resulting in minimization of tissue scalloping
Consistency	Firm and resilient	Tissue is soft and exhibits pitting edema
Bleeding on provocation	Negative	Positive
Gingival exudate Sulcular temperature	Minimal ~34°C	Significantly increased Slight increase

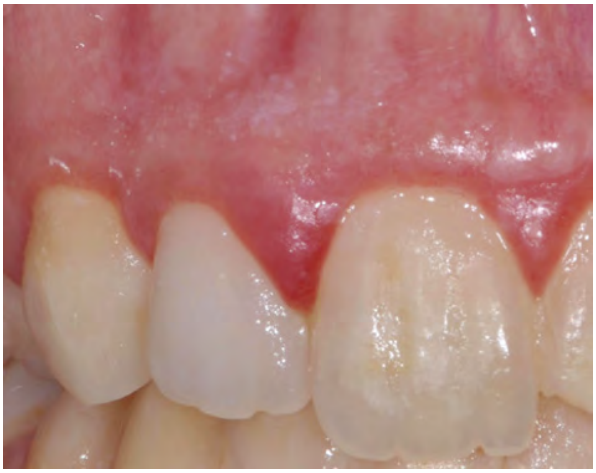


Fig. 15-1 Site-specific changes in gingival color and contour associated with plaque-induced gingivitis in an intact periodontium.

two subpopulations of individuals presenting a substantially different gingival inflammatory response to plaque have been identified in a 3-week experimental gingivitis trial. These individuals showed significantly different severity of gingivitis to similar plaque exposure (Trombelli *et al*. 2004a) (Fig. 15-2). Evidence also indicates that individuals differ in the rate at which their gingiva develop an inflammatory response after *de novo* plaque accumulation (Nascimento *et al*. 2019). Data stemming from experimental gingivitis trials support the hypothesis that differences observed by Trombelli *et al*. (2004a) are an early indication of an individual susceptibility to plaque-induced gingival inflammation. First, differences could still be observed even when self-performed supragingival plaque control was re-established (Trombelli *et al*. 2004b). Second, a consistently high or low inflammatory response to

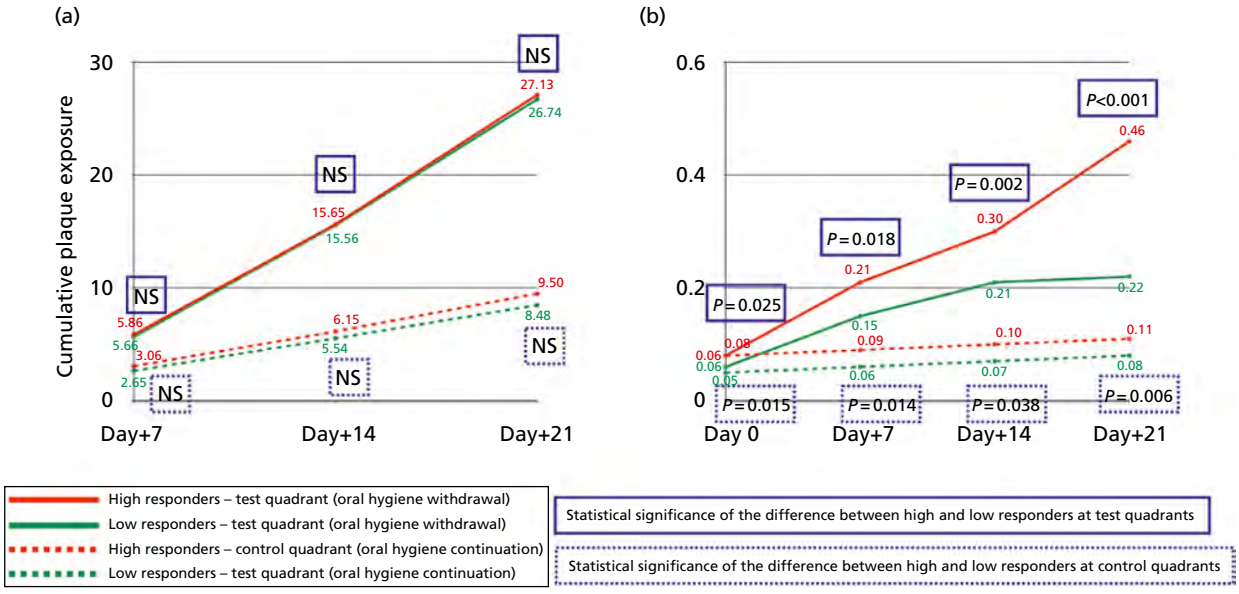


Fig. 15-2 Two subpopulations of individuals presenting a substantially different gingival inflammatory response to plaque exposure. (a) Cumulative plaque exposure. (b) Gingival crevicular fluid. NS, not significant. (Source: Based on Trombelli *et al*. 2004a.)

de novo plaque accumulation was observed in a percentage of repeatedly tested participants (Watts 1978; van der Weijden *et al*. 1994; Trombelli *et al*. 2008) (Fig. 15-3). The potential microbiological and immunological biomarkers associated with resistance to the development of gingivitis or its regression remain to be elucidated (Lee *et al*. 2012; Morelli *et al*. 2014; Kaczor-Urbanowicz *et al*. 2018; Zemouri *et al*. 2019). Interestingly, susceptibility to gingivitis was shown to be related to susceptibility to periodontitis (Dietrich *et al*. 2006; Trombelli *et al*. 2006a) (Fig. 15-4), thus potentially representing one of the key elements underlying the transition from gingivitis to periodontitis in a fraction of the population (Trombelli 2004). Patient-related modifying factors that may influence the inflammatory gingival response to plaque have been widely investigated (Trombelli *et al*. 2004c; Scapoli *et al*. 2005; Trombelli *et al*. 2005, 2006a,b; Scapoli *et al*. 2007; Trombelli *et al*. 2008, 2010; Farina *et al*. 2012; see Tatakis & Trombelli 2004 and Trombelli & Farina 2013 for review), and will be discussed in detail, together with local modifying factors for gingivitis, later in this chapter.

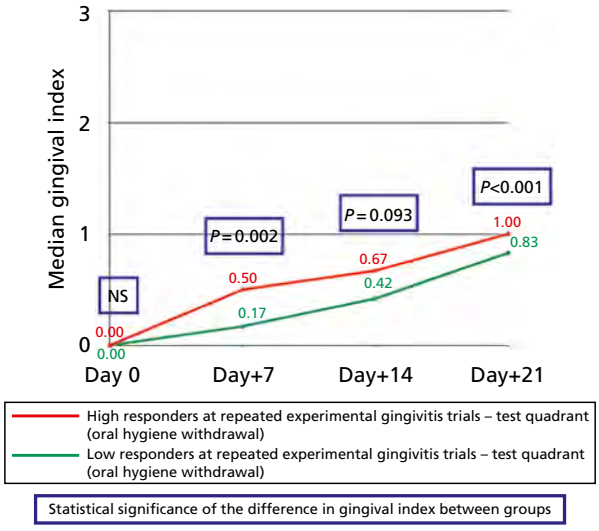


Fig. 15-3 Gingival inflammatory response to similar plaque deposits as measured in consistently low responder and high responder subjects at repeated experimental trials. (Source: Based on Trombelli *et al*. 2008.)

Diagnostic criteria to assess a gingivitis lesion

Clinical methods to assess the presence and severity of plaque-induced gingival inflammation at the site level are based on the evaluation of crude macroscopic changes occurring in the marginal gingival tissues during the healthy-inflamed transition (Lang & Bartold 2018) (Table 15-2). The volume of the gingival crevicular fluid has been largely adopted in clinical trials to assess the severity of gingival inflammation at the site level. However, the most commonly used clinical measures for gingival inflammation mainly consist of qualitative or semiquantitative indices based on visual assessment of gingival characteristics (edema/swelling, redness, etc.) and/or the evaluation of the tendency of the marginal gingiva to bleed upon mechanical stimulation exerted typically by a periodontal probe. These methods were first described more than 45 years ago and have not changed much since then (Trombelli *et al*. 2018).

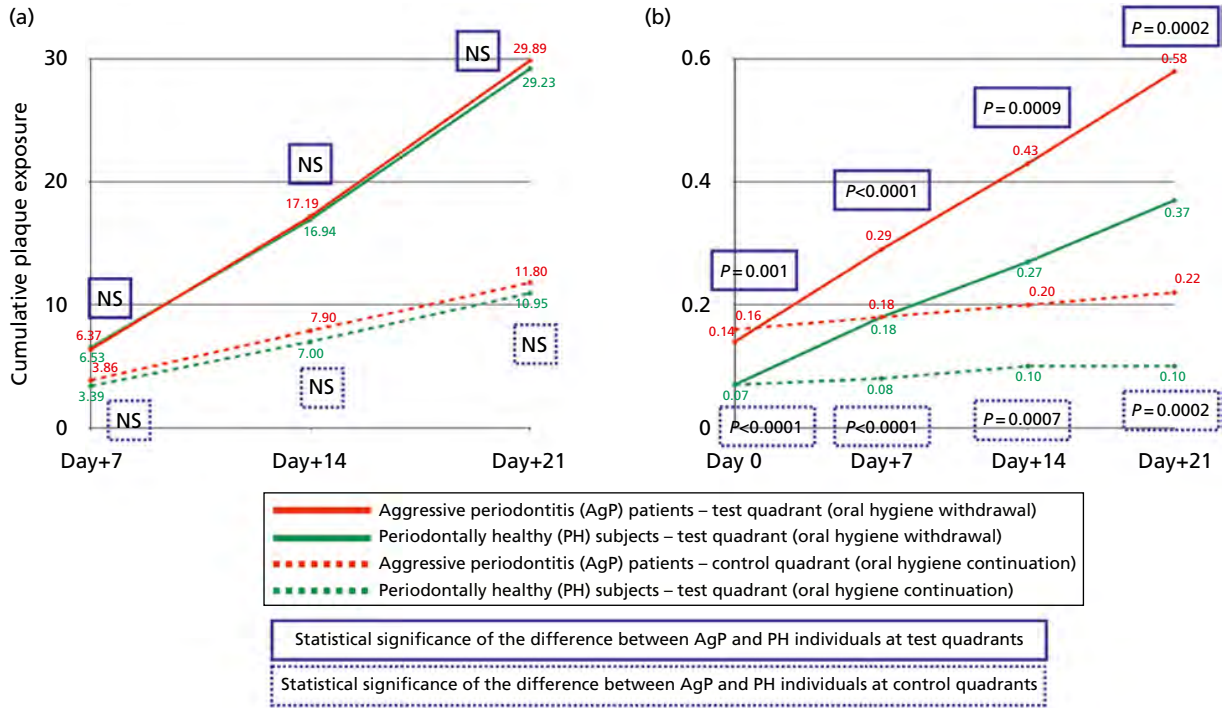


Fig. 15-4 Gingival inflammatory response to plaque in periodontally healthy subjects and aggressive periodontitis patients. (a) Cumulative plaque exposure. (b) Gingival crevicular fluid. NS, not significant. (Source: Based on Trombelli *et al*. 2006.)

Table 15-2 Gingival indices. (Source: Trombelli et al. 2018.)

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
PMA Index (Schour & Massler 1947)	Visual assessment	Each gingival unit is scored Only the labial surfaces are examined	Not stated	P (papillary) 0 = normal; no inflammation 1 = mild papillary engorgement; slight increase in size 2 = obvious increase in size of gingival papilla; hemorrhage on pressure 3 = excessive increase in size with spontaneous hemorrhage 4 = necrotic papilla 5 = atrophy and loss of papilla (through inflammation) M (marginal) 0 = normal; no inflammation visible 1 = engorgement; slight increase in size; no bleeding 2 = obvious engorgement; bleeding upon pressure 3 = swollen collar; spontaneous hemorrhage; beginning infiltration into attached gingivae 4 = necrotic gingivitis 5 = recession of the free marginal gingiva below the CEJ due to inflammatory changes A (attached) 0 = normal; pale rose; stippled 1 = slight engorgement with loss of stippling; change in color may or may not be present 2 = obvious engorgement of attached gingivae with marked increase in redness; pocket formation present 3 = advanced periodontitis; deep pockets evident.
Gingival Index (Löe & Silness 1963)	Probe	It scores the marginal and interproximal tissues (four areas for each tooth The bleeding is assessed by probing gently along the wall of soft tissue of the gingival sulcus	Not stated	0 = normal gingiva 1 = mild inflammation – slight change in color and slight edema but no bleeding on probing 2 = moderate inflammation – redness, edema and glazing, bleeding on probing 3 = severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding
Sulcus Bleeding Index (Mühlemann & Son 1971)	Probe	Four gingival units are scored systematically for each tooth: the labial and lingual marginal gingival (M units) and the mesial and distal papillary gingival (P units)	Not stated	Score 0 = health looking papillary and marginal gingiva no bleeding on probing Score 1 = healthy looking gingiva, bleeding on probing Score 2 = bleeding on probing, change in color, no edema Score 3 = bleeding on probing, change in color, slight edema Score 4 = bleeding on probing, change in color, obvious edema Score 5 = spontaneous bleeding, change in color, marked edema
Gingival Bleeding Index (Carter & Barnes 1974)	Unwaxed dental floss	The mouth is divided into six segments and flossed in the following order: upper right, upper anterior, upper left, lower left, lower anterior and lower right	Not stated; 30 s is allowed for reinspection	Bleeding is recorded as present or absent
Gingival Bleeding Index (Ainamo & Bay 1975)	Probe	Gentle probing of the orifice of the gingival crevice	10	If bleeding occurs within 10 seconds a positive finding is recorded

Table 15-2 (*Continued*)

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
Papillary Bleeding Index (Mühlemann 1977)	Probe	A periodontal probe is inserted into the gingival sulcus at the base of the papilla on the mesial aspect, and then moved coronally to the papilla tip. This is repeated on the distal aspect of the papilla	Not stated	Score 0 = no bleeding Score 1 = a single discreet bleeding point Score 2 = several isolated bleeding points or a single line of blood appears Score 3 = the interdental triangle fills with blood shortly after probing Score 4 = profuse bleeding occurs after probing; blood flows immediately into the marginal sulcus
Papillary Bleeding Score (PBS) (Loesche 1979)	Wooden interdental cleaner	This is performed using a Stim-U-dent®, which is inserted interproximally. The PBS is determined on all papillae anterior to the second molars	Not stated	0 = healthy gingiva, no bleeding upon insertion of Stim-U-dent® interproximally 1 = edematous, reddened gingiva, no bleeding upon insertion of Stim-U-Dent® interproximally 2 = bleeding, without flow, upon insertion of Stim-U-dent ® interproximally 3 = bleeding, with flow, along gingival margin upon insertion of Stim-U-dent® interproximally 4 = copious bleeding upon insertion of Stim-U-dent ® interproximally 5 = severe inflammation, marked redness and edema, tendency to spontaneous bleeding
Modified Papillary Bleeding Index (PBI) (Barnett *et al*. 1980)	Probe	Modified the PBI index (Mühlemann 1977) by stipulating that the periodontal probe should be gently placed in the gingival sulcus at the mesial line angle of the tooth surface to be examined and carefully swept forward into the mesial papilla. The mesial papillae of all teeth present from the second molar to the lateral incisor were assessed	0–30	0 = no bleeding within 30 s of probing 1 = bleeding between 3 and 30 s of probing 2 = bleeding within 2 s of probing 3 = bleeding immediately upon probe placement
Bleeding Time Index (Nowicki *et al*. 1981)	Probe	Inserting a Michigan "0" probe in the sulcus until slight resistance was felt and then the gingiva was stroked back and forth once over an area of approximately 2 mm	0–15	0 = no bleeding within 15 seconds of second probing (i.e. 30 seconds total time) 1 = bleeding within 6–15 seconds of second probing 2 = bleeding within 11–15 of seconds of first probing or 5 seconds after second probing 3 = bleeding within 10 seconds after initial probing 4 = spontaneous bleeding
Eastman Interdental Bleeding Index (Caton & Polson 1985)	Wooden interdental cleaner	A wooden interdental cleaner is inserted between the teeth from the facial aspect, depressing the interdental tissues 1–2 mm. This is repeated four times	0–15	Bleeding within 15 s is recorded as present or absent

(*Continued*)

Table 15-2 (*Continued*)

Index name (authors and year)	Instrument	Sites for assessment	Time delay (seconds)	Graded response
Quantitative Gingival Bleeding Index (Garg & Kapoor 1985)	Toothbrush	Takes into consideration the magnitude of blood stains covering toothbrush bristles on brushing and squeezing gingival tissue units in a sextant	Not stated	0 = no bleeding on brushing; bristles free from blood stains 1 = slight bleeding on brushing; bristle tips stained with blood 2 = moderate bleeding on brushing; about half of bristle length from tip downwards stained with blood 3 = Severe bleeding on brushing; entire bristle length of all bristles including brush head covered with blood
Modified Gingival Index (Lobene *et al*. 1986)	No instrument (visual assessment)	Same as Gingival Index	Not applicable	0 = absence of inflammation 1 = mild inflammation or with slight changes in color and texture but not in all portions of gingival marginal or papillary 2 = mild inflammation, such as the preceding criteria, in all portions of gingival marginal or papillary 3 = moderate, bright surface inflammation, erythema, edema and/or hypertrophy of gingival marginal or papillary 4 = severe inflammation: erythema, edema and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion or ulceration
Modified Gingival Index (Trombelli *et al*. 2004a)	No instrument (visual assessment)	Same as Gingival Index, but without the bleeding on probing component	Not applicable	0 = normal gingiva 1 = mild inflammation – slight change in color and slight edema 2 = moderate inflammation – redness, edema and glazing 3 = severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding
Bleeding on Interdental Brushing Index (Hofer *et al*. 2011)	Interdental brush	Inserting a light interdental brush placed buccally, just under the contact point and guided between the teeth with a jiggling motion, without force. Bleeding is scored for each interdental site.	30	Bleeding is scored as either present or absent

Diagnostic criteria to define and grade a gingivitis case

Defining and grading a gingival inflammatory condition at the site level (i.e. a "gingivitis lesion") (Murakami *et al*. 2018) is different from defining and grading a gingivitis case (GC) (i.e. a patient affected by gingivitis), because one "gingivitis site" does not necessarily equate to a GC. In fact, when shifting from the description of a "gingivitis site" to the identification of a GC, the classification process is complicated by the absence of clear-cut criteria that allow for discriminating a patient with a certain extent/severity of inflamed gingival sites from a periodontally healthy patient. In this respect, while clinical gingival inflammation is a well-defined site-specific condition for which several measurement systems have been proposed and validated, the concept of a GC is intended as the means to define the disease at the patient level. Such a definition, i.e. the selection of appropriate, distinct, and valid criteria

for a GC, becomes more challenging when applied to a patient who has experienced attachment loss in the past and has been successfully treated. A universal case definition is essential to facilitate population surveillance, for clinicians setting therapeutic targets, and to enable assessment of the efficacy of prevention and/or treatment regimes.

Based on available methods to assess gingival inflammation (Table 15-2), a GC could be simply, objectively, and accurately defined and graded using a bleeding-on-probing percentage (BoP%) score assessed as the proportion of bleeding sites (dichotomous yes/no evaluation) when stimulated by a standardized (dimensions and shape) manual probe with a controlled (~25 g) force to the bottom of the sulcus/pocket at six sites (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) on all present teeth (Ainamo & Bay 1975). BoP may be used for: (1) discriminating between a healthy and gingivitis patient (Lang & Bartold 2018), and (2) classifying a GC (localized, generalized) (Murakami *et al*. 2018). Use of BoP to identify a GC case would have the following advantages: (1) it is an objective, universally accepted, reliable, and accurate clinical sign that may be easily assessed and recorded (Lenox & Kopczyk 1973; Carter & Barnes 1974; Greenstein *et al*. 1981; Caton *et al*. 1988; Farina *et al*. 2011, 2013, 2017) as part of probing assessments necessary for a comprehensive periodontal examination; (2) extensive gingival bleeding represents a clinical sign often perceived by the patient, whereas low levels of BoP% are consistent with self-reported perception of healthy gingival conditions (Baser *et al*. 2014); (3) BoP recording is user-friendly, economic, and requires minimal/no technology. With suitable training, it is possible for general dental practitioners to achieve and maintain high levels of interexaminer consistency in assessing bleeding (Eaton *et al*. 1997); and (4) bleeding score can be effectively used to inform and motivate the patient (Mühlemann 1977; Saxer *et al*. 1977; Engelberger *et al*. 1983; Greenstein 1984) as well as monitor the efficacy of preventive and treatment strategies aimed to control periodontal diseases (Lang *et al*. 1986; Schwarz 1989; Lang *et al*. 1990).

Probing to the bottom of the sulcus/pocket may diagnose the presence of gingival inflammation while simultaneously assessing other relevant clinical parameters (attachment level, probing depths). Since a site (and thus, a patient) with gingivitis should not present with attachment loss, a single probing maneuver allows collection of the information necessary to detect the presence of both gingival inflammation and attachment loss.

A GC on an intact periodontium and a GC on a reduced periodontium in a patient without a history of periodontitis, is defined as ≥10% bleeding sites (Trombelli *et al*. 2018) with probing depths ≤3 mm. Localized gingivitis is defined as 10–30% bleeding sites; generalized gingivitis is defined as >30% bleeding sites (Table 15-3). A direct implication of the proposed GC definition is that a patient presenting with a BoP score <10% without attachment/bone loss (intact periodontium) or a reduced periodontium but without a history of periodontitis is considered "clinically periodontally healthy" (Table 15-3). Representative patients for GC on an intact periodontium, GC on a reduced periodontium in a patient without a history of periodontitis, and clinically periodontally healthy condition are illustrated in Figs. 15-5, 15-6, and 15-7, respectively.

Epidemiology of gingivitis

Although epidemiologic studies indicate consistently that gingival inflammation is a highly prevalent condition, there is heterogeneity in the reported prevalence of gingivitis (Table 15-4). Even though part of this heterogeneity can be interpreted in the light of real, genuine differences in disease occurrence among studied populations, it is evident that differences among cohorts may well be related to variations in the diagnostic criteria used to define the disease at the patient level, i.e. the employed GC definition.

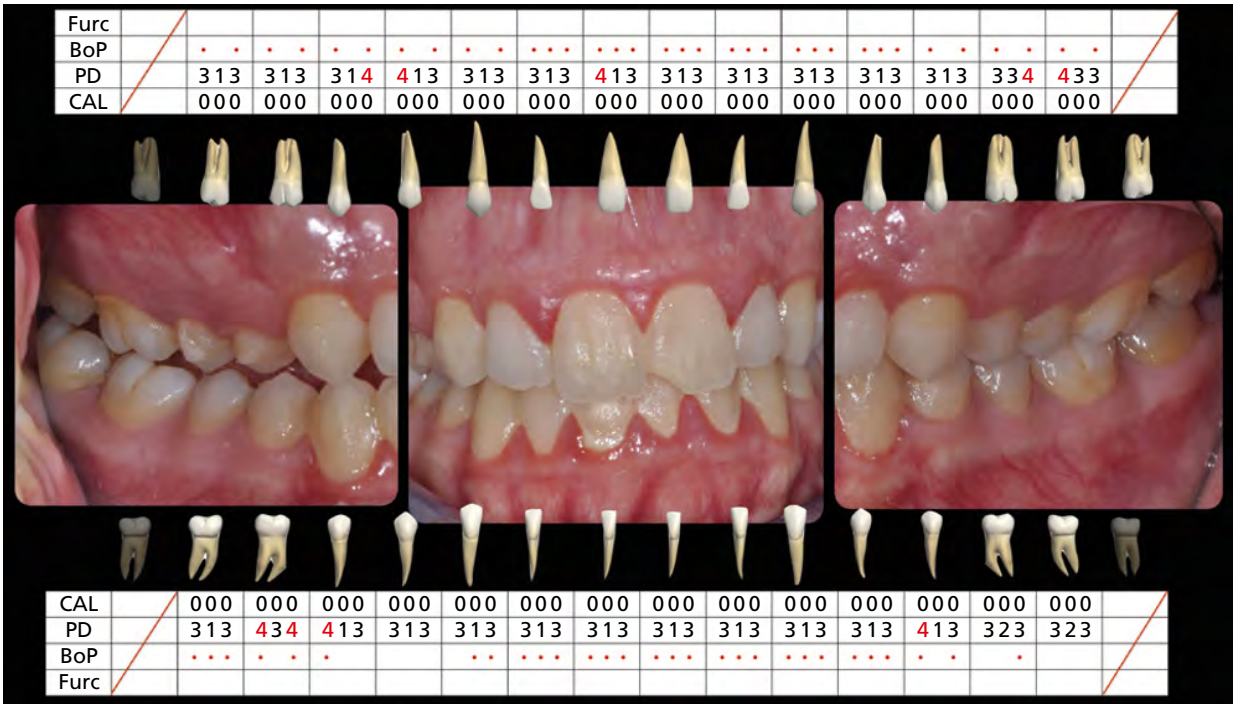
Epidemiological studies have based the definition of a patient affected by gingivitis on epidemiological indices such as: Community Periodontal Index of Treatment Need (CPITN/CPI); average severity of gingival inflammation (as assessed using gingival indices or bleeding scores); average extent of gingival inflammation (assessed as the prevalence of sites with a certain gingival index or bleeding score); combinations of severity and extent measures. The majority of epidemiologic studies investigating the prevalence of periodontal diseases, including gingivitis, are based on the use of CPITN (Ainamo *et al*. 1982; World Health Organization 1997). Unfortunately, CPITN is designed to screen for the presence of periodontitis, and consequently none of the clinical parameters

Table 15-3 Diagnostic look-up table for gingival health or plaque-induced gingivitis (when occurring in a non-periodontitis patient) in clinical practice. (Source: Chapple *et al*. 2018.)

Intact periodontium	Health	Gingivitis
Probing attachment loss	No	No
Probing pocket depths (assuming no pseudopockets)*	≤3 mm	≤3 mm
Bleeding on probing*	<10%	Yes (≥10%)
Radiological bone loss	No	No
Reduced periodontium in a non-periodontitis patient		
Probing attachment loss	Yes	Yes
Probing pocket depths (assuming no pseudopockets)*	≤3 mm	≤3 mm
Bleeding on probing*	<10%	Yes (≥10%)
Radiological bone loss	Possible	Possible

* Assumes a light probing pressure of 0.2–0.25 N.

(a)



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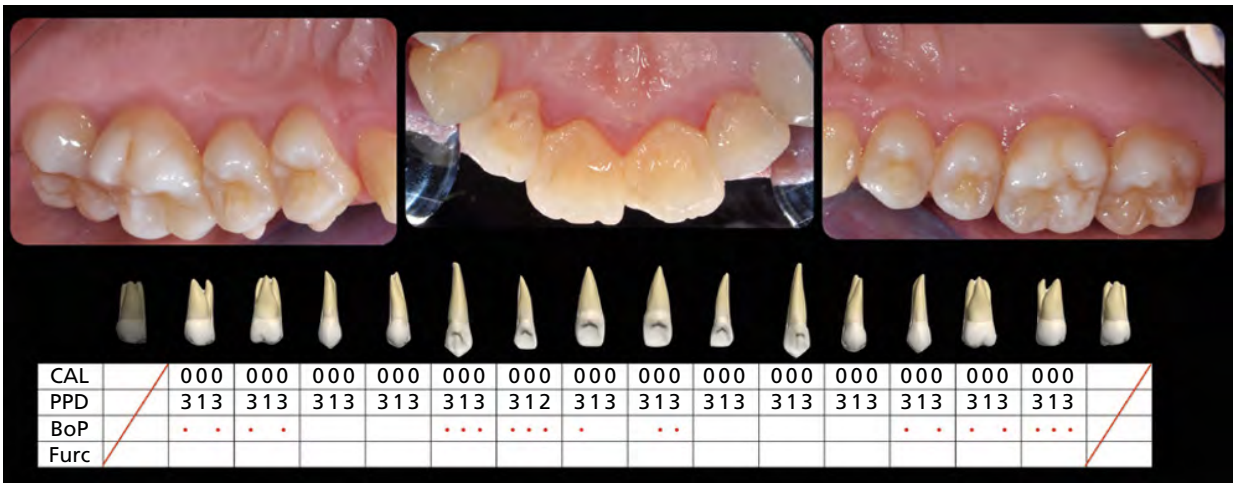

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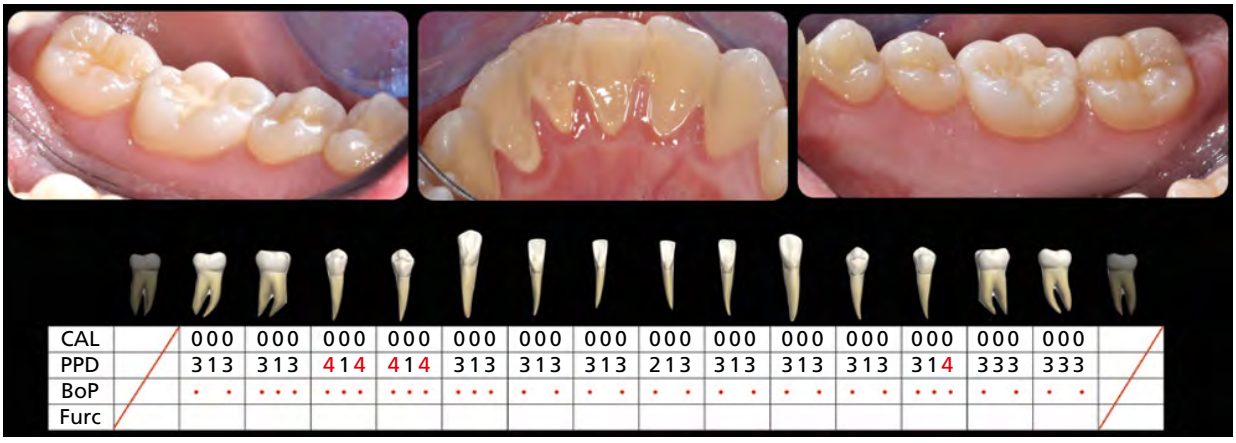
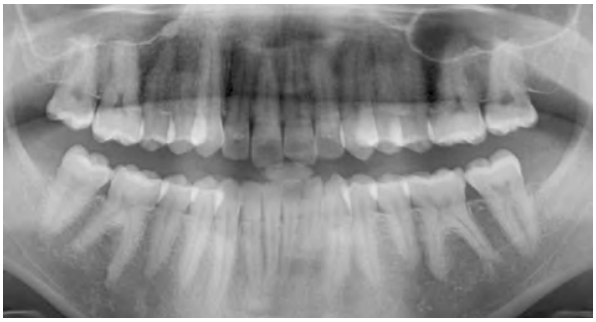


Fig. 15-5 Plaque-induced gingivitis on an intact periodontium. Clinical attachment level (CAL, in mm), probing depth (PD, in mm), bleeding on probing (BoP), and furcation lesions (Furc) as assessed at the (a) buccal, (b) palatal, and (c) lingual tooth aspects.

(d)



(e)

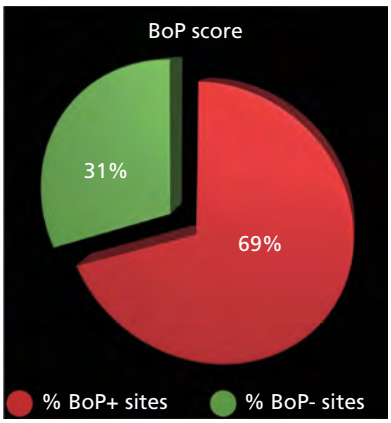


Fig. 15-5 *(Continued)*. (d) Orthopantomography. (e) BoP score (Source: Based on Trombelli et al. 2004a.)

included in the scoring system (i.e. bleeding, supra- or subgingival calculus, pockets) are unique to gingivitis. When using more specific indices to assess gingival inflammation, wide variations of gingivitis prevalence are recorded in relation to varying cut-off values. In general, the more extended and severe the manifestations of the disease that are considered, the less prevalent the gingivitis.

These observations reinforce the need to identify and grade a GC based on the criteria listed in Table 15-3. This new GC definition has been successfully implemented in recent studies on diverse populations, examining various epidemiological (Botelho *et al*. 2019; Erchick *et al*. 2019; Machado *et al*. 2019) (Table 15-4), interventional (Al Asmari *et al*. 2020), and biological (Wang *et al*. 2020a) questions relating to gingivitis.

Impact of gingivitis on patient-reported quality of life

Few studies evaluated the impact of gingivitis on oral health-related quality of life (OHRQoL) (Tsakos *et al*. 2006; Krisdapong *et al*. 2012; Tomazoni *et al*. 2014). In a cohort of 1034 Thai children, Tsakos *et al*. (2006) showed that, while the prevalence of periodontal treatment need (CPI>0) was 97%, the perception of a condition-specific (CS) impact was limited to 27.1% of subjects. Specificity with respect to individuals with no CS-impact among periodontally healthy subjects was 0.83. Similarly, in a sample of 1100 12-year-old and 871 15-year-old Thai children, less than 30% of subjects had CS-impact on their quality of life related to gingivitis and calculus despite the high prevalence (about 80%) of gingivitis and/or calculus. The impact of gingivitis on children's OHRQoL was mostly at low levels of extent and intensity. However, extensive gingivitis was significantly associated with a moderate/higher level of CS-impacts (Krisdapong *et al*. 2012). In a random sample of 1134 12-year-old Brazilian schoolchildren, gingivitis extent showed an impact on OHRQoL, with mean quality of life scores being 1.15 higher for children with ≥15% BoP-positive sites than for children with <15% BoP-positive sites (Tomazoni *et al*. 2014). Extent of gingival bleeding (>15% BoP) was significantly associated with emotional well-being, oral symptoms, functional limitations, and social well-being domains (Tomazoni *et al*. 2014). Evidence suggests that plaque-induced gingivitis is associated with significant changes in somatosensory sensitivity (response to mechanical and thermal stimuli), both at the gingiva and the periodontal ligament (Wang *et al*. 2020a), providing a possible mechanistic explanation for at least part of the altered OHRQoL perception.

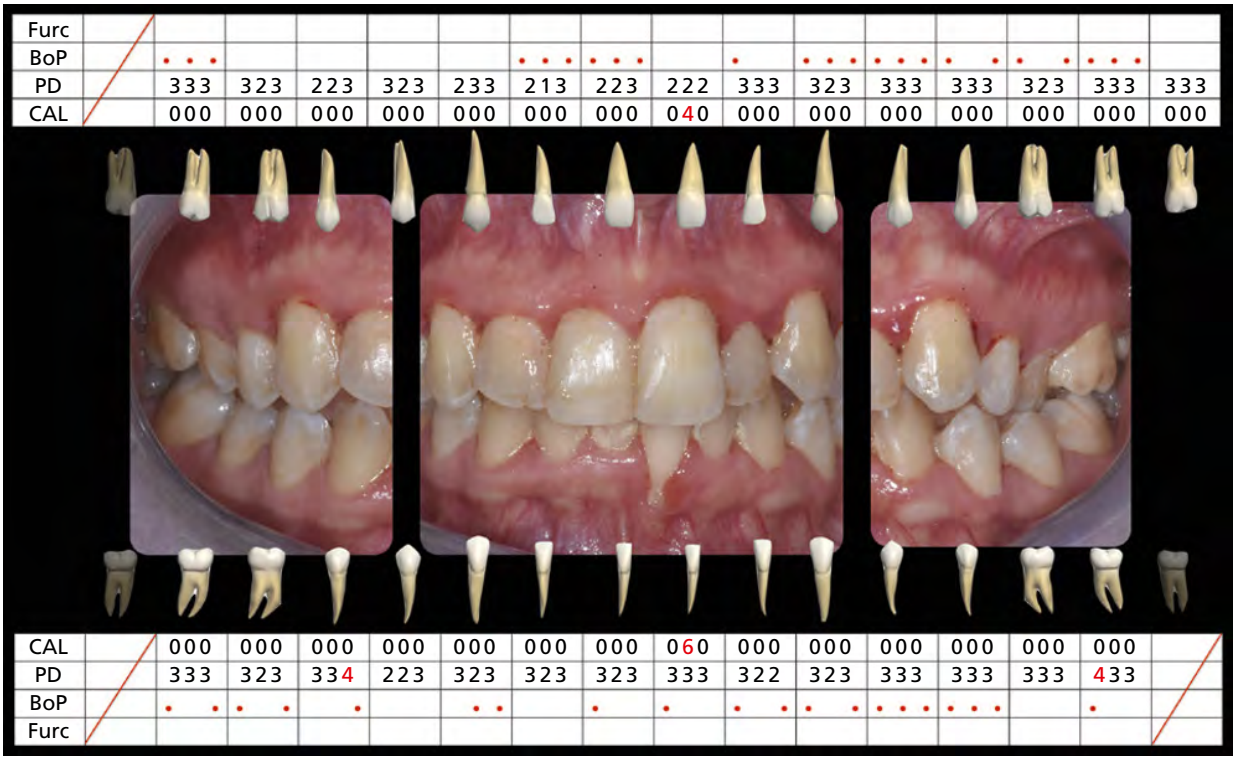
Collectively, data from these studies indicate that, although highly prevalent, gingivitis has a limited impact on OHRQoL. However, gingivitis extent, in terms of BoP score, may increase the negative effects on CS and general OHRQoL. Interestingly, an increasing level of agreement between the impact of gingivitis (Community Periodontal Index [CPI] = 1 versus CPI = 2) on patient's quality of life and the presence of a normative need for periodontal treatment has been reported (Tsakos *et al*. 2006).

Impact of gingivitis on systemic inflammation

As for other chronic inflammatory diseases, the relationship between periodontal diseases (including gingivitis) and systemic levels of inflammatory markers has been evaluated (see also Chapter 16). The biological mechanisms supporting the plausibility of this association rely on the entry of pathogenic bacteria from the biofilm of periodontally diseased sites into the blood stream and on the entry into the circulation of "excess" local levels of host-derived inflammatory mediators.

Among the investigated biomarkers, particular attention has been paid to C-reactive protein (CRP), which is produced in response to many forms of trauma or diseases and contributes to host defense as part of the innate immune response. Studies that evaluated the association between gingivitis and serum levels of CRP universally identified gingivitis as a condition characterized by serum CRP levels which are intermediate between those measured in periodontal health and periodontitis, although differences in serum CRP levels observed between gingivitis and

(a)



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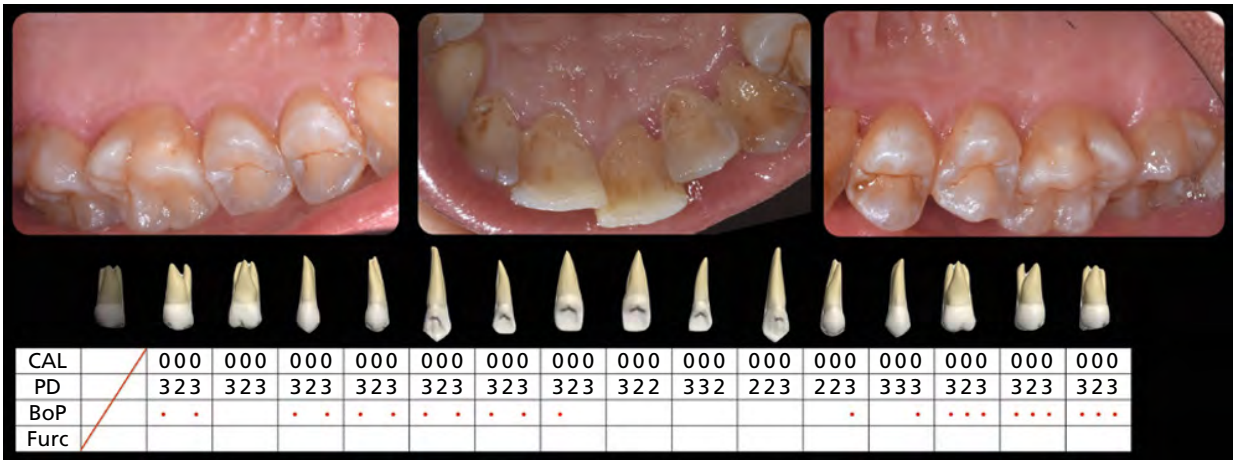

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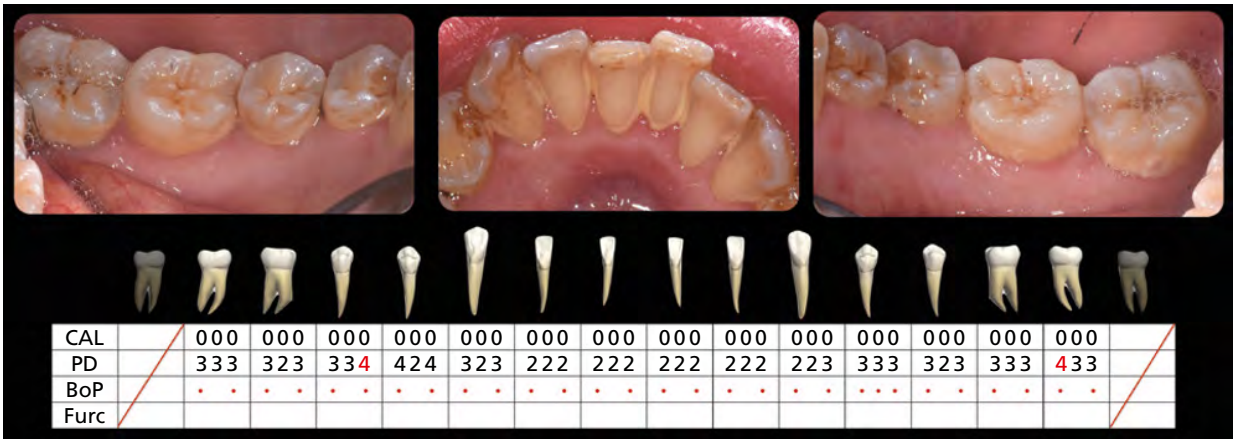
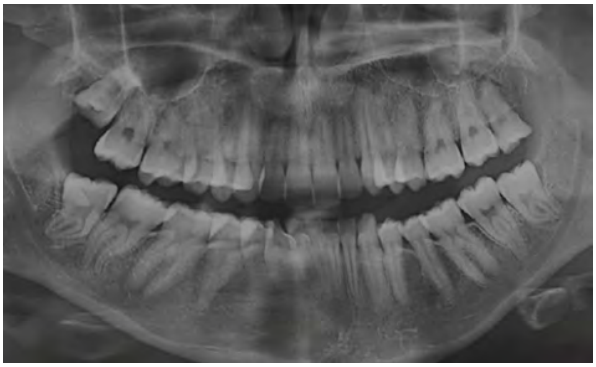


Fig. 15-6 Plaque-induced gingivitis on a reduced periodontium in a patient without a history of periodontitis. Clinical attachment level (CAL, in mm), probing depth (PD, in mm), bleeding on probing (BoP), and furcation lesions (Furc) as assessed at the (a) buccal, (b) palatal, and (c) lingual tooth aspects.

(d)



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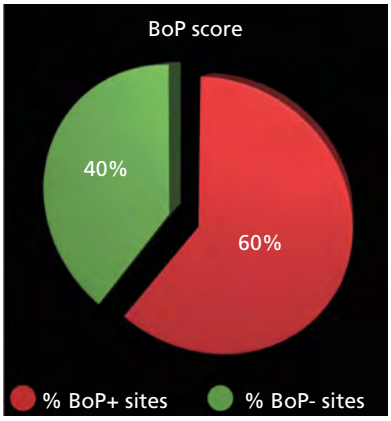


Fig. 15-6 *(Continued)*. (d) Orthopantomography. (e) BoP score (Source: Ainamo & Bay 1975.)

the other periodontal conditions did not consistently reach statistical significance in all studies (Pradeep *et al*. 2010; Bansal *et al*. 2014; Podzimek *et al*. 2015). In subjects with gingivitis, the severity and extent of gingival inflammation were evaluated for their relationship with CRP levels in serum. While in some studies CRP levels were found to be significantly positively correlated with papillary bleeding index (Podzimek *et al*. 2015) or gingival inflammation (Pradeep *et al*. 2010), other authors failed to find an association between CRP levels and gingival inflammation (Bansal *et al*. 2014), BoP (Wohlfeil *et al*. 2009; Bansal *et al*. 2014), or the number of sextants with at least one BoP-positive site (Pitchika *et al*. 2017).

Overall, the abovementioned findings seem to demonstrate that the inflammation of marginal gingival tissues determines an increase in systemic inflammation, assessed in terms of CRP levels. However, other studies have failed to demonstrate potentially relevant systemic effects during gingivitis development (Kinane *et al*. 2015). Therefore, the relationship between severity of gingival inflammation and severity of systemic inflammation in gingivitis patients remains unclear.

Prognostic value of gingivitis

When compared with periodontitis, a peculiarity of plaque-induced gingivitis lesion is the complete reversibility of the clinical tissue alterations once the dental biofilm is removed. Notwithstanding the reversibility of the gingivitis-elicited tissue changes, gingivitis at a site level holds particular clinical significance because it is considered the precursor of periodontitis. The evidence supporting the relationship between gingivitis and periodontitis lesions stems from longitudinal studies, where development and progression of attachment loss was associated with greater baseline levels of gingival inflammation (Löe *et al*. 1986; Ismail *et al*. 1990; Clerehugh *et al*. 1995; Albandar *et al*. 1998; Schätzle *et al*. 2003; Ramseier *et al*. 2017). In contrast, sites with no or minimal progression of attachment loss over time were characterized by the consistent absence of gingival inflammation over time (Page & Sturdivant 2002; Walters & Chang 2003; Schätzle *et al*. 2003; Axelsson *et al*. 2004; Repeke *et al*. 2012; Kina *et al*. 2016). Gingival inflammation has prognostic relevance for periodontal deterioration at the site level, when persistently present during multiple observation intervals. In this respect, it has been demonstrated that sites BoP have higher odds for attachment loss and exhibit greater prevalence of progressive severe attachment loss when compared with non-bleeding sites (Schätzle *et al*. 2003).

Overall, these observations suggest that effective long-term control of gingival inflammation could prevent progressive attachment loss (Schätzle *et al*. 2003).

Potential modifying factors of plaque-induced gingivitis

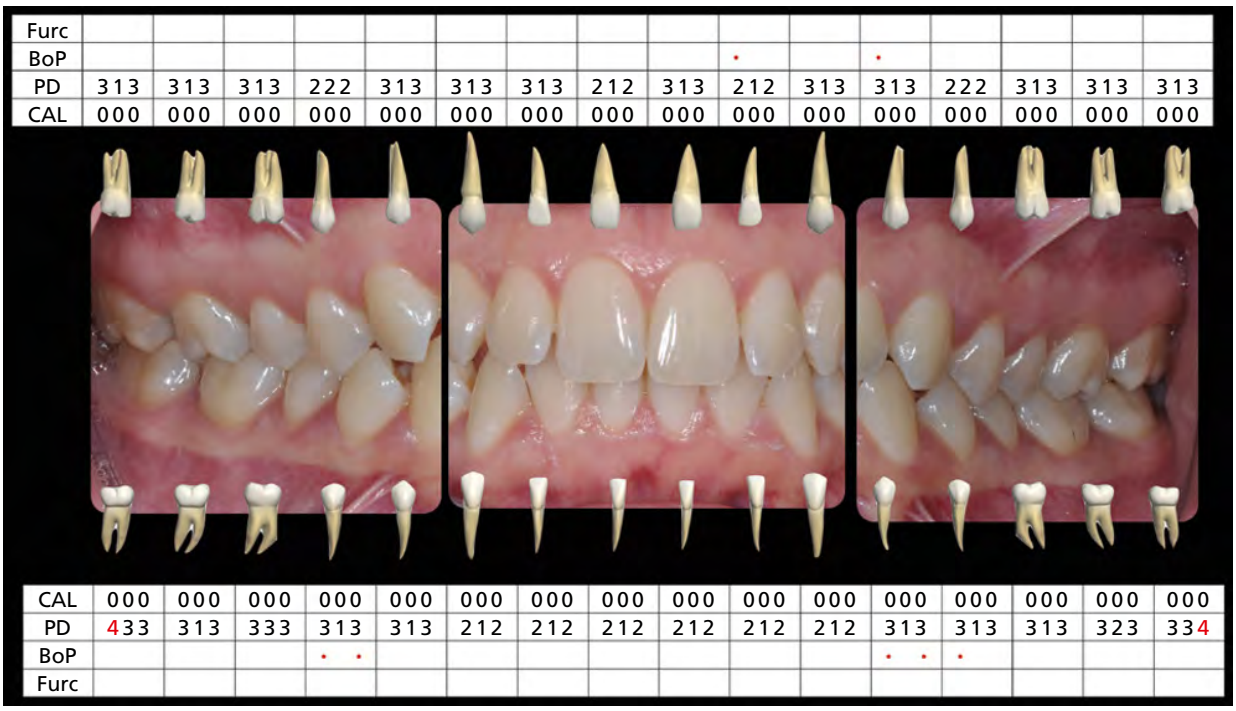
As mentioned above, individuals may differ in the clinical manifestation of plaque-induced gingivitis, even in the absence of discernible differences in systemic health and plaque accumulation. Such variable responses to similar plaque levels have been ascribed to possible, as yet unidentified, genetic differences (Trombelli *et al*. 2004a,b). However, there are several clearly identified patient factors, both at the systemic and the local level (Tatakis & Trombelli 2004; Trombelli & Farina 2013) that can affect the gingival response to the accumulated plaque, the tissue response to mechanical stimulation with a probe, and/or the underlying level of gingival inflammation in the absence of plaque, thus modifying the development of plaque-induced gingivitis.

Among the systemic factors established as modifiers of plaque-induced gingivitis, the most common or significant ones, such as smoking, changes in sex hormones, malnutrition, specific diseases and conditions, and systemic drugs, will be briefly reviewed here.

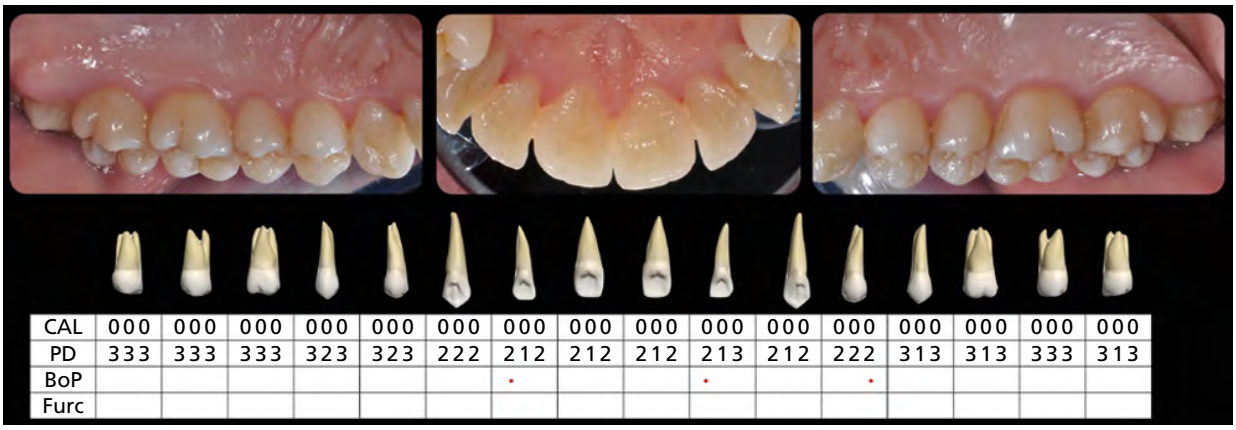
Smoking

Smoking, which is an established risk factor for periodontitis (Tomar & Asma 2000), has been consistently shown to suppress the gingival bleeding

(a)



(b)



(c)

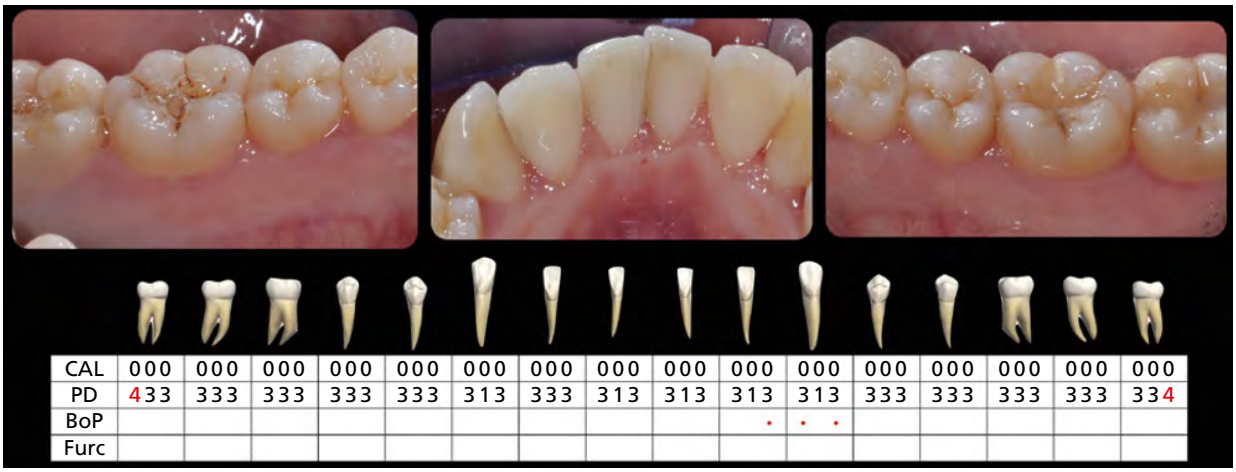
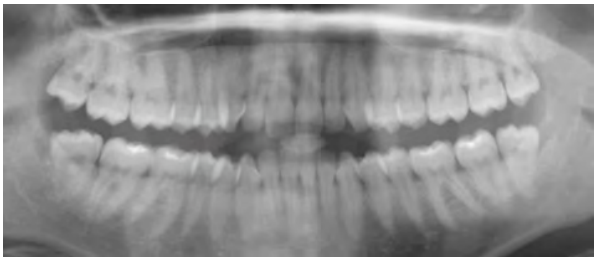


Fig. 15-7 Periodontal health in an intact periodontium. Clinical attachment level (CAL, in mm), probing depth (PD, in mm), bleeding on probing (BoP), and furcation lesions (Furc) as assessed at the (a) buccal, (b) palatal, and (c) lingual tooth aspects.

(d)



(e)

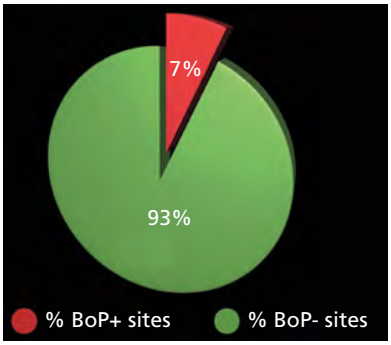


Fig. 15-7 *(Continued)*. (d) Orthopantomography. (e) BoP score (Source: Ainamo & Bay 1975.)

response during development of gingivitis (Preber & Bergström 1985; Lie *et al*. 1998; Bergström & Boström 2001; Nair *et al*. 2003; Peruzzo *et al*. 2016). The smoking-induced decreased gingival bleeding in the presence of accumulated plaque is evident across tooth types (Holde *et al*. 2020) and manifests itself even in the presence of other systemic factors known to increase the bleeding response of the gingiva (Tarnowski *et al*. 2018). The potential mechanisms by which smoking alters the gingival inflammatory response to plaque accumulation include qualitative changes in the accumulating biofilm (Shiloah *et al*. 2000; Kumar *et al*. 2011; Matthews *et al*. 2013), alterations of the steady state (Wang *et al*. 2020b) and plaque-elicited gingival immune responses (Kumar *et al*. 2011), and effects on the physiological responses of the gingival vasculature (Morozumi *et al*. 2004; Buduneli & Scott 2018).

Sex steroid hormones

Sex steroid hormone changes, such as those occurring during puberty (Mombelli *et al*. 1989) and pregnancy (Raber-Durlacher *et al*. 1994; Gürsoy *et al*. 2008), impact and exacerbate the inflammatory response of the gingiva, even in the presence of minimal plaque levels (Mombelli *et al*. 1989; Raber-Durlacher *et al*. 1994; Gürsoy *et al*. 2008; Murakami *et al*. 2018). Changes in sex steroid hormones elicit complex changes in the immunobiology of the tissues (Raber-Durlacher *et al*. 1993; Carrillo-de-Albornoz *et al*. 2012; Yarkac *et al*. 2018) and appear to contribute to qualitative alterations of the associated dental plaque (Kornman & Loesche 1980; Raber-Durlacher *et al*. 1994; Balan *et al*. 2018). Although changes in sex steroid hormone levels occur also during the menstrual cycle and in response to oral contraceptive use, the associated gingival changes are typically modest, if not minimal, likely because the associated hormonal changes are also relatively small (Preshaw *et al*. 2001; Baser *et al*. 2009; Becerik *et al*. 2010; Preshaw 2013).

Malnutrition

Malnutrition and lack of specific nutrients have been shown to modify the gingival tissue response to plaque. Scurvy, the severe deficiency of vitamin C (ascorbic acid), is characterized by bleeding gingiva and other manifestations (Lind 1953), explained by the critical contribution of ascorbic acid to collagen synthesis and the significance of the latter to the maintenance of vascular structures and the renewal of blood vessel walls following mechanical trauma. Although scurvy is quite rare today where there is adequate food supply, unique and persistent dietary habits may precipitate the disease (Ellis *et al*. 1984). Controlled nutritional ascorbic acid deficiency experiments in humans (Leggott *et al*. 1986, 1991) result in increased gingivitis, relative to non-deficient controls with similar plaque levels and the same type of microflora. Conversely, dietary intervention, including supplementation with vitamin C and other nutrients with anti-inflammatory properties, results in significant reduction of gingival bleeding in the absence of any apparent microbiological changes (Amaliya *et al*. 2018; Woelber *et al*. 2019).

Specific systemic diseases and conditions

Specific systemic diseases and conditions known to modify the development of plaque-induced gingivitis include trisomy 21 (Down's syndrome), hyperglycemia and diabetes, and hematologic malignancies (e.g. leukemia). *Down's syndrome* patients manifest more extensive and severe gingival inflammation, and much earlier, compared with age- and sex-matched genetically healthy controls, despite no differences in plaque accumulation rates (Reuland-Bosma *et al*. 1986, 1988). Although the specific underlying mechanisms remain unclear, there is no doubting the genetic basis behind this modifying factor. *Hyperglycemia*, whether due to diabetes or other conditions, has been strongly associated with gingival bleeding (Hujoel & Stott-Miller 2011). When diabetic patients are compared with non-diabetics they experience significantly greater gingival inflammation with similar plaque levels, regardless of the underlying diabetic etiology (de Pommereau *et al*. 1992; Cutler *et al*. 1999; Salvi *et al*. 2005). The level of metabolic control (e.g. as expressed by HbA1c levels), is strongly associated with the prevalence of gingival bleeding (Ervasti *et al*. 1985; Hujoel & Stott-Miller 2011) and suggests that the increased

Table 15-4 Prevalence of gingivitis as derived from national, large-scale epidemiological studies or reviews. (Source: Modified from Trombelli *et al*. 2018.)

Country	Study	Population	Sample size	Clinical indices to assess gingivitis	Criteria used to identify a gingivitis case	Gingivitis prevalence
USA	Albandar & Kingman 1999	Individuals aged 30–90, representing approximately 105.8 million civilian, non-institutionalized Americans	9689	BoP	Individuals with 6 or more teeth present were classified according to the following criteria: (1) extensive gingivitis: 5 or more teeth (or 50% or more of the teeth examined) with gingival bleeding (2) limited gingivitis: 2–4 teeth (or 25–50% of the teeth examined) with gingival bleeding Individuals who did not fulfill these criteria were regarded as not having an appreciable level of gingival inflammation	32.3% (limited: 21.8%; extensive: 10.5%)
USA	Li *et al*. 2010	Subjects recruited by placing advertisements in local publications	1000	GI	Mean full-mouth GI	GI <0.5%: 6.1% of subjects GI >0.5: 93.9% of subjects GI ≥1: 55.7% of subjects
UK	Murray *et al*. 2015	5–15-year-old individuals	69 318	Not reported in the review (reported only in surveys included in the review)	Not reported in the review (reported only in surveys included in the review)	About 50% of subjects had gum inflammation
Greece	Mamai-Homata *et al*. 2010	35–44-year-old individuals	1182	CPI	Highest CPI score = 1 (gingival bleeding)	16.2%
Romania	Funieru *et al*. 2016	10–17-year-old individuals	1595	GI	Prevalence of gingivitis: proportion of any GI mean score >0 Extent of gingivitis: site prevalence – proportion of gingival surfaces affected by gingivitis Prevalence of gingival bleeding: proportion of any gingival bleeding (score 2 and 3 of the GI) present in at least one gingival surface	Gingivitis prevalence: 91%
Sweden	Norderyd *et al*. 2015	Randomly selected individuals in each of the age group of 3, 5, 10, 15, 20, 30, 40, 50, 60, 70, and 80 years	1010	GI	GI = 2 or 3	Mean % of sites with gingivitis ranged between 1.8% and 19.5% depending on age cohort

(*Continued*)

Table 15-4 (*Continued*)

Country	Study	Population	Sample size	Clinical indices to assess gingivitis	Criteria used to identify a gingivitis case	Gingivitis prevalence
Hungary	Hermann *et al.* 2009	Dentate or partially edentulous adults	4153	CPI	Highest CPI score = 1 (gingival bleeding)	8%
China	Zhang *et al.* 2010	Adults with ≥20 teeth	1143	GI	Mean GI	GI ≥1: 82.2%
India	Kundu *et al.* 2011	Individuals aged 15 years or more	22 366	CPI	Highest CPI score = 1 (gingival bleeding)	4.3%
Australia	Australian Research Center for Population Oral Health 2009	Individuals aged 15 years or more	4967	GI	Mean GI ≥2	19.7%
Argentina	de Muniz 1985	7–8- and 12–13-year-old individuals	2279	CPI	CPI = 1	2.7–27.2% (depending on age cohort)
Algeria, Benin, Burkina Faso, Cap Verde, Djibouti, Egypt, Ethiopia, Ghana, Kenya, Lesotho, Libya, Malawi, Mauritius, Morocco, Namibia, Niger, Nigeria, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Zaire, Zimbabwe	Baelum & Scheutz 2002	15–44-year-old individuals	Reported in each study included for review	CPI	Highest CPI score = 1 (gingival bleeding)	0–52% (depending on the country/study)
Studies employing the new Gingivitis Case Definition						
Portugal	Botelho *et al.* 2019	18 to >80-year-old individuals	1064	BoP	2018 Gingivitis case definition	8% (27.4% in 18–30- year-olds, 3.6–9.3% in all other age groups)
Portugal	Machado *et al.* 2019 (Subsample of the Botelho *et al.* 2019 study)	18 to >80-year-old individuals	571	BoP	2018 Gingivitis case definition	11.7%
Nepal	Erchick *et al.* 2019	15–41-year-old pregnant women	1452	BoP	2018 Gingivitis case definition	40.1% (80.4% of gingivitis cases were localized and 19.6% were generalized)

BoP, bleeding on probing; CPI, Community Periodontal Index; GI, Gingival Index.

bleeding in chronic hyperglycemia is attributable to the attendant microvascular injury. Metabolic control also affects subgingival biofilm composition (Ganesan *et al*. 2017). Furthermore, hyperglycemia causes cellular changes, affecting both immune and connective tissue cells, that result in the establishment of a proinflammatory state (Verhulst *et al*. 2019). Improved metabolic control following appropriate systemic therapy may reduce some but not all of the clinical signs of gingival inflammation (Sastrowijoto *et al*. 1990).

Leukemia, in both children and adults, may result in thrombocytopenia and/or clotting-factor deficiencies and may manifest in the gingiva with excess bleeding and other signs of inflammation (redness, swelling, enlargement) that are not consistent with the observed levels of biofilm acccumulation (Levin & Kennedy 1973; Dreizen *et al*. 1984; Bergmann *et al*. 1992; Guan & Firth 2015). Similarly, heightened gingival inflammation is also evident in patients affected by any of the many forms of *neutropenia* (Andrews *et al*. 1965; Reichart & Dornow 1978; Donadieu *et al*. 2011).

Systemic drugs

Besides the aforementioned systemic conditions and diseases that modify plaque-induced gingivitis, *systemic drugs* are a well-established cause of altered gingival responses to plaque accumulation. Such drugs may include agents that exacerbate the gingival bleeding response because of anticoagulant properties, for example aspirin (Schrodi *et al*. 2002; Royzman *et al*. 2004; Kim *et al*. 2007; Sundram *et al*. 2012). Others include endocrine hormone preparations (e.g. see information on sex steroid hormones previously) and drugs with strong anti-inflammatory activity, which may reduce the typically anticipated gingival inflammation. Both steroidal (Sutton & Smales 1983; Vogel *et al*. 1984; Markitziu *et al*. 1990) and non-steroidal (Vogel *et al*. 1984; Heasman *et al*. 1993) anti-inflammatory medications can have such an effect. Similarly, topical application of anti-inflammatory drugs can also reduce the gingival inflammatory response to plaque accumulation (Vogel *et al*. 1984; Jones *et al*. 1999). Several drugs have been identified that exacerbate the plaque-induced gingival inflammatory response in a more unique and specific manner; they cause severe gingival enlargement (Seymour *et al*. 1996; Seymour 2006). Drugs causing gingival enlargement include antihypertensive calcium channel blockers, for example nifedipine (Nery *et al*. 1995; O'Valle *et al*. 1995), anticonvulsants such as phenytoin (Angelopoulos 1975), and immunosuppressants, for example cyclosporin (Seymour & Jacobs 1992; O'Valle *et al*. 1995). Although the exact mechanisms through which these drugs lead to enlargement are not fully elucidated, it is apparent that direct and indirect effects on gingival connective tissue cells, especially fibroblasts, are involved in these responses (Fu *et al*. 1998; Mariotti *et al*. 1998; Seymour 2006; Gulati 2012).

In addition to the drugs that may modify the gingival response to plaque accumulation, development of gingivitis may also be altered by drugs that either enhance or inhibit plaque accumulation. Systemic antibiotics are a good example of a systemic factor that may limit biofilm development and thus prevent or slow the establishment of gingivitis (Listgarten *et al*. 1979; Heijl & Lindhe 1980). Drugs that may cause *hyposalivation*, such as sedatives, antidepressants, antihistamines, and antihypertensives, can lead to increased plaque accumulation and greater likelihood of caries and other oral complications, including inflammation of the oral mucosa and gingiva (Mizutani *et al*. 2015; Turner 2016). Hyposalivation can also be the result of systemic diseases, such as Sjögren syndrome and diabetes, and of head and neck radiation (López-Pintor *et al*. 2016; Turner 2016).

Local factors

A local factor commonly implicated in increased plaque accumulation and subsequent gingival inflammation is the presence of poor or prominent subgingival *restoration margins*. Inadequate subgingival restoration margins may facilitate plaque development both directly, by providing additional, rough surface areas, and indirectly, by making more difficult plaque removal during oral hygiene procedures. The end result, especially after long-term presence of such restorative irregularities, is detrimental to gingival health (Schätzle *et al*. 2001).

Local factors that may modify the gingival response to plaque have also been identified. One such potential factor is *thin periodontal phenotype*. Although evidence suggests a greater susceptibility of thin gingival tissues to mechanical trauma (Claffey & Shanley 1986; Olsson & Lindhe 1991) the significance of gingival quality/dimensions (i.e. periodontal phenotype) for the gingival bleeding response remains unresolved (Muller & Heinecke 2002; Trombelli *et al*. 2004c). Recent studies identified two other patient groups with gingival anatomical variants that may exhibit a modified response to plaque accumulation. The first group is patients with altered passive eruption, whose gingival response to similar levels of *de novo* plaque accumulation is much more severe than controls and less quick to resolve after reintroduction of oral hygiene measures (Aghazada *et al*. 2019). The second group is patients who have received a subepithelial connective tissue graft to treat gingival recession defects. The sites treated with the autogenous grafts, when compared with contralateral control sites, developed significantly less inflammation following plaque accumulation (Graziano *et al*. 2014). In the case of the grafted sites one could speculate that the graft-induced increase in gingival thickness may explain in part the resulting reduced susceptibility to

gingivitis development. However, in the case of the patients with altered passive eruption the mechanisms underlying the increased susceptibility to gingivitis development remain unclear.

Prevention and management of plaque-induced gingivitis

Tissue alterations that characterize plaque-induced gingivitis may be prevented or completely reversed by proper removal of the dental biofilm to ensure the maintenance or the restoration of a periodontally healthy condition (Table 15-3). The latter is perceived as such by the patient (Baser *et al*. 2014) and associates with better quality of life compared with gingivitis (Tomazoni *et al*. 2014). The reversion from gingivitis to periodontally healthy status holds particular clinical significance due to the well-established relationship between gingivitis and periodontitis as shown in longitudinal studies (Löe *et al*. 1986; Ismail *et al*. 1990; Clerehugh *et al*. 1995; Albandar *et al*. 1998; Schätzle *et al*. 2003; Ramseier *et al*. 2017). Gingivitis treatment also represents the key action to prevent progressive attachment loss in the long-term (Chapple *et al*. 2015; Ramseier *et al*. 2017).

The mechanical disruption of the dental biofilm through self-performed oral hygiene is the primary means to prevent and manage gingivitis (Chapple *et al*. 2015). Treatment success may be facilitated by adequate patient information, motivation, and personalized instruction (Newton & Asimakopoulou 2015), implementation of oral hygiene procedures with powered instruments (Van der Weijden & Slot 2015), proper interdental cleaning devices (Sälzer *et al*. 2015; Worthington *et al*. 2019), and chemical agents with antiplaque and/or anti-inflammatory properties (Van Strydonck *et al*. 2012; Trombelli & Farina 2013; Biesbrock *et al*. 2019; Figuero *et al*. 2019). The adjunctive use of probiotics (Akram *et al*. 2020) and dietary supplements or micronutrients (Montero *et al*. 2017; Amaliya *et al*. 2018) may also be suggested.

When self-performed oral hygiene is not or partly effective in re-establishing a periodontally healthy condition (e.g. due to the reduced ability of the subject or presence of plaque-retaining factors), professional intervention mainly based on mechanical plaque removal and elimination of local plaque-retentive factors is required. In this respect, it has been shown that professional removal of supra- and subgingival plaque in combination with oral hygiene instructions results in a greater reduction of gingival bleeding than no treatment. In the long-term, the frequency of professional sessions should be decided on the basis of the desired effect on plaque and bleeding (Needleman *et al*. 2015).

In instances where the gingival response to the dental biofilm is modified by systemic factors, multidisciplinary management of the gingivitis case involving appropriate medical professionals is recommended.

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Chapter 16

Current Classification of Periodontitis

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Introduction

A new classification of periodontal diseases and conditions was introduced in 2018 (Caton *et al*. 2018; Tonetti *et al*. 2018b), following the deliberations and the consensus report (Papapanou *et al*. 2018a) of an International Workshop that took place in Chicago in November 2017. The new system replaced the classification scheme used over the last two decades, which defined *chronic* and *aggressive* as the two principal forms of periodontitis (Armitage 1999). In this chapter, we will first provide a brief overview of terms that have been used in the recent literature to classify the main phenotypes of periodontitis, and their evolvement over the years. We will next explain in detail the main reasons that necessitated the most recent revision and will describe in depth the principles of the current system. Lastly, we will exemplify the implementation process in clinical practice by reviewing a number of clinical cases and highlighting clinical situations that may pose interpretational challenges.

A brief historical perspective: recently used periodontitis classification systems

Specific features defining different periodontitis-related phenotypes have formed the basis of classification systems ever since periodontal pathologies were first described in the literature. Inevitably, these systems have continuously evolved reflecting the prevalent scientific paradigms of the time (for a thorough review of periodontitis classification systems since the late nineteenth century, the reader is referred to Armitage 2002). Here we will briefly account for the main classification systems for periodontitis that have evolved over the past 50 years.

Early epidemiologic findings established that the severity of periodontitis in the population is associated with age and oral hygiene (Scherp 1964). Consequently, the observation that older cohorts, and individuals with poor oral hygiene, inevitably present with a certain amount of clinical attachment loss and bone loss permeated the literature and

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

influenced the definition of the main categories of periodontitis. A "bird's eye" view of the more recent periodontitis classification schemes prior to the introduction of the current system indicates that these systems have largely attempted to segregate patients with levels of periodontal tissue destruction that are commensurate to their age and level of local etiology from those with more severe but less prevalent manifestations (Table 16-1). Barring specific clinical phenotypes whose characteristics were attributed to underlying systemic conditions or necrotizing forms of periodontitis (both of which are still recognized until today as separate entities), a distinction was drawn between periodontitis manifesting itself in adults from those forms that affect children or individuals of young age. For example, the two main categories recognized by the 1989 World Workshop in Clinical Periodontics (Consensus Report, Discussion Section I, 1989) were Adult Periodontitis and Early Onset Periodontitis, setting the age threshold for distinction between the two at 30 years. Early Onset Periodontitis was further subdivided in three subcategories: *prepubertal* (Page *et al*. 1983), *juvenile* (Tsai *et al*. 1981) and *rapidly progressive* periodontitis (Page *et al*. 1983). The first subcategory included children with loss of periodontal tissue support affecting their deciduous teeth. The second included teenagers with a characteristic bone loss pattern affecting incisors and first molars and with periodontal pockets heavily colonized by *Aggregatibacter actinomycetemcomitans* (then termed *Actinobacillus actinomycetemcomitans*). Note that this particular phenotype had been earlier attributed to degenerative processes, including "cementopathia" and "diffuse atrophy of the alveolar bone" (Gottlieb 1928), and was later termed "periodontosis" (Hirschfeld 1948). The third subcategory included individuals in their twenties, with generalized and rapid periodontitis progression. Interestingly, the 1989 classification also included a main category separate from both Early Onset and Adult Periodontitis, termed Refractory Periodontitis, which included patients who were found to be unresponsive to a variety of periodontal treatment modalities.

Acknowledging the difficulties associated with an accurate assessment of the age of onset of periodontitis in many patients, and recognizing that the Refractory Periodontitis category was extremely heterogeneous, a new International Workshop that took place in 1999 abolished these terminologies and defined two major forms of periodontitis termed Chronic and Aggressive Periodontitis (Armitage 1999). Chronic periodontitis now encompassed the more common form of the disease where the extent and severity of tissue loss is largely commensurate with the amount of local etiology. In contrast, Aggressive Periodontitis was characterized by more rapid destruction of the periodontal supporting tissues and manifested itself

Table 16-1 Evolution of the classification systems of periodontal diseases over the last 50 years.

1977	1986	1989	1999	2018
			Gingival diseases A. Dental plaque-induced B. Non plaque-induced	Gingival diseases and conditions
Juvenile periodontitis	Juvenile periodontitis A. Prepubertal B. Localized juvenile c. Generalized juvenile	Early-onset periodontitis A. Prepubertal 1. Localized 2. Generalized B. Juvenile periodontitis 1. Localized 2. Generalized C. Rapidly progressive	Aggressive periodontitis A. Localized B. Generalized	Periodontitis classified according to a 2-vector system on the basis of Stage and Grade
Chronic periodontitis	Adult periodontitis	Adult periodontitis	Chronic periodontitis	
	Necrotizing ulcerative gingivo-periodontitis	Necrotizing ulcerative periodontitis	Necrotizing periodontal diseases A. Necrotizing ulcerative gingivitis B. Necrotizing ulcerative periodontitis	Necrotizing periodontal diseases
	Refractory periodontitis	Refractory periodontitis		
		Periodontitis associated with systemic disease	Periodontitis as a manifestation of systemic diseases	Periodontitis as a manifestation of systemic disease
			Abscesses of the periodontium	
			Periodontitis associated with endodontic lesions	Other conditions affecting the
			Developmental or acquired deformities and conditions	periodontium

in either a localized or a generalized form. Note that imprecision in the stipulated primary and secondary features of these novel categories, along with the fact that age was no longer considered a primary classification criterion – allowing individuals to be classified as having either chronic or aggressive periodontitis irrespective of their age – made the 1999 classification rather difficult to apply in everyday clinical practice.

Need for the new classification

The etiological role of microbial plaque in the initiation of gingivitis has been well-established (Löe *et al*. 1965) and classical experimental animal studies expanded the role of bacteria in the pathogenesis of periodontitis (Lindhe *et al*. 1973). Subsequent longitudinal studies conducted between the early 1970s through the 1980s informed the core principles that allowed successful prevention and treatment of periodontitis (Knowles *et al*. 1972; Axelsson & Lindhe 1981a, b; Ramfjord *et al*. 1982). In subsequent years, however, clinicians and researchers started to report exceptions and variations to the simple paradigms that suggested that periodontitis susceptibility and severity are a mere function of the intensity and the duration of bacterial exposure and that prevention and treatment are predictable outcomes if there is adequate bacterial control (Scherp 1964; Lindhe & Nyman 1975; Nyman *et al*. 1977; Hirschfeld & Wasserman 1978; McFall 1982; Lindhe *et al*. 1984; Löe *et al*. 1986; Westfelt *et al*. 1998). Instead, what has emerged in epidemiologic and treatment studies is that multiple risk factors, including environmental exposures and genetic predispositions, can modify an individual's phenotypic response to the bacterial challenge and/or the outcome of periodontal therapy (Papapanou 1996; see Chapter 6). Although the majority of periodontitis cases respond predictably to mechanical biofilm disruption and subsequent plaque control, a relatively small percentage of patients will respond unfavorably to standard periodontal treatment. Moreover, although average levels of attachment loss at different ages are generally consistent throughout the world, there are individuals in each age group who have experienced a level of disease severity that is disproportionate to that expressed by the majority of their peers (Billings *et al*. 2018).

These clinically observable exceptions in periodontitis expression indicated that there was a need for additional information beyond the current level of severity to more specifically characterize a patient's type of periodontitis. Important questions that arose and challenged older paradigms were (1) whether the clinically observed distinct disease phenotypes are truly different diseases or, rather, variations of a common disease entity; (2) whether these phenotypes were indeed the result of different infections by specific bacteria or bacterial complexes that had been earlier implicated as causative factors; and (3) the exact role of multiple risk factors including genetic susceptibility. Importantly, the acknowledged difficulty to distinguish between chronic and aggressive periodontitis based on clinically identifiable traits (Armitage *et al*. 2010) and the diagnostic imprecision of primary criteria used to classify these principal categories (Armitage 1999) was further sustained by the presence of common microbiological, immunological, and histopathological features of the two entities (Armitage 2010; Ford *et al*. 2010; Smith *et al*. 2010). For example, the postulated differences in the intensity in serum antibody responses between subtypes of periodontities were disproved (Picolos *et al*. 2005; Hwang *et al*. 2014) and transcriptomic profiles of gingival lesions from chronic and aggressive periodontitis were largely overlapping (Kebschull *et al*. 2013). These observations were corroborated by a position paper that reviewed the literature pertaining to aggressive periodontitis (Fine *et al*. 2018) in preparation for the 2017 World Workshop for the Classification of Periodontal and Peri-implant Diseases and Conditions as well as a recent review on the nexus between periodontal inflammation and microbial dysbiosis (Van Dyke *et al*. 2020).

Key concepts and ground rules of the new classification of periodontitis

The new periodontitis classification system is fundamentally different from the 1999 scheme, because, with the exception of specific forms (necrotizing periodontal diseases and periodontitis as a manifestation of systemic disease) (Albandar *et al*. 2018; Herrera *et al*. 2018), periodontitis is recognized as a single nosological entity which is further classified using a two-vector system (*Stage* and *Grade*) (Tonetti *et al*. 2018a). *Stage* reflects the severity of the disease (expressed through *attachment loss* and *bone loss*), but also factors in *tooth loss* that has occurred as a result of periodontitis (Table 16-2). In addition, it reflects the anticipated complexity of the treatment that is required to eradicate/reduce the current level of microbial challenge and inflammation, and to restore patient masticatory function. *Grade* describes additional biological dimensions of the disease including the observed or inferred progression rate, the risk for further deterioration due to environmental exposures (such as smoking) and co-morbidities (such as diabetes), and the risk that the disease or its treatment may adversely affect the particular patient's general health status (Table 16-3). The key steps of the process that need to be followed when implementing the new scheme are outlined in the following sections.

Assessment of Stage

It is important to realize that, before beginning an assessment of Stage, the clinician first needs to determine if the patient in question indeed has periodontitis. This assessment is ideally done on the

Table 16-2 Classification of periodontitis based on Stages defined by Severity (according to the level of interdental clinical attachment loss, radiographic bone loss and tooth loss), Complexity, and Extent and Distribution.

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1–2 mm	3–4 mm	≥5 mm	≥8 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15–33%)	Extending to middle third of the root	Extending to apical third of the root
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to Stage II Complexity: Probing depth 6–7 mm Vertical bone loss ≥ 3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to Stage III Complexity: Probing depth ≥8 mm Need for complex rehabilitation due to: masticatory dysfunction; secondary occlusal trauma; tooth mobility degree ≥2; bite collapse, drifting, flaring; less than 20 remaining teeth (10 opposing pairs); severe ridge defect
Extent and Distribution	Add to Stage as descriptor	For each Stage, describe extent as localized (<30% of teeth affected at the Stage-defining severity level), generalized (≥ 30% of teeth affected), or molar-incisor pattern			

CAL, clinical attachment loss; RBL, radiographic bone loss.

basis of full-mouth clinical attachment loss (CAL) measurements and is *not* an automatic process based on attachment loss thresholds: the determination involves clinical judgment. If interproximal attachment loss is present on at least two different, non-adjacent teeth, and the observed attachment loss cannot be attributed to traumatic factors or non-periodontitis-related etiologies (e.g. root fracture, endodontic infection, surgical trauma), then the patient is considered to have periodontitis. In the absence of interproximal attachment loss, but if attachment loss that cannot be ascribed to non-periodontitis-related causes is present at buccal or lingual surfaces, a diagnosis of periodontitis requires concomitant presence of CAL of ≥ 3 mm and probing depth of ≥3 mm at ≥2 teeth. Clinicians frequently confirm the presence of interproximal attachment loss by assessing presence of alveolar bone loss on periapical or bite-wing radiographs. It must be remembered, however, that tissue loss needs to encompass a substantial portion of the buccal-lingual dimension before it can be visualized by conventional radiographs. Thus, absence of readily discernible bone loss does not preclude presence of frank periodontitis of incipient severity. This is exactly the reason why the diagnosis of periodontitis is based on attachment loss rather than bone loss which is admittedly more widely assessed; use of bone loss as the primary criterion would result in significant under-detection of incipient periodontitis and an increase in "false negatives".

After ascertaining that the patient has periodontitis, the clinician should proceed with an assessment of Stage. A key element of the new classification, supported by our current knowledge, is that Stage I and Stage II adult patients are likely very different from Stage III and Stage IV patients in terms of how the host has coped with and/or has responded to the bacterial challenge. Stage I and II patients show periodontitis of incipient or moderate severity, have not lost any teeth due to the disease, and are likely to respond predictably to standard therapy based on the principles of sustainable reduction of the bacterial burden. In contrast, in stage III and stage IV periodontitis patients, it is most likely that one or several intrinsic or environmental risk factors have adversely affected the ability of the host to respond to the bacterial infection and to contain the tissue damage; thus, these patients seem to have experienced a different "disease trajectory" than patients of the same age with stage I or stage II periodontitis. Moreover, Stages III and IV represent more complex cases (due to angular defects, furcation involvements, tooth mobility, extensive tooth loss, loss of function) that require more specific knowledge, broader training, and more in-depth clinical experience to manage the patient's condition in a sustainably successful manner.

Based on the above, the initial staging of a case should involve a focused, high-level assessment of the patient's medical history, radiographs, and probing measurements to distinguish between Stage I or II versus Stage III or IV periodontitis, using two key discriminatory variables that can differentiate between the two aggregate groups: (1) the severity of tissue damage and (2) the presence of

Table 16-3 Classification of periodontitis based on Grades that reflect biologic features of the disease including evidence of, or risk for, rapid progression, anticipated treatment response, and effects on systemic health.

	Periodontitis grade		Grade A Slow rate of progression	Grade B Moderate rate of progression	Grade C Rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (PA radiographs or CAL loss)	Evidence of no loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	Bone loss/age	<0.25	0.25–1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease, e.g. molar incisor pattern; lack of expected response to standard bacterial control therapies
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normo-glycemic, no prior diagnosis of diabetes	HbA1c <7.0 in diabetes patient	HbA1c ≥7.0 in diabetes patient
Risk of systemic impact of periodontitis	Inflammatory burden	High sensitivity CRP	< 1 mg/L	1-3 mg/L	>3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, GCF, serum	?	?	?

CAL, clinical attachment loss; CRP, C reactive protein; GCF, gingival crevicular fluid; PA, periapical.

periodontitis-associated tooth loss. Note that the second point is an important novelty of the new classification when compared with its predecessors, as it incorporates in the diagnosis past experience of periodontitis that is inevitably not measurable at the current time point. For example, consider a situation when most periodontitis-affected teeth have been lost already, and the patient has been left with teeth that are intact, or affected at much lower severity. Assessment of the patient's overall susceptibility status on the basis of these "healthy survivor" teeth would be unquestionably erroneous.

This high-level assessment uses a narrow set of parameters to make a first distinction of whether a periodontitis case is either Stage I or II versus Stage III or IV, as indicated by the vertical red line in Fig. 16-1, and provides a starting point for a more detailed assessment. The distinction between Stage I and II periodontitis will be primarily carried out by evaluating whether the severity of bone loss at the areas of the dentition that exhibit the most advanced destruction extends either within or beyond one half of the coronal third (i.e. up to 15% of the root length versus between 15% and 33% of the root length). Clearly, the point here is not to scrutinize the level of bone loss with precision extending to single percentage points, but to distinguish between an incipient stage of periodontitis that has barely resulted in alveolar bone loss, from more substantial bone loss that extends within the coronal third of the root length. Readily discernible interproximal bone loss within the coronal third of the root length will, in most situations, be commensurate with Stage II rather Stage I disease. In contrast, Stage I disease is usually characterized by incipient attachment loss in the presence of early radiographic evidence of disruption in the alveolar bone support (for example, a break in the integrity of *the lamina dura*) rather than pronounced increase in the cementoenamel junction (CEJ)–bone crest distance.

If the high-level assessment indicates the patient is more likely to be a Stage III or IV, the clinician will need to evaluate the more complex parameters listed to the right of the red vertical line in Fig. 16-1. In this step, the clinician needs to study in detail the available full-mouth periodontal charting and full-mouth series of intraoral radiographs. The distinction between these two stages will be based either on the amount of tooth loss that can be attributed to periodontitis (1–4 teeth versus 5 or more teeth lost) or on the presence of the various complexity factors listed in Fig. 16-1 that need to be appreciated in detail. It must be realized that either Stage III or Stage IV disease may reflect severe or very severe periodontitis. However, the primary distinction between the two requires that an experienced clinician ponders the following two central questions that essentially represent a distillation of the case's treatment: (1) does the patient's extent and severity of periodontitis constitute a threat for the survival of *individual teeth* or rather of the survival of *the entire dentition*? and (2) does the total therapy envisioned to address the sequelae of periodontitis in the particular patient involve extensive, multidisciplinary oral rehabilitation? If the assessment is that the current level of periodontitis threatens the entire dentition and, consequently, treatment requires extensive oral rehabilitation involving collaboration of multiple experts (beyond the need for occasional extractions and a limited prosthetic reconstruction), then the

Staging a Periodontitis Patient		Initial Periodontitis	Moderate	Severe with potential for tooth loss	Advanced with potential for dentition loss
Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	1 to 2 mm	3 to 4 mm	≥ 5 mm	≥ 5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤ 4 teeth	Tooth loss due to periodontitis of ≥5 teeth
Complexity	Local	Maximum probing depth ≤ 4 mm Mostly horizontal bone loss	Maximum probing depth ≤5 mm Mostly horizontal bone loss	In addition to stage II complexity: Probing depth ≥ 6 mm Vertical bone loss ≥ 3 mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree >2) Severe ridge defect Bite collapse, drifting, flaring Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

Fig. 16-1 The initial assessment of Stage distinguishes between Stage I or II versus Stage III or IV periodontitis (on either side of the red line), on the basis of the severity of the loss of supporting tissue and the presence of periodontitis-associated tooth loss.

appropriate Stage for the patient is IV rather than III. Importantly, this determination involves a *collective* assessment of the potential complexity factors, rather than a mere "checking of a box" approach of isolated features.

It needs to be emphasized that Stage is a *patient based-attribute*, not a *tooth-based assessment*; consequently, a single Stage is ascribed to an individual patient at a given time. After Stage has been determined, Extent is added as a secondary descriptor, and reflects the percentage of teeth in the dentition that are affected by attachment or bone loss at the level of severity that defined the Stage (Sanz *et al*. 2020). For example, in a particular case that has been diagnosed to exhibit Stage III periodontitis, the Extent will be determined to be "localized", if the percentage of teeth with bone loss *beyond* the coronal third of the root is less than 30%. In contrast, if a larger proportion of teeth is affected by bone loss of that severity, the Extent will be considered "generalized". Note that because a patient with localized Stage III periodontitis may frequently include segments of the dentition with mild or moderate severity of attachment/bone loss, Extent describes the distribution of the severity that is characteristic of Stage III in the specific patient (Sanz *et al*. 2020) *not* the fraction of the dentition that is affected by periodontitis at any level of severity. Therefore, whenever communicating with patients or with each other, clinicians need to acknowledge this important distinction and to report the presence of less severely affected teeth that still need treatment in the "narrative" portion of the case description.

Another frequently raised question is whether a patient's Stage can change over time. If a patient who has been staged at a given time point experiences significant disease progression or disease recurrence after therapy that results in increased severity and/or more complex treatment needs, then stage must be shifted upwards at the time of the subsequent examination, as appropriate. However, although the severity of attachment loss and/or bone loss can be reduced substantially in case of successful regeneration therapy, it is advised that the patient retains the Stage originally assigned prior to the treatment.

Assessment of grade

Research data that have accumulated over the past decades indicate that the majority of periodontitis patients are on a disease trajectory that is compatible with predictably favorable clinical responses, provided that adequate therapy is rendered and diligent plaque control and maintenance visits at appropriately scheduled intervals are sustained. However, a proportion of patients ranging between 20% and 25% are on a different trajectory and are less likely to respond predictably to these standard approaches (Giannobile *et al*. 2013). The primary goal of grading is thus to determine the disease trajectory that a specific patient is likely following, and to use this information to guide the most appropriate intervention strategy to achieve a successful outcome.

The assessment of Grade is based on three fundamental principles:

- Not all individuals are equally susceptible to periodontitis (Baelum *et al*. 1986; Löe *et al*. 1986; Billings *et al*. 2018).
- Periodontitis progression and severity is a function of multiple influences that interact with each other, modify the individual patient's host response to the microbial challenge, and influence the clinical phenotypes (Struch *et al*. 2008; Giannobile *et al*. 2013; Morelli *et al*. 2017).
- More comprehensive strategies are required for certain subsets of patients to successfully treat their periodontitis and arrest its progression (McGuire 1991).

Consequently, the assessment of Grade serves three primary purposes:

- To stratify patients with respect to periodontitis trajectory in one of two groups: one group that includes patients with minimal likelihood of disease progression, and with expected predictable clinical responses to prevention and treatment based on standard principles of biofilm disruption and regular plaque control; or a second group that consists of patients with an increased likelihood of disease progression and less predictable clinical responses.
- To assist in developing new protocols for clinical and behavioral management of periodontitis cases that are less likely to respond favorably to current standard principles.
- To assist in determining additional approaches to the management of periodontitis that may also favorably influence systemic health.

Grade is thus defined as a three-level variable: a moderate rate of progression of periodontitis (Grade B) is assumed as the default Grade, unless the current clinical status and the overall oral and general health history either provide evidence of more rapid progression or presence of risk factors that increase the probability of more rapid progression (Grade C), or suggest a slower rate of progression than one might expect given the amount of current etiology and the patient's age (Grade A). Consequently, factors to be assessed to determine the patient's grade include *observed* or *inferred* rate of periodontitis progression and presence and control of risk factors. It is expected that accumulating data on the effects of periodontitis on the systemic inflammatory status, and reliable biomarkers of periodontitis presence and progression, will also be incorporated in the assessment of Grade in the future.

Currently, disease progression or stability is currently most accurately captured by serial assessments

of radiographic bone loss or CAL over time. However, since longitudinal data are typically not available, the progression rate for an individual can be inferred using the observed bone loss at the most affected segment of the dentition in relation to the patient's age, i.e. the ratio of the maximum percentage bone loss over age. The assessment of bone loss as a percentage of the root length is inherently a rough estimate based on the clinician's best interpretation of the radiographic images regarding the most apical location of the alveolar bone support, the location of the CEJ, and the location of the apex of the root. In a 50-year-old patient, bone loss extending to 60% of the root length at the most affected site would represent a percent bone loss/age ratio greater than 1.0 which would classify the patient as being Grade C based on rate of progression. The same severity of bone loss in a 90-year-old patient would result in a ratio of 0.66 and translate into Grade B. Given the limited precision of assessments used to calculate the ratio of greatest radiographic bone loss by age, the clinician should use clinical judgment if the ratio is very close to 1.0.

In addition to the direct or indirect assessments of periodontitis progression, the assessment of Grade factors in the patient's risk profile, as well as aspects related to the potential impact of periodontitis on systemic health.

Impact of risk factors

Periodontitis is a chronic disease of multifactorial etiology; individual exposures influence susceptibility to the disease and responsiveness to therapy in either an additive or a synergistic fashion. The Grade table explicitly includes the two most established risk factors for periodontitis, namely smoking (Bergström 1989; Haber *et al*. 1993; Johnson & Guthmiller 2007) and diabetes mellitus (Hugoson *et al*. 1989; Taylor *et al*. 1998; Lalla & Papapanou 2011) and stipulates threshold levels of current smoking or of metabolic control in diabetes, in an attempt to 'quantify' the risk conferred by these exposures. However, the clinician is encouraged to carefully consider additional risk factors that may influence the progression of periodontitis and its response to treatment in the assessment of Grade. These include obesity, other chronic inflammatory diseases such as rheumatoid arthritis, chronic depression, and other factors that emerge from a comprehensive medical history (Monteiro da Silva *et al*. 1996; Genco *et al*. 1999; Mercado *et al*. 2000; Suvan *et al*. 2014; Morelli *et al*. 2017). The goal for the clinician is to identify patients who are likely to require more intensive monitoring, intervention, and physician collaboration to help control systemic factors that may complicate host modulation of the chronic inflammatory component of severe periodontitis.

Patients classified with incipient (Stage I) or moderate (Stage II) periodontitis will most likely not display evidence of sufficient periodontitis progression to qualify for Grade C, unless they are very young and have a bone loss/age ratio of >1. However, some Stage I or II patients may be heavy smokers or have poorly controlled Type II diabetes and may therefore qualify for a Grade C diagnosis through their risk profile. The exposures that account for a Grade C should certainly be targets for behavioral modification (i.e. smoking cessation) or additional therapeutic intervention in collaboration with the patients' physician (i.e. better metabolic control in diabetes), as they entail greater risk for less predictable clinical outcomes using standard principles of disease management.

In Stage III and IV patients, assessment of Grade may often be defined indirectly by the apparent rapid bone loss relative to the patient's age; however, Grade modifiers, beyond being informative of the risk of further progression and the likelihood of a successful treatment outcome are obvious interventional targets.

Systemic health considerations

Evidence indicates that the presence of certain chronic inflammatory diseases influence the likelihood of a second chronic disease to be concomitantly manifested (Dregan *et al*. 2014, 2019; Dregan 2018). Although there is substantial evidence associating periodontitis with other diseases such as cardiovascular disease, Type 2 diabetes, and adverse pregnancy outcomes, evidence that treatment of periodontitis will result in predictable benefits with respect to any of those systemic conditions is rather limited (Beck *et al*. 2019). The systemic inflammatory burden of periodontitis is well-documented, at least as measured by high sensitivity C-reactive protein (hsCRP) (Amabile *et al*. 2008; Demmer *et al*. 2013; Artese *et al*. 2015). Given the well-established role of elevated hsCRP in cardiovascular diseases and other chronic conditions, the impact of effective treatment of periodontitis on hsCRP levels may be an important parameter to monitor in certain patients with Stage III or IV periodontitis.

The role of biomarkers

Current evidence indicates that certain combinations of salivary biomarkers may add value in the assessment of periodontal therapy relative to the stability of the case post-treatment (Kinney *et al*. 2011; Salminen *et al*. 2014). It is expected that additional evidence of their clinical utility and further advances in the field of novel biomarkers will better inform and refine an objective assessment of Grade. Likewise, the currently defined boundaries for smoking and metabolic control may be revised in the future, and stratification based on the severity of additional chronic conditions or novel risk factors that are presently not included in the Grade table may be appended, as new research data accumulate.

A common question is whether Grade can change over time. An upwards revision of Grade is possible if the percentage bone loss/age ratio increases substantially, or the risk profile of the patient deteriorates. Conversely, downgrading is also possible, if the determinants of Grade when it was originally assigned are no longer prevalent. However, the clinician is urged to carry out such modifications judiciously and after thorough consideration of the totality of the risk factors at play as well as of the consequences of the altered Grade on the patient's overall management plan.

Implementation of the current classification: clinical examples

For assisting in the implementation of this new classification of periodontitis in clinical practice, advisory algorithms have been published to guide the clinician into the decision-making process of defining a periodontitis case and then further assisting in the definition of the Stage and Grade (Tonetti & Sanz 2019). It is important, however, to emphasize the need for a *holistic* interpretation of the variables involved in the correct diagnosis, rather than uncritical adherence to particular threshold values quoted. As stated above, CAL is the primary diagnostic tool for detecting a patient with periodontitis. Therefore, clinicians should recognize the signs of CAL and differentially diagnose other clinical conditions also associated with CAL that are not attributed to periodontitis. Detecting alveolar bone loss from diagnostic quality radiographs may also be used as a proxy measure of CAL.

The first step in the diagnostic process is to determine if a patient is periodontally healthy, has gingivitis, or has periodontitis. If full-mouth radiographs of good diagnostic quality are available, the clinician should carefully examine them to detect bone loss. If no bone loss is detectable, the clinician should probe around all teeth in the dentition to detect signs of inter-dental CAL. If no CAL is detected, then full-mouth bleeding on probing (BoP) scores will differentiate between a diagnosis of periodontal health (BoP <10%) or gingivitis (BoP ≥10%). If either CAL or bone loss attributed to periodontitis has been detected, the clinician should proceed with a comprehensive examination to determine periodontitis Stage, Grade, and Extent.

The following clinical examples summarize the decision-making process in cases with variable Stage/Grade/Extent combinations.

Case 1 (Fig. 16-2)

The patient is a 24-year-old Caucasian male who has received sporadic dental care during the last decade. The patient has seen his physician recently for a physical examination and routine blood-work, both of which were unremarkable. The patient has never smoked. Clinical examination reveals a full-mouth BoP score of 55%, and a range of probing depths between 1 and 5 mm. Although no interproximal bone loss is readily visible on the available radiographs, interproximal CAL ranging between 1 and 2 mm is noted in more than 30% of the teeth present. No tooth mobility or furcation involvements are present. Given the incipient severity of interproximal attachment loss and the absence of risk factors that may act as Grade modifiers, the patient was diagnosed with periodontitis Stage I, Grade A, generalized.

Case 2 (Fig. 16-3)

The patient is a 29-year-old Hispanic female who reports sporadic dental care; the most recent dental visit was 4 years previously. The patient is under medication for Type I diabetes mellitus diagnosed 8 years ago, and her most recent hemoglobin A1c assessment obtained 2 months ago was 7.8%. The patient is a former smoker with an 8 pack-year history who quit smoking 6 years ago. Available radiographs reveal presence of several teeth with clearly discernible bone loss which extends within the coronal third of the root length. Full-mouth BoP is 89%, probing depths range between 1 and 6 mm, and interproximal attachment loss between 3 and 4 mm is noted at 10 teeth. Degree I furcation involvements are present buccally at both maxillary right molars and at the first maxillary left molar, as well as lingually at the first mandibular left molar. The maxillary lateral incisor shows Degree 1 mobility. Given the maximum severity of bone loss within the coronal third of the root, the presence of interproximal attachment loss between 3 and 4 mm at more than one third of the teeth present, and the poor metabolic control of the patient's diabetes, the assigned diagnosis was periodontitis Stage II, Grade C, generalized.

Case 3 (Fig. 16-4)

The patient is a 19-year-old African-American male freshman college student, who reports attending annual visits to his general dentist for the past few years. The dentist referred him to a periodontist after the last visit after having detected "bone loss at the lower back teeth". The patient has never smoked, and has been recently seen by a student health services physician who carried out a physical examination and obtained a routine blood test; both were unremarkable. The patient reports that his mother has lost several teeth due to "gum disease". Available full-mouth periapical radiographs show intact interproximal bone levels at all areas apart from the mesial surfaces of the first mandibular molars bilaterally, where angular bony defects are visible extending beyond the coronal third of the root. The first right and the first left mandibular molars present with mesial probing depths of 9 and 10 mm, respectively, and corresponding CAL of 7 and 8 mm. No probing

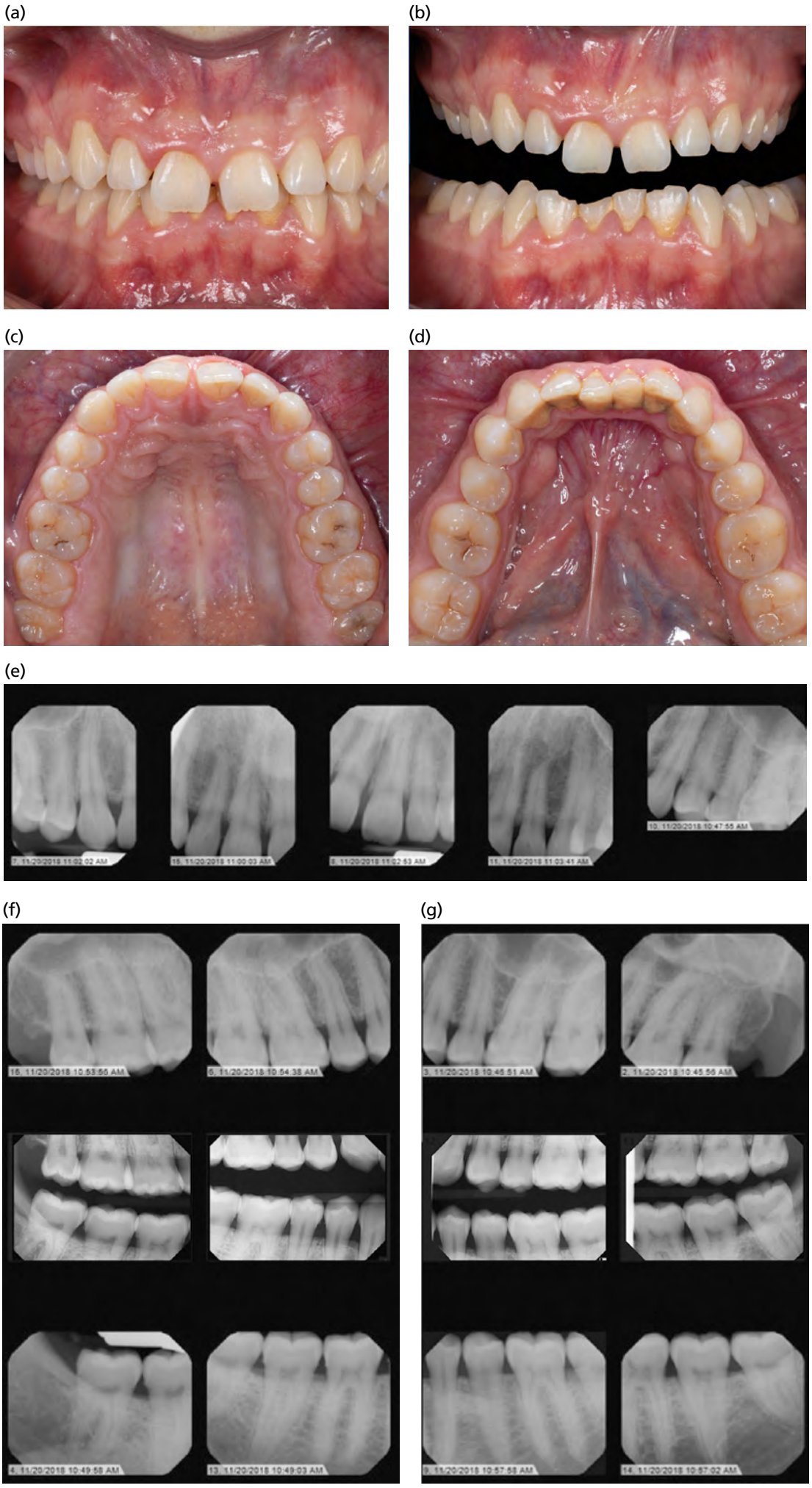


Fig. 16-2 Case 1. (a–d) Clinical and (e–g) radiographic images of a case diagnosed as Stage I, Grade A, generalized. (Source: Courtesy of Dr. Gustavo Avila-Ortiz, University of Iowa, USA.)

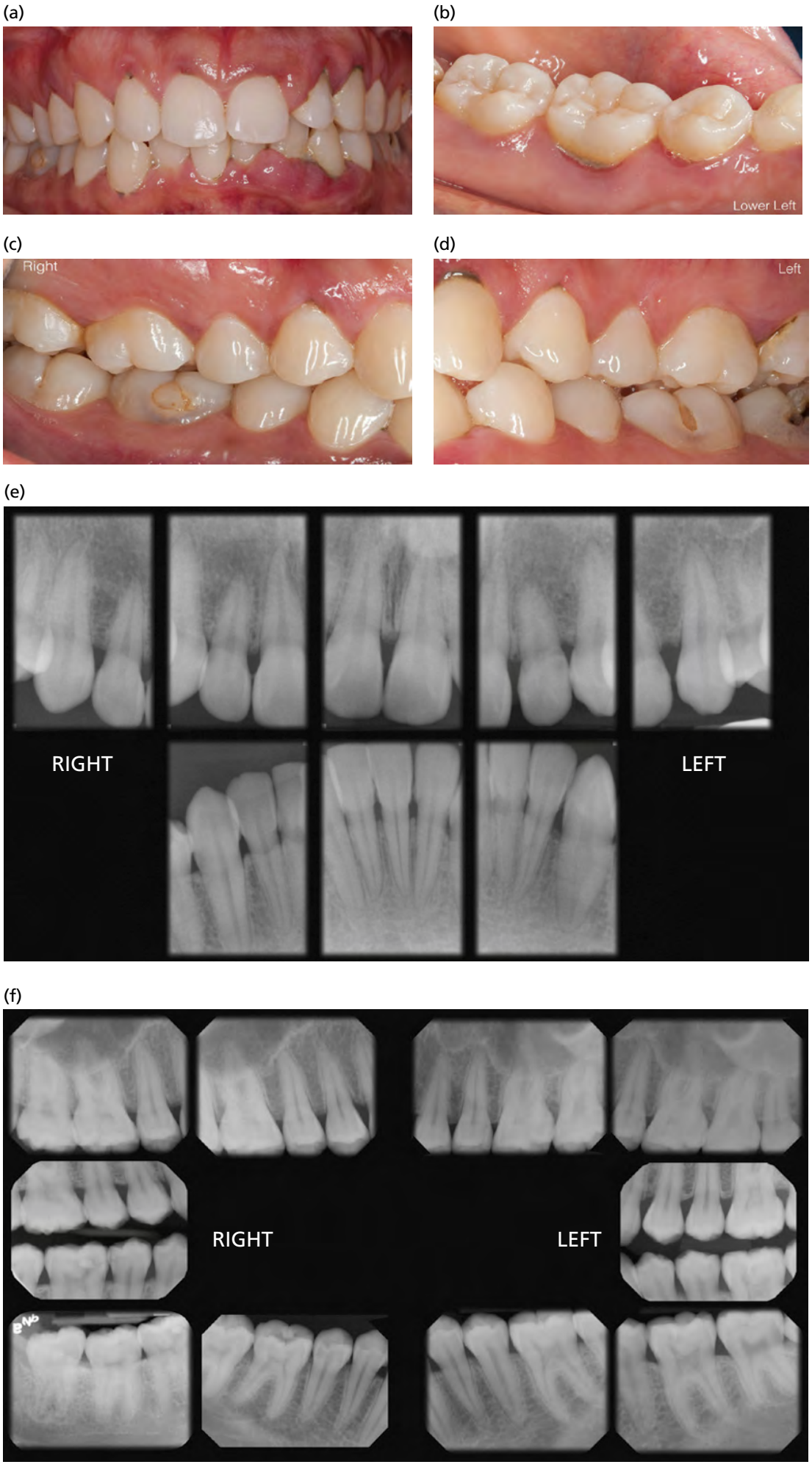


Fig. 16-3 Case 2. (a–d) Clinical and (e, f) radiographic images of a case diagnosed as Stage II, Grade C, generalized. (Source: Courtesy of Dr. Gustavo Avila-Ortiz, University of Iowa, USA.)

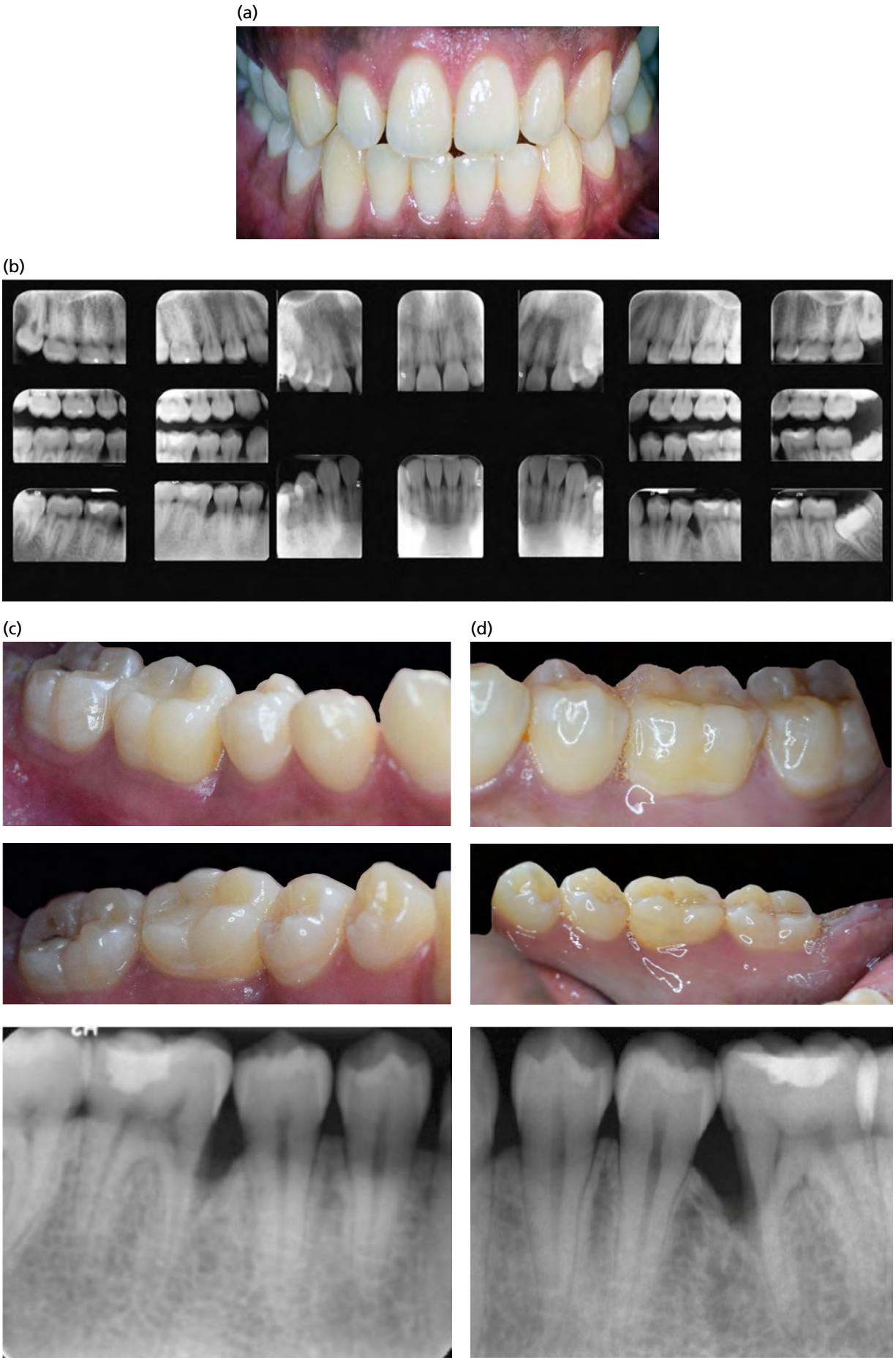


Fig. 16-4 Case 3. (a–d) Clinical and radiographic images of a case diagnosed as Stage III, Grade C, localized. (Source: Courtesy of Drs. Flora Momen-Heravi and Philip Kang, Columbia University, USA.)

depths exceeding 3 mm or any interproximal CAL >1 mm are present at any other teeth. Given the maximum severity of bone loss beyond the coronal third of the root, accompanied by presence of interproximal attachment loss of 7–8 mm, affecting only two teeth in the dentition, and the young age of the patient resulting in a percentage bone loss over age ratio exceeding 1, the assigned diagnosis was periodontitis Stage III, Grade C, localized (molar pattern).

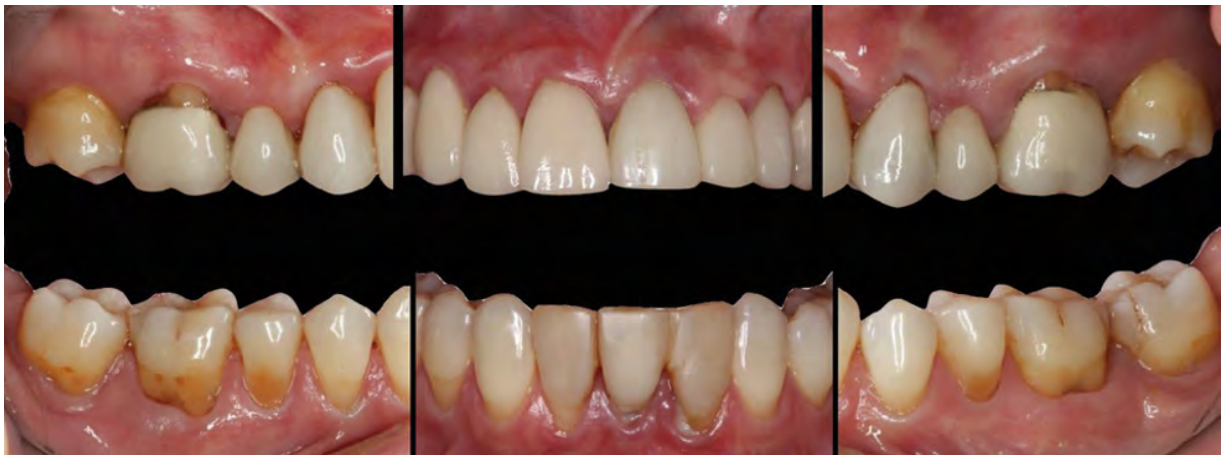
Case 4 (Fig. 16-5)

The patient is a 60-year-old Caucasian female in good general health, and currently medicates for hypercholesterolemia. The patient does not smoke and has been alternating seeing her general dentist and a dental hygienist every 6 months for several years. She is aware that she has "issues with her gums". Available full-mouth periapical radiographs reveal generalized bone loss that extends up to the apical third of the root at the right central mandibular incisor. Clinical charting shows deep pockets between 6 and 8 mm at multiple teeth. There are several teeth with Degree 2 mobility, and the first right mandibular molar shows a lingual furcation involvement. Importantly, radiographs obtained 3 years prior to the current examination are available and indicate progression of bone loss exceeding 2 mm at a number of teeth, notably at the distal surface of the upper left central incisor and the distal surface of the upper first molar. Given the severity of attachment loss and bone loss, and the documented progression of periodontitis, the patient was assigned a diagnosis of periodontitis, Stage III, Grade C, generalized.

Case 5 (Fig. 16-6)

The patient is a 58-year-old Caucasian male who has smoked one pack of cigarettes per day for "as long as he can remember" and is medicated for hypertension and chronic obstructive pulmonary disease. He reports that he has been visiting his dentist sporadically over the years, primarily to have some "shaky teeth removed". He would now like "to get some more teeth to chew better and fill the gaps". The patient has poor plaque control and multiple teeth with probing depths between 6 and 9 mm and Degree 2 mobility. Available radiographs confirm presence of generalized bone loss extending to the apical third of the root. The patient has lost more

(a)



(b)

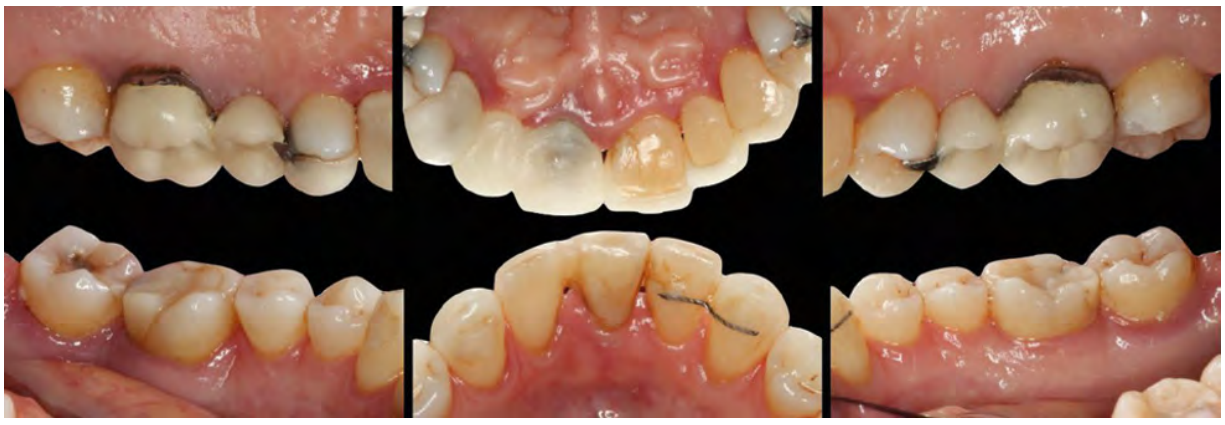
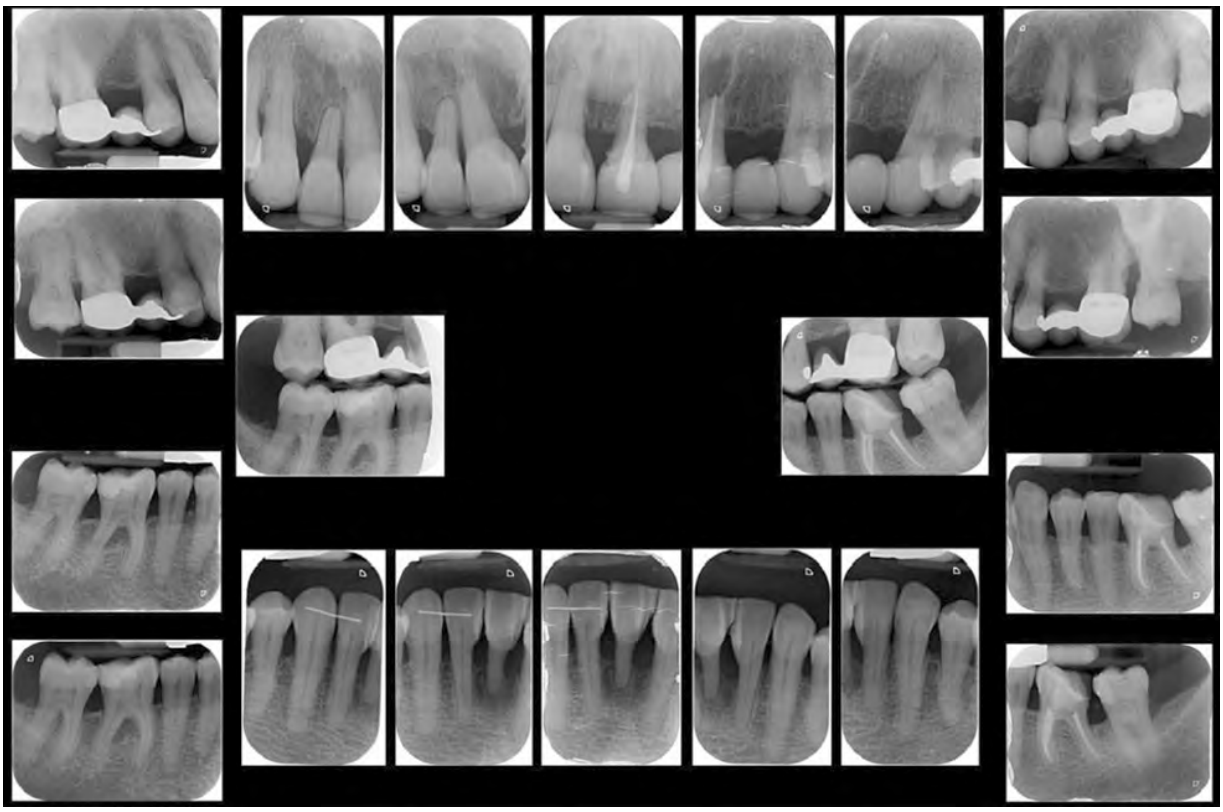


Fig. 16-5 Case 4. (a, b) Clinical

(c)



(d)

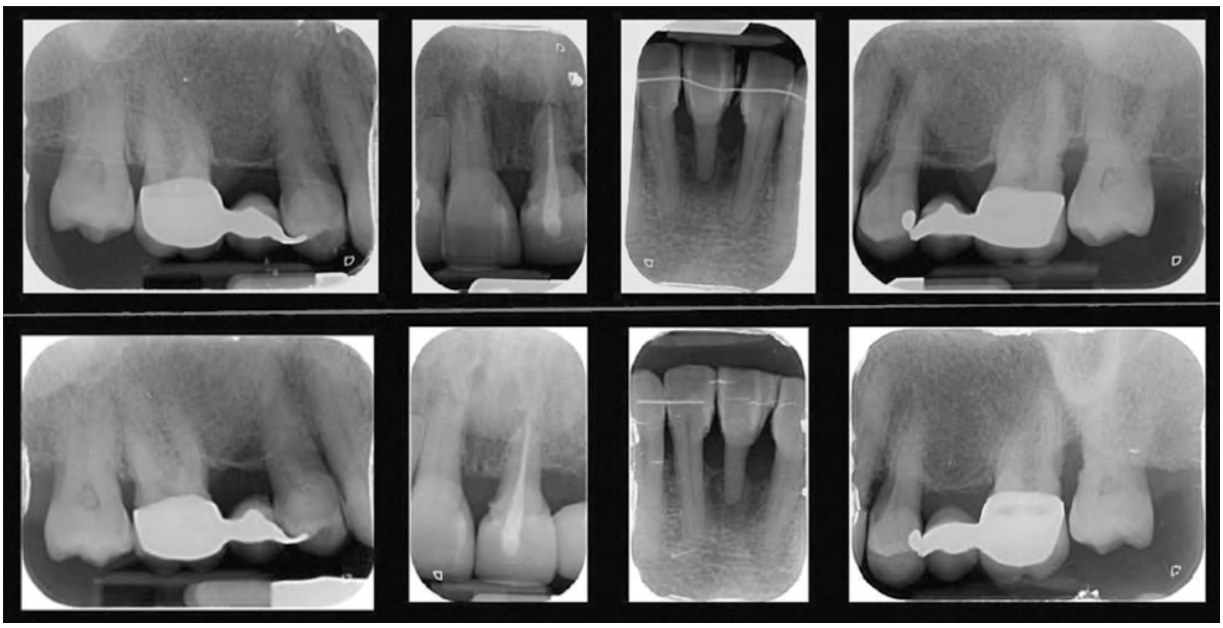


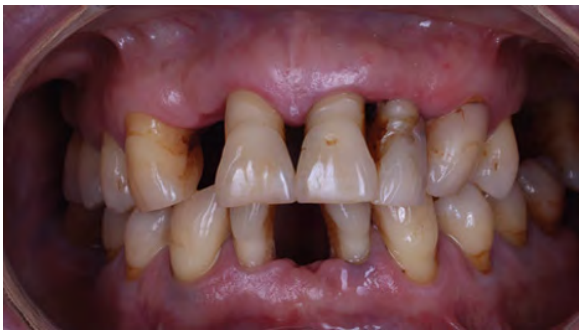
Fig. 16-5 *(Continued).* (c, d) radiographic images of a case diagnosed as Stage III, Grade C, generalized. Note the lower set of radiographs (d) that includes images obtained 3 years apart and indicate significant progression of bone loss. (Source: Courtesy of the Postgraduate Periodontics Clinic, University Complutense of Madrid, Spain.)

than four teeth, most likely due to periodontitis according to his own recollection and consistent with the current status of his remaining dentition. In addition, he requires extensive oral rehabilitation to restore esthetics and function, and also presents with a persisting risk factor for further progression (heavy smoking). Thus, the assigned diagnosis was periodontitis, Stage IV, Grade C (note that assignment of extent is not meaningful in Stage IV periodontitis).

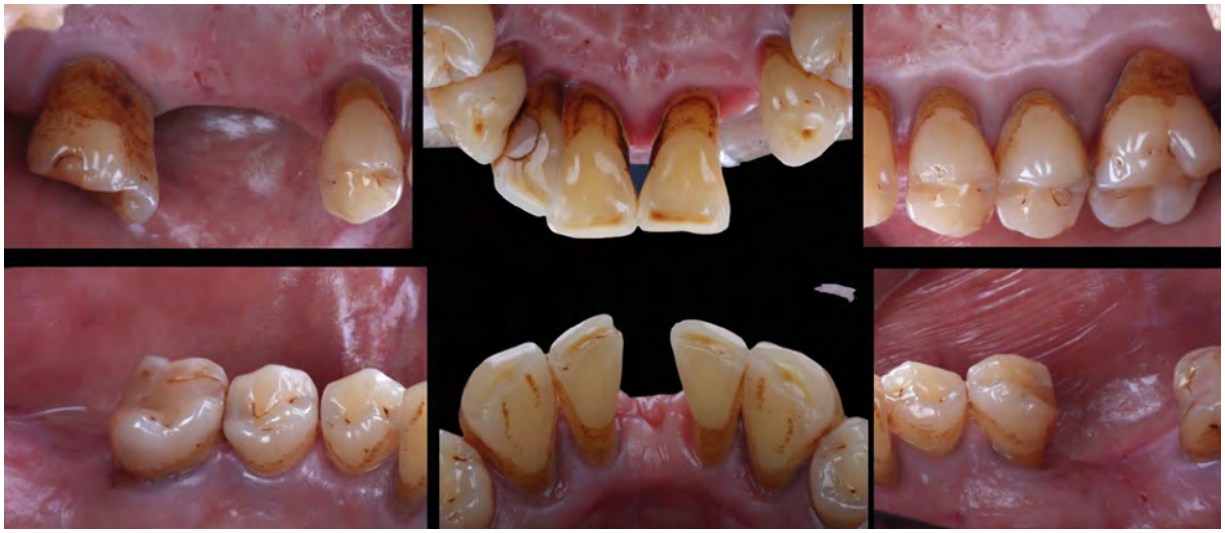
Case 6 (Fig. 16-7)

The patient is a 48-year-old Caucasian male, with non-contributory medical history. He has smoked one pack of cigarettes per day for the past 21 years. The

(a)



(b)



(c)

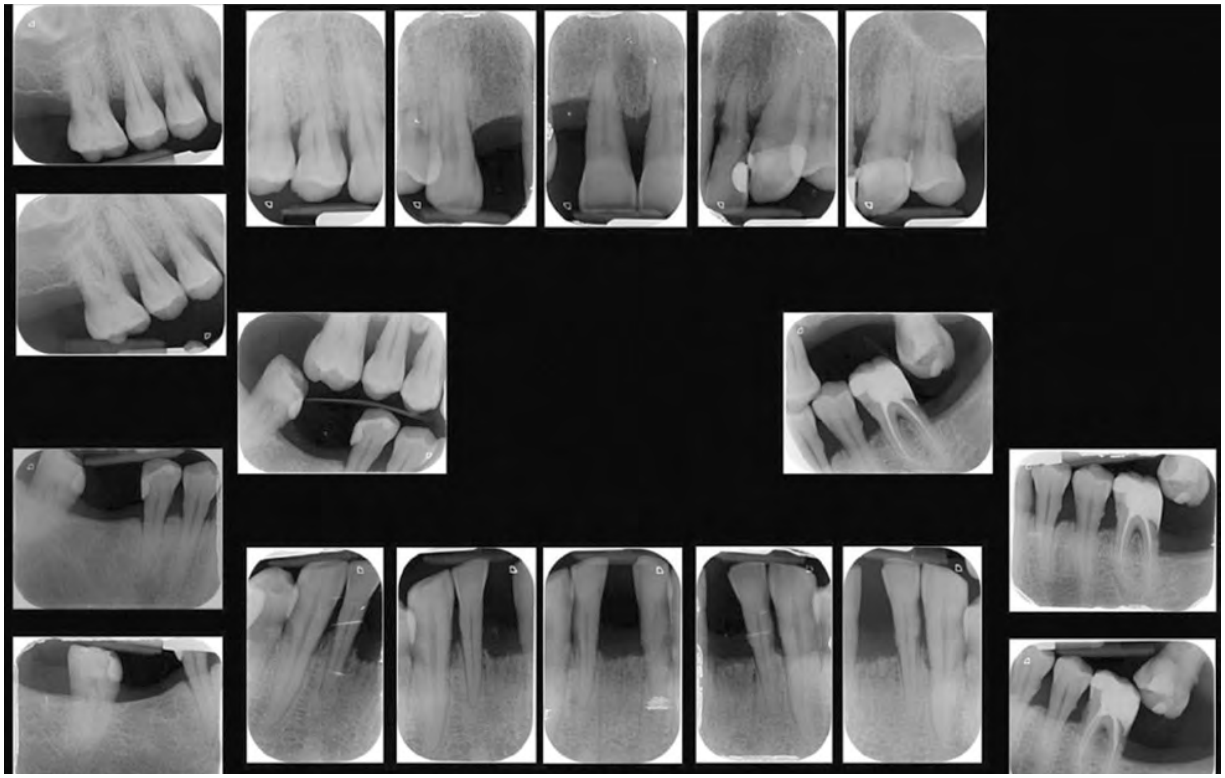


Fig. 16-6 Case 5. (a, b) Clinical and (c) radiographic images of a case diagnosed as Stage IV, Grade C. (Source: Courtesy of the Postgraduate Periodontics Clinic, University Complutense of Madrid, Spain.)

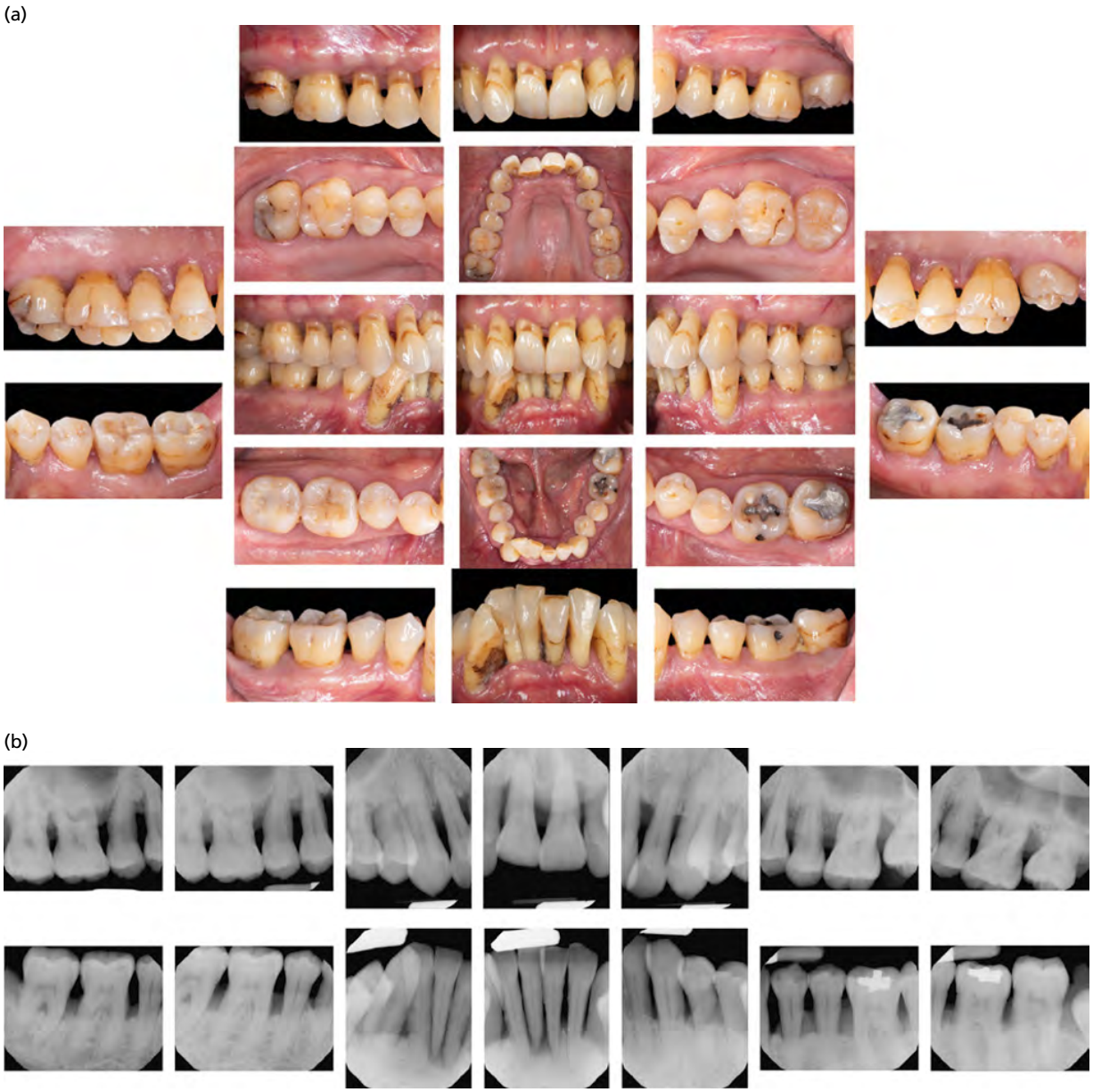


Fig. 16-7 Case 6. (a) Clinical and (b) radiographic images of a case diagnosed as Stage IV, grade C. (Source: Courtesy of Dr. Gustavo Avila-Ortiz, University of Iowa, USA.)

patient has not seen a dentist for the past 7 years and has only received dental care sporadically prior to his last dental visit. He has noticed that his teeth have become increasingly mobile lately and he reports that he is currently uncomfortable when he chews. Deep pockets with BoP are detected at virtually all teeth and periapical radiographs show terminal bone loss at multiple areas. Although this patient has not yet experienced any tooth loss due to periodontitis, more that five teeth can reasonably be considered to be non-salvageable due to severe loss of support. In this patient, periodontitis is clearly not merely a threat for individual teeth, but rather for the dentition as a whole. Thus, the combination of current periodontitis extent and severity, the presence of heavy smoking, and the need for complex therapy to control periodontitis and rehabilitate function resulted in a diagnosis of periodontitis Stage IV, Grade C.

Interpretational challenges and "gray zones"

In a time of evidence-based healthcare and comparative effectiveness research, some clinicians would desire that a simple algorithm be developed to automatically convert a patient's clinical findings to an accurate determination of Stage and Grade. However, what becomes increasingly apparent across the health sciences is that, despite the exponential increase in new information and the ever-increasing opportunities to formulate evidence-guided clinical decisions, new technologies and more research evidence often expand "gray zones" and do not necessarily contribute to simple decision guidelines (Chandra *et al.* 2015). We must realize that both knowledge and clinical judgment will be required for classification in all instances. Below, we provide narrative examples of

commonly encountered diagnostic "gray zones" and offer suggestions of how they can be addressed.

1. *A male 65-year-old patient has experienced no tooth loss, is radiographically intact, and has no interproximal pockets with a depth greater than 3 m. The level of the gingival margin (GM) interproximally is, at most sites, coronal to the CEJ, with the exception of a few surfaces located at non-adjacent teeth where the GM is located at the CEJ. A loss of attachment of 2 mm is recorded at these few surfaces. Does this patient have periodontitis?*

This is a borderline case. According to the above description, the probe tip apparently penetrates *within* the junctional epithelium to a level *apical* to the CEJ at a few interproximal sites with shallow probing depth, no visible recession, and no radiographic evidence of alveolar bone loss. Since this middle-aged patient appears to be periodontally intact, a diagnosis of "periodontitis" is not justified. It must be emphasized, however, that the same phenotype in a much younger patient, may signify "true" incipient periodontitis. Again, clinical judgment is paramount for arriving at a correct diagnosis after assessing the totality of the patient data.

2. *The severity of periodontitis in a 50-year-old patient, based on radiographic bone loss at the sites of the most advanced destruction, is compatible with Stage II disease (e.g. the bone loss extends within the coronal third of the root). Does presence of one or a few 6 mm pockets necessarily upshift the diagnosis to Stage III?*

Not necessarily. If the severity of bone loss does not extend beyond the coronal third of the root length, presence of a couple of 6 mm pockets does not automatically entail a need for more complex treatment. Upstaging because of "complexity factors" requires a meaningful, integrated appraisal of these factors by an experienced clinician. Correct implementation of the Staging system does not lend itself to automated algorithms based on checkboxes or presence/absence of isolated features.

3. *According to the new classification, a diagnosis of periodontitis requires a minimum of "at least two teeth" affected by interproximal attachment loss. Does this mean that a patient that presents with attachment loss, or bone loss, that affects only a single tooth should not be diagnosed as having periodontitis?*

The requirement of "at least two affected teeth" has been incorporated in the classification to minimize false positives, that is, to preclude an inflation of periodontitis prevalence due to incidental attachment loss. This restriction was also introduced in recognition of the fact that "true" periodontitis seldom affects only a single tooth in the dentition. However, if according to the clinician's judgment an observed attachment loss/bone loss lesion that affects a single tooth in an otherwise intact dentition cannot be ascribed to a cause other than periodontitis (e.g. root fracture, endodontic lesion, etc.), then the clinician should bypass the rule, proceed with assigning a diagnosis of periodontitis, stage it appropriately, and further describe it as "localized".

The value of the 2018 periodontitis classification

Well-controlled longitudinal clinical studies of periodontitis treatment have demonstrated that the standard principles for control of periodontitis are remarkably successful in the long-term control of the disease, but not for everyone. Over the years, classification schemes have drawn attention to different clinical phenotypes that may be expressed in some patients with periodontitis. The 2018 periodontitis classification uses the Stage and Grading vectors (Papapanou *et al*. 2018b; Tonetti *et al*. 2018a), as discussed previously, to allow clinicians to consistently (1) assess the current level of severity of periodontitis and its impact on the treatment required, and (2) determine whether a periodontitis patient is highly likely or less likely to respond predictably to standard principles for treating periodontitis. Importantly, the new classification guides a clinician to recognize factors that indicate that the patient's disease trajectory is more complex and should be managed accordingly. Lastly, the classification is constructed in a way that allows, by design, periodic, evidence-based modifications to incorporate new research data. In other words, new findings will be reviewed regularly and will further inform and refine the threshold values and definitions included in the grids of the Stage and Grade vectors, without radically altering the fundamental principles of the classification scheme. This essential feature of the 2018 classification will hopefully facilitate its seamless utilization by clinicians and researchers for a longer period than its immediate predecessors.

Acknowledgment

Parts of the chapter contain adapted text originally published by Kornman and Papapanou (2020).

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Chapter 17

Effect of Periodontal Diseases on General Health: Periodontal Medicine

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Introduction

The concept that oral and general health are interrelated was already known in ancient civilizations. As "strong teeth" often were a sign of good health, poor oral health was considered an important contributor to distant body complications (O'Reilly & Claffey 2000). It was at the end of the nineteenth century and in the early years of the twentieth century that the dental and medical communities took interest in the concept of "oral sepsis" and "focal infection" (Fig. 17-1). In the article titled "The human mouth as a focus of infection" and published by the American dentist W.D. Miller in 1891, the collective term "oral sepsis" was described for the first time as a possible cause of "chronic dyspepsias, intestinal disorders, ill health, anemias and nervous complaints" (Miller 1891). An influential London physician William Hunter (Hunter 1900, 1910) corroborated this hypothesis when he published in the most eminent medical journals at the time. This was just before the oral–systemic concept evolved into that of "focal infection" (Billings 1912). A localized area of infection of the oropharyngeal space (not only affecting teeth or gingival tissues) was described by Billings as a source of the dissemination of pathogens and thus resulted in infection of contiguous or non-contiguous organs. These beliefs were accompanied by clinical recommendations of removal of these infectious sites

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

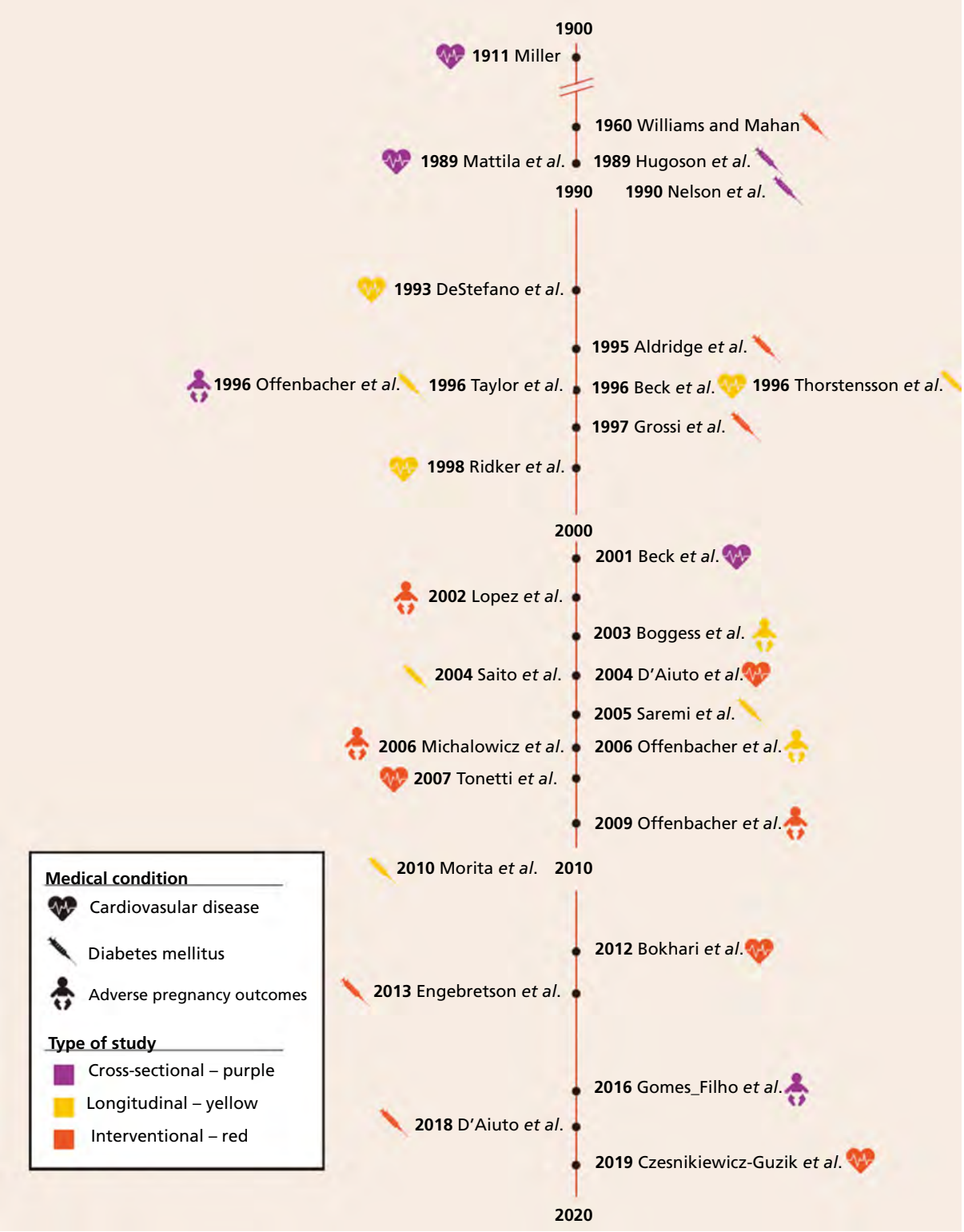

Fig. 17-1 An overview of "landmark studies" in periodontal medicine published during the last 120 years, with particular focus on the effects of periodontitis on three pathologic conditions: cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes throughout the chapter. The highlighted studies were either the 'first' of their kind, as they provided novel observations or contributed to shifting paradigms. The figure was modified from a figure presented by Beck *et al.* (2019) and presents the studies using symbols to specify the medical outcome (cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes) while the color of the symbol represents the type of study (cross-sectional, longitudinal, and interventional).

and translated into drastic treatment decisions. The removal of infectious foci of infection was advocated as an essential step in the resolution or even to prevent multiple diseases. As is usually the case, empirical evidence gradually revealed that these radical practices were unsound (Cecil & Angevine, 1938), the purported associations were increasingly refuted, and more conservative approaches to the treatment of oral pathologic conditions eventually prevailed.

At the end of the twentieth century, the accumulation of newer evidence on the potential role of inflammation in the development of many chronic diseases

that were traditionally viewed as non-inflammatory encouraged periodontal researchers to explore the concept that chronic exposure to oral infection/inflammation could impact on other non-communicable diseases. These conditions are responsible for over 70% of overall deaths worldwide, with cardiovascular diseases, cancer, and diabetes being the most prominent (WHO 2013). Most non-communicable diseases share a cluster of common risk factors (tobacco usage, alcohol intake, diet, stress, physical inactivity, social inequalities) which inevitably are linked to poorer oral health and especially to periodontitis. When interpreting the association between periodontitis and other comorbidities, this is an important factor to consider as it would strongly impact on the nature and strength of the association.

A series of experimental studies collectively known as research in "periodontal medicine" describe how periodontal infection/inflammation may impact extraoral health. The number of non-communicable diseases and conditions that have been linked to periodontitis has increased exponentially in the last two decades. A recent umbrella review identified 1219 systematic reviews of clinical trials linking poor oral health to several systemic diseases (Seitz *et al*. 2019) confirming that the two most common oral diseases (periodontitis and dental caries) were associated mainly with type 2 diabetes mellitus and cardiovascular diseases among more than 50 systemic conditions.

This chapter will first briefly focus on the common biological mechanisms and then review the observational and interventional epidemiologic evidence related to the association between periodontitis and (1) atherosclerotic vascular disease; (2) diabetes mellitus; and (3) adverse pregnancy outcomes, with smaller reviews for the newer areas of (4) chronic renal disease; (5) cognitive decline/dementia; and (6) cancer.

The epidemiologic evidence will be reviewed under two different types of studies: (1) *association studies* (cross-sectional, case–control, or longitudinal cohort studies) focusing on either *surrogate markers* of the main disease (i.e. biomarkers of disease) or *clinical outcomes* (i.e. clinical events such as myocardial infarction [MI] or stroke) and (2) *intervention studies, examining the effects of periodontal therapy on disease-related outcomes (surrogate markers or events)*. Data from intervention studies are of public health importance, as they reveal whether targeting a specific exposure (i.e. periodontitis) by means of prevention or therapy translates into substantial benefits in terms of incidence reduction of the disease/systemic outcome or of its complications (this is usually assessed using randomized, placebo-controlled clinical trials).

When interpreting data from epidemiologic studies, it must be realized that in each study the *exposure*, in this case periodontitis as a potential risk factor for the systemic outcome, could have been defined using a variety of clinical measures reflecting a poor periodontal status (either as categorical or continuous parameters). Some studies have used traditional clinical or radiographic parameters, such as average probing pocket depth, number of periodontal pockets greater than a specific threshold of probing pocket depth or attachment level, and presence of gingival inflammation (bleeding), whereas in other epidemiologic studies authors might have used self-reported periodontal health or even surrogate markers, such as tooth loss or edentulism. The latter two, although related to poor periodontal status, are however clearly not synonymous with periodontitis as they could have been the result of other oral diseases (i.e. dental caries, fracture). To further complicate the matter, several epidemiologic studies might have used systemic biomarkers of exposure to periodontitis or the dental biofilm including subgingival microbial profiles or systemic levels of serum antibodies to periodontal bacteria. These markers could reflect the infectious nature of or the immune response to periodontitis rather than its clinical phenotype, as the exposure variable. It is only recently that a universally acceptable case definition of periodontitis has been published and implemented across the dental community (Tonetti *et al*. 2018). Not many studies, however, have been published and/or incorporated these new case definitions in their experimental design.

The last point that needs to be emphasized as a key determinant of the quality of an epidemiologic study is whether the association between the exposure under investigation (i.e. periodontitis) and the outcome (i.e. cardiovascular diseases) has been adjusted for *additional exposures* that are known to affect the systemic disease status (e.g. hyperlipidemia, hypertension, or physical activity in cardiovascular diseases), as well as for potential *confounders*, in other words, common risk factors that are associated with both periodontitis and the systemic disease (e.g. diabetes mellitus or smoking). This last methodological point is that the choice of *exposure variable* to define periodontitis as a risk factor for other non-communicable diseases varied enormously across the published evidence reviewed and could explain at times the inconclusive findings of some studies.

Evidence of common biologic mechanisms

Periodontal diseases, as elegantly discussed in Chapter 16, are chronic inflammatory diseases of the periodontal tissues associated with a dysbiotic supra- and subgingival biofilm enriched with Gram-negative bacteria (Haffajee & Socransky 1994). A progressive gingival inflammation results in the deepening of the periodontal sulcus and in a shift of the composition of the dental biofilm, resulting in levels reaching 10^9 or 10^{10} bacterial cells within a single pathologic periodontal pocket. The ulcerated epithelial lining of the periodontal pocket may constitute a substantial inflamed surface area in cases of generalized periodontitis (Hujoel *et al*. 2001) and is in constant contact with the biofilm of the subgingival

dental plaque. The ulcerated pocket epithelium hence provides a gate through which bacterial toxins/components such as lipopolysaccharide, bacterial outer membrane vesicles, fimbriae, and other antigenic structures may challenge the immune system and elicit not only a local but a substantial systemic inflammatory response (Ebersole & Taubman 1994). This section will briefly review the two main mechanisms linking periodontitis and systemic health outcomes under the heading of (1) oral microbiome and (2) systemic inflammation (Fig. 17-2).

Oral microbiome

Oral bacteria and especially those present in the subgingival dental biofilm can co-locate in other distant sites either via bacteremia or due to the aspiration and/or ingestion.

Several pathogenic species involved in periodontal infections display tissue invasion properties (Meyer *et al*. 1991; Sandros *et al*. 1994; Lamont *et al*. 1995). Further, frequent transient bacteremias occurring as a result of daily activities such as toothbrushing or chewing (Silver *et al*. 1977; Kinane *et al*. 2005; Forner *et al*. 2006; Crasta *et al*. 2009), as well as during invasive oral therapeutic procedures (Heimdahl *et al*. 1990; Lockhart *et al*. 2008) may confer a significant systemic bacterial challenge. Similarly, proinflammatory mediators, including several interleukins, are produced locally in the inflamed gingival tissues (Salvi *et al*. 1998) and can also be disseminated systemically through the bloodstream. A plethora of preclinical and at times clinical experimental studies have examined direct and indirect effects of key pathogenic microbes implicated in the development and progression of periodontitis. This chapter will briefly discuss their role within the context of the relevant non-communicable disease linked to periodontitis.

Systemic inflammation

Periodontitis is known to induce chronic low-grade systemic inflammation which might be relevant to the onset or progression of numerous non-communicable diseases.

Periodontitis patients exhibit higher white blood cell counts, high sensitivity C-reactive protein (hsCRP), and fibrinogen levels (Kweider *et al*. 1993; Ebersole *et al*. 1997; Loos *et al*. 2000) than periodontally healthy controls. These biomarkers are commonly used to characterize systemic inflammation (body response to any pathogenic stimulus). A series of analyses of large studies reporting on the periodontal status (case definition of severe periodontitis) or using alternative measures of periodontal exposure (i.e. high serum IgG levels to *P. gingivalis*) have confirmed that poor periodontal status is associated with increased CRP and fibrinogen levels (Slade *et al*. 2003; Slade *et al*. 2000; Schwahn *et al*. 2004; Dye *et al*. 2005). These associations were independent of age, gender, diabetes mellitus, cigarette use, medical conditions, and use of anti-inflammatory medications.

A recent meta-analysis of observational studies reporting levels of hsCRP (Paraskevas *et al*. 2008) confirmed that patients suffering from periodontitis had consistently higher levels of hsCRP when compared

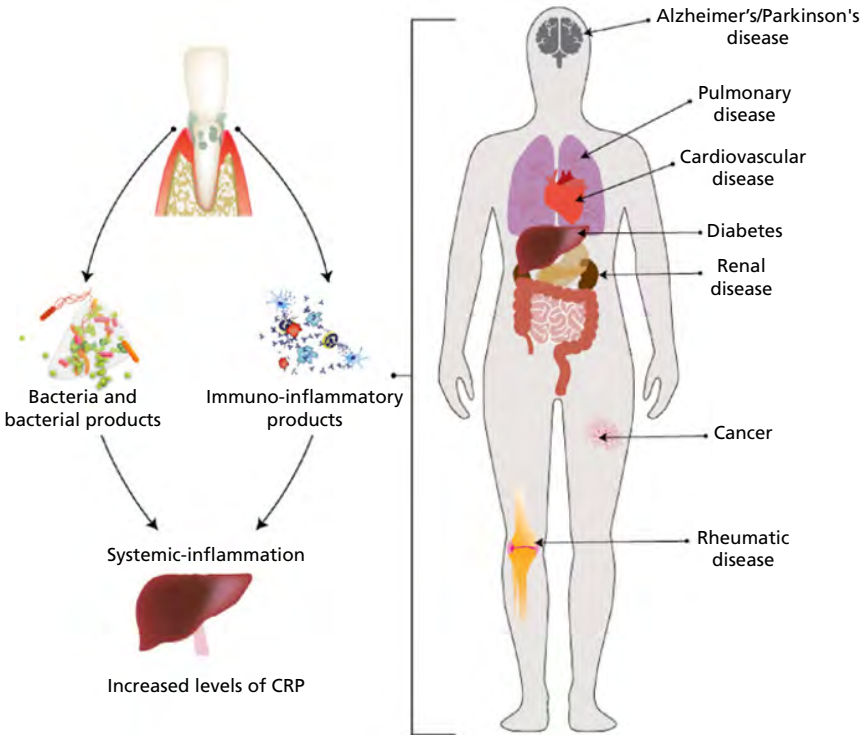

Fig. 17-2 Oro-systemic inflammatory link. Several systemic diseases associated with periodontitis are depicted and the possible common pathways responsible for these associations with emphasis on the role of systemic inflammation.

with controls without periodontitis (average between group difference of 1.56 mg/L). Further evidence on the causal association between periodontitis and systemic inflammation is reported in the same review, as modest evidence confirmed that periodontal treatment resulted in a statistically significant average reduction of 0.50 mg/L in hsCRP levels within 6 months of the therapy (95% CI 0.08–0.93). A heterogeneous response to periodontal treatment in terms of changes in the level of systemic inflammatory biomarkers is now universally acknowledged. Indeed Behle *et al*. (2009) using a composite score ("summary inflammatory score") to represent the aggregate post-treatment response to a panel of 19 individual biomarkers confirmed that approximately one-third of the treated patients with periodontitis showed a marked reduction in inflammation, an almost similar number of participants exhibited an increase in systemic inflammation, whereas the remainder remained seemingly unchanged. The obvious variability in the extent of resolution of systemic inflammation after periodontal treatment should be interpreted within the context that not all individuals will mount the same magnitude of systemic inflammatory response to periodontitis and that it has been widely accepted that periodontal treatment modalities *per se* (i.e. whole mouth instrumentation as opposed to quadrant by quadrant therapy) are responsible for short-term acute inflammatory responses (D'Aiuto *et al*. 2005). This concept was collectively reviewed and interpreted by the periodontal researcher community in a consensus manuscript (Sanz *et al*. 2020).

Atherosclerotic vascular disease

Biologic mechanisms

Atherosclerotic vascular disease (AVD) represents a group of non-communicable conditions, affecting primarily the heart and blood vessels, including coronary heart disease and stroke and to some extent peripheral artery disease. AVD is the most common cause of death worldwide with the largest impact on society and health care systems. Seminal epidemiological work, such as the Framingham Study, helped identify the classic risk factors for AVD including: male sex, increasing age, family history, smoking habit, presence of diabetes, obesity, hypertension, hyperlipidemia, and a sedentary lifestyle (O'Donnell & Elosua, 2008). Emerging AVD risk factors nevertheless have been identified, confirming the crucial role of inflammation in the development of atheroma and to its rupture leading to clinical events such as MI and stroke (Ross 1999; Libby, 2002). Circulating levels of common inflammatory mediators such as CRP or interleukin (IL)-6 confirmed their predictive role as biomarkers of AVD (Ridker, 2003, Hackam and Anand, 2003, Hansson, 2005, Libby *et al*. 2019). Further convincing evidence from large AVD intervention trials highlighted that harnessing upstream systemic inflammation can prevent events like MI and stroke, particularly in patients with high residual inflammatory risk. The extent of chronic systemic inflammation linked to increased future AVD has been defined by serum levels of hsCRP: values between 1 and 2 mg/L are associated with an intermediate future risk for AVD and levels exceeding 3 mg/L are associated with high AVD risk (Ridker 2003). Notwithstanding the opportunity for novel pharmacological approaches to reducing inflammation, the research community is now focused on the identification and management of unconventional but common sources of systemic inflammation as a novel approach to reduced AVD at population level (Libby *et al*. 2018). Periodontitis and its subsequent inflammatory response as described earlier in this chapter might represent an overlooked novel risk factor to AVD.

Further evidence of the link between periodontal infections and AVD comes from several studies confirming the presence of oral bacteria in atheromas (Chiu 1999; Haraszthy *et al*. 2000; Stelzel *et al*. 2002; Fiehn *et al*. 2005) and extended by Kozarov *et al*. (2005) who demonstrated that viable and invasive *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* could be recovered from human atheromas. These observations were further corroborated by experimental preclinical studies that demonstrated that oral infection of either atherosclerosis-prone (apolipoprotein-E deficient) or normocholesterolemic animals with *P. gingivalis* resulted in accelerated atherosclerosis and in the concomitant presence of *P. gingivalis* DNA in their aortic tissue (Lalla *et al*. 2003; Jain *et al*. 2003; Gibson *et al*. 2004; Brodala *et al*. 2005). For a comprehensive review of the evidence on the potential biologic mechanisms of periodontitis-induced atherogenesis, the reader is referred to Chapter 18 and the review by Schenkein *et al*. (2020).

Epidemiologic evidence

Observational evidence

Association studies with AVD surrogate markers

Among the first studies that proposed an association between periodontitis and AVD, Mattila *et al*. (1989) documented the association between poor dental health (using a composite index of dental and periodontal diseases) and coronary heart disease, independent of age, total cholesterol, high-density lipoprotein (HDL), triglycerides, C-peptide, hypertension, diabetes, and smoking. Since this publication a series of observational investigations have attempted to confirm an association between periodontitis and traditional or novel cardiovascular risk markers. In particular, a close link between periodontitis and inflammatory biomarkers is highly relevant when assessing its role in the development and progression of atheroma formation. Of interest are those investigations that have focused on the potential link between periodontitis and vascular surrogates of AVD.

Endothelial dysfunction is considered the earliest vascular change preceding the development of atheroma formation and AVD progression (Verma *et al*. 2003). It can be defined as the reduced vasodilator capability of peripheral blood vessels and is assessed by measuring the difference in the diameter of a peripheral artery prior to and after reactive hyperemia induced through occlusion of blood flow (Celermajer *et al*. 1992). When assessed in the coronary arteries this early measure of AVD is linked to future clinical events (Matsuzawa *et al*. 2015). A meta-analysis of 14 prospective studies reported a 13% lowering of future cardiovascular disease for every 1% increase in endothelial function assessed by flow-mediated dilatation of the brachial artery (FMD) (Inaba *et al*. 2010).

There is moderate convincing evidence that endothelial dysfunction is more pronounced in patients with periodontitis than periodontally healthy controls (Amar *et al*. 2003; Mercanoglu *et al*. 2004). A recent systematic review confirmed that patients with periodontitis had stiffer brachial arteries (average difference in vasodilatation of 5.1%; 95% CI 2.08–8.11) than controls with no signs of periodontitis (Orlandi *et al*. 2014).

A separate group of studies have investigated the association between periodontitis and subclinical atherosclerosis, commonly assessed by means of carotid artery intima–media thickness (IMT). Increased IMT has been documented to be directly associated with increased risk of MI and stroke (O'Leary *et al*. 1999). Beck *et al*. (2001) provided the first evidence that periodontitis may be linked to subclinical atherosclerosis. These authors analyzed cross-sectional data from 6017 participants in the Atherosclerosis Risk in Communities (ARIC) Study and demonstrated that severe periodontitis conferred increased odds for higher carotid artery IMT (odds ratio [OR] 2.09; 95% CI 1.73–2.53 for IMT of ≥1 mm). In the same year a prospective population-based survey titled the Bruneck study confirmed that chronic infections (including periodontitis) amplified the risk of atherosclerosis development in the carotid arteries. The association was most pronounced in participants free of carotid atherosclerosis at baseline (age-/sex-adjusted OR 4.08; 95% CI 2.42–6.85 for any chronic infection versus none) and applied to all types of chronic (bacterial) infections (Kiechl *et al*. 2001). A couple of years later, the Oral Infection and Vascular Disease Epidemiology Study (INVEST), a prospective population-based cohort study of 1056 participants aged ≥55 years with no baseline history of stroke, MI, or chronic inflammatory conditions, investigated the relationship between carotid artery plaque and IMT with tooth loss and measures of periodontitis. In a first report based on data from 711 participants (Desvarieux *et al*. 2003), loss of 10–19 teeth were associated with increased prevalence of atherosclerotic plaques (OR 1.9; CI 1.2–3.0). Because a higher number of lost teeth paralleled an increased severity of periodontitis at the remaining teeth in this cohort, it was assumed that tooth loss reflected, in part, current or cumulative periodontitis. In a subsequent publication, Engebretson *et al*. (2005) reported on a subsample of 203 participants from the INVEST cohort with available panoramic radiographs. Bone loss was associated with the presence of carotid atherosclerotic plaque in a dose-dependent manner. A third INVEST report (Desvarieux *et al*. 2005) included 657 participants with available dental and medical variables as described above, as well as data on the prevalence and level of 10 bacterial species. The data revealed that IMT and white blood cell counts increased significantly over tertiles of "etiologic" periodontal bacterial burden (defined as the aggregate colonization per participant by *A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola*).

Interestingly, serum IgG antibody levels to specific periodontal pathogens (in particular combined titer against *Campylobacter rectus* and *Micro monas micros)* were associated with carotid IMT of ≥1 mm in a subgroup of 4585 ARIC participants (Beck *et al*. 2005b). Pussinen *et al*. (2005) reported similar findings on IMT in a subsample of 1023 men aged 46–64 years from the Kuopio Ischemic Heart Disease Risk Factor study. Incident IMT thickening, assessed 10 years postbaseline in participants with no prior cardiovascular diseases, increased significantly across tertiles of IgA titer levels to *A. actinomycetemcomitans* and *P. gingivalis*. Analyzing the progression rate of participants in the INVEST study and based on 430 participants followed up over a median of 3 years with periodontitis, Desvarieux *et al*. (2013) detected a difference in IMT of approximately 0.1 mm in the 3-years follow-up. The clinical relevance of this finding should be interpreted within the context of current evidence suggesting that a 0.03 mm/year increase in IMT is associated with a 2.3-fold increased risk for cardiovascular events (Hodis *et al*. 1998). Two recent systematic reviews and meta-analyses demonstrated that the diagnosis of periodontitis was associated with a mean increase in IMT of 0.08 mm (95% CI 0.07–0.09) (Orlandi *et al*. 2014) and with carotid atherosclerosis (OR 1.27; 95% CI 1.14–1.41) (Zeng *et al*. 2016).

Recent evidence has confirmed a moderate but consistent association between periodontitis and hypertension, defined as values ≥140 mmHg systolic blood pressure (SBP) and/or ≥90 mmHg diastolic blood pressure (DBP). As summarized in a recent systematic review, diagnoses of moderate–severe periodontitis (OR = 1.22; 95% CI 1.10–1.35) and severe periodontitis (OR = 1.49; 95% CI, 1.09–2.05) were associated with hypertension. Meta-analysis of prospective studies confirmed diagnosis of periodontitis increased by at least 50% the likelihood of hypertension occurrence (OR = 1.68; 95% CI, 0.85–3.35) and that patients with periodontitis exhibited higher mean SBP (weighted mean differences [WMD] of 4.49 mmHg; 95% CI 2.88–6.11) and DBP (2.03 mmHg;

95% CI 1.25–2.81) when compared with control participants without periodontitis (Munoz Aguilera *et al*. 2020). A large observational study using genetic variation as a natural experiment to investigate the causal relation between periodontitis and hypertension (Mendelian Randomization) included almost 750 000 participants from two large genome wide association studies (UK-Biobank and ICBP-GWAS). The analysis confirmed a strong link between common genetic variants linked to both periodontitis and hypertension (Czesnikiewicz-Guzik *et al*. 2019).

The stiffness of the large central arterial system, such as the aortic tree, is another surrogate marker of AVD and it has been associated with systolic hypertension (Chae *et al*. 1999), coronary artery disease, and stroke (Sutton-Tyrrell *et al*. 2005). Measurement of pulse wave velocity (PWV) as the gold standard method for the assessment of arterial stiffness has been recommended as a tool to evaluate arterial system damage, vascular adaptation, and therapeutic efficacy (Mancia *et al*. 2014). A meta-analysis of 10 observational studies concluded that periodontitis is associated with an increased arterial stiffness expressed by a PWV mean difference of 0.85 m/s (95% CI 0.53–1.16) (Schmitt *et al*. 2015).

Association studies with clinical events

Longitudinal studies have shed light on the incidence of cardiovascular events in relation to periodontitis as well as the type of individuals most affected. The first of such studies was a national sample of 9760 US adults by DeStefano *et al*. (1993) who found that study participants with periodontitis had a 25% increased risk of coronary heart disease relative to those with minimal periodontitis.

A variety of case-definitions of periodontitis have been used in these studies. A critical appraisal of most observational trials linking periodontitis and AVD events is greatly affected by large heterogeneity of the findings across studies, with many – but clearly not all – reporting statistically significant associations after appropriate adjustments for covariates and potential confounders.

A summary of data from selected epidemiologic studies with a sample size of at least 1000 participants that have used periodontal status as an exposure and have reported AVD outcomes was conducted (Table 17-1). OR, hazard ratios (HR), or relative risk (RR) for clinical AVD outcomes varied from 1.0 to 2.7 for studies focusing on any vascular events (coronary heart, coronary vascular, or cardiovascular diseases), from 1.1 and 3.8 for studies on MI or acute coronary syndrome (ACS) (Table 17-2), and from 1.1 to 2.2 for studies on stroke (Table 17-3). A critical appraisal of most of these studies at a glance is largely affected by heterogeneity of study designs and the findings across studies, with many–but clearly not all – reporting statistically significant associations after appropriate adjustments for co-variates and potential confounders. Although consistently raised estimates of vascular events were reported, a plethora of case-definitions of periodontitis have been used in these studies ranging from self-reported measures to registry case definitions and clinically confirmed diagnoses.

At least seven meta-analyses over the last two decades have been published summarizing the association between periodontitis and AVD clinical outcomes (Danesh 1999; Janket *et al*. 2003; Bahekar *et al*. 2007; Mustapha *et al*. 2007; Humphrey *et al*. 2008; Blaizot *et al*. 2009; Sfyroeras *et al*. 2012) consistently concluding that the available evidence suggests a moderate, but consistent positive association (RR ratios ranging from 1.1 to 1.8) between periodontal diseases and AVD (Fig. 17-3).

Interestingly, the effect of periodontitis on AVD events appears to differ with age and to be stronger with cerebrovascular events. This finding was highlighted already in the first longitudinal study reporting an association between periodontitis and AVD events. De Stefano *et al*. (1993) indeed reported that in men younger than 50 year of age at baseline, periodontitis was a strong risk factor of future coronary heart disease outcomes. Further, in two publications from the Normative Aging Study (NAS) cohort, periodontitis was more strongly associated with incident coronary heart disease (Dietrich *et al*. 2008) and stroke (Jimenez *et al*. 2009) in younger versus older (>60 years) men. Sen *et al*. (2013) studied prospectively a cohort of 106 patients admitted to hospital with stroke or transient ischemic attack. Study participants grouped based on the recorded extent of periodontal attachment loss (highest versus lowest tertile using a threshold of CAL equal to 1.3%) were followed for a median period of 24 months for the occurrence of vascular events such as stroke, acute MI, and death. Participants with a high level of periodontitis experienced about 60% of the total number of recurrent CVD events (16 out of 27 total events including MI, stroke, and vascular death) when compared with those in the group of a low level of periodontitis. Lastly, Chen *et al*. (2016), using a large retrospective cohort of more than 750 000 participants, investigated the impact of periodontitis on the onset of atrial fibrillation, one of the most common causes of cardioembolic stroke. Patients with periodontitis experienced an increased risk of atrial fibrillation when compared with controls over an 11 year follow-up (HR 1.31; 95% CI 1.25–1.36). Two recent meta-analyses of cohort studies confirmed a 1.6–2.9-fold risk of stroke in the presence of periodontitis (Lafon *et al*. 2014; Leira *et al*. 2017).

A contentious issue that has been vigorously debated is whether the association between periodontitis and AVD events (or indeed with other non-communicable diseases) can be attributed to the confounding effect of smoking (Hujoel *et al*. 2002; Spiekerman *et al*. 2003) or may be entirely spurious (Hujoel *et al*. 2006). A series of earlier studies did not present data for patients who

Table 17-1 Selected epidemiologic studies with sample size >1000, associating periodontal status with coronary heart disease (CHD), coronary artery disease (CAD) or cardiovascular disease (CVD).

Study	n	Country	Age (years)[a]	Design	Exposure[b]	Outcome	Adjustment[c]	Measure of association
de Oliveira *et al*. (2010)	11 869	Scotland, UK	50	Cross-sectional	Toothbrushing <1 time/day	CVD	1–9	HR of 1.7 (1.3–2.3) for those brushing <1 time/day versus those who brushed >2 times/day
Beck *et al*. (2005a)	5002	USA (subset of the ARIC study)	45–64	Cross-sectional	Periodontitis (clinical) Serum IgG to 17 periodontal species	CHD	1–9	No association with clinical periodontal status OR for high vs low IgG in ever smokers: ***Td*** 1.7 (1.2–2.3); ***Pi*** 1.5 (1.1–2.0); ***Co*** 1.5 (1.1–2.1); ***Vp*** 1.7 (1.2–2.3) OR for high vs low IgG in never smokers: ***Pn*** 1.7 (1.1–2.6); ***Aa*** 1.7 (1.2–2.7); ***Co*** 2.0 (1.3–3.0)
Elter *et al*. (2004)	8363	USA (ARIC)	52–75	Cross-sectional	Periodontitis (clinical) Tooth loss	CHD	5–9, 12	OR for combined high attachment loss and tooth loss: 1.5 (1.1–2.0) OR for edentulism: 1.8 (1.4–2.4)
Park *et al*. (2019)	247 696	Korea	46–60	Retrospective cohort	ICD-10 codes (K052-K056) Tooth loss	CHD and CVD mortality	1–9	No association with periodontitis ICD diagnosis HR for tooth loss 1.44 (1.24–1.67) (22–28 teeth versus 0)
Beukers *et al*. (2017)	60 174	Netherlands	>35	Cohort (Registry Study)	Periodontitis (insurance code)	CVD	1–6	OR 1.59 (1.39–1.81)
Hansen *et al*. (2016)	100 694	Denmark	≥18	Cohort (Registry Study)	Periodontitis (hospital diagnosis)	CVD	1, 3, 6	IRR 2.02 (1.87–2.18) for cardiovascular death IRR 2.70 (2.60–2.81) for all-cause mortality.
Holmlund *et al*. (2010)	7674	Sweden	20–89	Cohort	Tooth loss Periodontitis (clinical)	CHD and CVD mortality	1, 3, 5	***CVD mortality:*** HR ***for*** <10 teeth vs >25 teeth: 4.41 (2.47–7.85); HR for severe periodontal disease vs no disease: 1.62 (0.59–4.46) ***CHD mortality:*** HR for <10 teeth vs >25 teeth: 7.33 (4.11–13.07); HR for severe periodontal disease vs no disease: 0.78 (0.27–2.21)
Dietrich *et al*. (2008)	1203	USA (Normative Aging Study)	21–84	Cohort	Periodontitis (clinical/radiographic)	CHD	1–10	HR for ages <60 years: clinical: 1.94 (1.23–3.05); radiographic: 2.12 (1.26–3.60) HR for ages ≥60 years: clinical: 0.73 (0.45–1.19); radiographic: 1.81 (NR)
Heitmann and Gamborg, (2008)	2932	Denmark (MONICA)	30–60	Cohort	Tooth loss	Fatal/non-fatal CVD, CHD	1, 2, 4, 5, 6, 8–10	HR (5th vs 1st quintile) for CVD: 1.50 (1.02–2.19) HR for CHD: 1.31 (0.74–2.31)

Table 17-1 (*Continued*)

Study	n	Country	Age (years)[a]	Design	Exposure[b]	Outcome	Adjustment[c]	Measure of association
Tu *et al*. (2007)	12 223	Scotland	≤39	Cohort	Tooth loss	CVD mortality	1, 3–5, 8, 9	HR for those having >9 missing teeth: 1.35 (1.03–1.77)
Pussinen *et al*. (2005)	1023 men	Finland (Kuopio Ischemic Heart Disease Study)	46–64	Cohort	Serum IgA and IgG to *Aa*, *Pg*	CHD	1, 4–8, 13	RR for: high *Aa* IgA 2.0 (1.2–3.3); high *Pg* IgA 2.1 (1.3–3.4)
Tuominen *et al*. (2003)	6527	Finland	30–69	Cohort	Periodontitis (clinical) Tooth loss	CVD mortality	1, 4–8	RR for tooth loss: in men 0.9 (0.5–1.6); in women 0.3 (0.1–1.0) RR for periodontitis: in men 1.0 (0.6–1.6); in women 1.5 (0.6–3.8)
Abnet *et al*. (2001)	29 584	China	40–69	Cohort	Tooth loss	CVD mortality	1, 3, 5	RR: 1.28 (1.17–1.40)
Howell *et al*. (2001)	22 071	USA (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	CVD mortality	1, 5, 6, 8, 9, 10, 11, 14	RR: 1.00 (0.79–1.26)
Hujoel *et al*. (2000)	8032	USA (NHANES I follow-up study)	25–74	Cohort	Periodontitis (clinical)	CHD events including mortality	1–12	HR for: gingivitis 1.05 (0.88–1.26); periodontitis 1.14 (0.96–1.36)
Morrison *et al*. (1999)	10 368	Canada	35–84	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 5–8	RR for: severe gingivitis 2.15 (1.25–3.2); periodontitis 1.37 (0.80–2.35); edentulism 1.90 (1.17–3.10)
Beck *et al*. (1996)	1147 men	USA	21–80	Cohort	Periodontitis (clinical/ radiographic)	Incident CHD	1, 7–9	Incidence OR for those with "high" bone loss: 1.5 (1.04–2.14) Incidence OR for those with pockets of >3 mm at all their teeth: 3.1 (1.30–7.30)
DeStefano *et al*. (1993)	9760	USA (NHANES I)	25–74	Cohort	Periodontitis (clinical)	Incident fatal and non-fatal CHD	1–11	RR for: gingivitis 1.05 (0.88–1.26); periodontitis 1.25 (1.06–1.48); edentulism 1.23 (1.05–1.44)

[a] For cohort studies, the reported age range applies to the baseline examination.
[b] Describes how periodontitis/oral health status was assessed (clinically, radiographically, by self-reported information, by serologic assessment of titers to specific periodontal bacteria, or by assessment of oral microbial colonization).
[c] Adjustments: numbers describe the following variables: 1, age; 2, race or ethnicity; 3, gender; 4, socioeconomic status (income and/or education); 5, smoking habits; 6, diabetes (presence or duration/HbA1c); 7, hyperlipidemia (or LDL cholesterol and/or HD-cholesterol and/or triglycerides); 8, hypertension (or systolic and/or diastolic blood pressure); body mass index or waist-to-hip ratio or obesity; 10, alcohol consumption; 11, physical activity; 12, current access to dentist; 13, fibrinogen; 14, history of CVD; 15, C-reactive protein; 16, vitamin E intake.
HR, hazard ratio; OR, odds ratio; RR, relative risk; ARIC, Atherosclerosis Risk in Communities; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; NHANES I, National Health and Nutrition Examination Survey I; *Aa*, *Aggregatibacter actinomycetemcomitans; Co*, *Capnocytophaga ochracea*; *Pi*, *Prevotella intermedia*; *Pn*, *Prevotella nigrescens*; *Td*, *Treponema denticola*; *Vp*, *Veillonella parvula*.

never smoked and adopted suboptimal statistical methodologies to account for a possible residual confounding effect related to tobacco or environmental cigarette exposure. Recent evidence, however, confirmed that periodontitis is linked to AVD also in patients who never smoked. Two case–control studies reported tripled odds of incident strokes among patients who never smoked with periodontitis compared with participants without periodontitis and this was particularly relevant in men (Pussinen *et al*. 2007; Sim *et al*. 2008). US data obtained from the Behavioral Risk Factor Surveillance Survey including 41 891 participants from 22 states showed that, among patients who never smoked, the respective OR for CHD among participants missing 1–5 or 6–31 teeth were 1.39 (95% CI 1.05–1.85) and 1.76 (95% CI 1.26–2.45), respectively (Okoro *et al*. 2005).

Table 17-2 Selected epidemiologic studies with sample size >1000, associating periodontal status with myocardial infarction (MI) or acute coronary syndrome (ACS).

Study	*n*	Country	Age range (years)	Design	Exposure	Outcome	Adjustments[a]	Measure of association
Senba *et al*. (2008)	29 904	Japan	Not reported	Cross-sectional	Periodontitis	MI	1–9	OR for: males 2.34 (1.05–5.23); females 1.76 (0.64-4.88)
Holmlund *et al*. (2006)	4254	Sweden	20–70	Cross-sectional	Periodontitis (clinical/ radiographic)	Self-reported, hospital-treated MI	1, 3, 5	OR for bone loss in ages 40–60 only: 2.69 (1.12–6.46)
Buhlin *et al*. (2002)	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Self-reported MI	Unadjusted	OR for: bleeding gums 0.55 (0.22–1.36); loose teeth 0.98 (0.32–3.04); deep pockets 1.32 (0.51–3.38); dentures 1.04 (0.47–2.30)
Arbes *et al*. (1999)	5564	USA (NHANES III)	40–90	Cross-sectional	Periodontitis (clinical)	Self-reported heart attack	1–9	OR for highest versus lowest extent of attachment loss: 3.77 (1.46–9.74)
Ryden *et al*. (2016)	1610	Sweden	62.5 ± 8	Case–control	Periodontitis (clinical)	MI	1–11	OR: 1.28 (1.03–1.60)
Andriankaja *et al*. (2011)	1060	USA	35–69	Case–control	Presence of six periodontal pathogens (***Pg, Tf, Pi, Cr, Fn, Es***)	MI	1, 3–8	OR for: ***Tf*** 1.62 (1.18–1.22); ***Pi*** 1.4 (1.02–1.92)
Lund Haheim *et al*. (2008)	1173 men	Norway	48–77	Case–control	Serum IgG to ***Pg, Aa, Td,*** and ***Tf***	Self-reported MI	5–9, 15	OR for seropositivity for any of the four titers: 1.30 (1.01–1.68)
Andriankaja *et al*. (2007)	1461	USA	35–69	Case–control	Periodontitis (clinical) Non-fatal	MI	1, 3, 5–8	OR for mean attachment loss: 1.46 (1.26–1.69)
Lee *et al*. (2015)	723 024	Taiwan	≥22	Retrospective cohort	ICD-9-CM codes 523.0–523.5	MI	1–9	IR: 1.23 (1.13–1.35)
Yu *et al*. (2015)	39 863 women	USA	49–60	Cohort	Periodontitis (clinical)	MI	1–11	RR: 1.39 (1.17–1.64)
Howell *et al*. (2001)	22 071	USA (PhysiciansHealth Study)	40–84	Cohort	Self-reported periodontitis	Non-fatal MI	1, 5, 6, 8, 9, 10,	RR: 1.01 (0.82–1.24) 11, 14
Joshipura *et al*. (1996)	44 119 men	USA	40–75	Cohort	Self-reported periodontitis	MI	1, 3, 5–8	RR: 1.04 (0.86–1.25)

[a] Numbers describe the variables as listed in Table 17-1.
OR, odds ratio; RR, relative risk; NHANES III, National Health and Nutrition Examination Survey III; ***Aa***, ***Aggregatibacter actinomycetemcomitans***; ***Cr***, ***Campylobacter rectus***; ***Es***, ***Eubacterium saburreum***; ***Fn***, ***Fusobacterium nucleatum***; ***Pi***, ***Prevotella intermedia***; ***Pg***, ***Porphyromonas gingivalis***; ***Td***, ***Treponema denticola; Tf***, ***Tannerella forsythia***.

Experimental evidence

Intervention studies with surrogate markers

When designing and conducting an intervention trial to reduce AVD events, a number of challenges are faced by researchers: firstly because of the extended time course of evolution of AVD (studies with follow-up of minimum 3 years), then due to the relatively low incidence of AVD-related clinical events (1–3% per year in a high-risk population as for example in patients who already experienced an AVD event). Large sample sizes (more than 4000 participants), longer follow-up (more than 3 years), and logistical challenges in delivering effective periodontal treatment across different centers/countries have impacted on the feasibility of performing such trials as well as highlighting the ethical considerations related to the follow-up of untreated periodontitis over prolonged time periods. Therefore, most intervention

Table 17-3 Selected epidemiologic studies with sample size >1000, associating periodontal status with stroke.

Study	*n*	Country	Age range (years)	Design	Exposure	Outcome	Adjustments[a]	Measure of association
Lee *et al.* (2006)	5123	USA	60–76+	Cross-sectional	Periodontal Health Status (PHS: a composite index of periodontitis and tooth loss)	Self-reported history of stroke	1, 5, 6, 8, 10, 15	OR for PHS class 5 vs. class 1: 1.56 (0.95–2.57)
Elter *et al.* (2003)	10 906	USA	Not reported	Cross-sectional	Periodontitis (clinical) Edentulism	Ischemic stroke or transient ischemic attack	1–9, 12	OR for highest quartile of attachment loss: 1.3 (1.02–1.7) OR for edentulism: 1.4 (1.5–2.0)
Buhlin *et al.* (2002)	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Ischemic and hemorrhagic stroke	Unadjusted	OR for: bleeding gums: 1.83 (0.78–4.31); loose teeth 1.83 (0.66–5.12); deep pockets 0.68 (0.22–2.05); dentures 1.81 (0.74–4.42)
Lee *et al.* (2013)	723 024	Taiwan	≥20	Retrospective cohort	ICD-9-CM codes 523.0–523.5	Stroke	1–10	IR of stroke total: 1.15 (1.07–1.24) IR of stroke (20–44 y): 2.17 (1.64–2.87) IR of stroke (45–64 y):1.19 (1.05–1.35) IR of stroke (≥65 y):1.13 (1.03–1.25)
Holmlund *et al.* (2010)	7674	Sweden	20–89	Cohort	Tooth loss Periodontitis (clinical)	Stroke mortality	1, 3, 5	HR for <10 teeth vs. >25 teeth: 0.91 (0.24–3.49); HR for severe periodontal disease vs no disease: 1.39 (0.18–10.45)
Choe *et al.* (2009)	867 256	Korea	30–95	Cohort	Tooth loss	Ischemic and hemorrhagic stroke	1, 5–11	HR for men having ≥7 missing teeth: 1.3 (1.2, 1.4) HR for women having ≥7 missing teeth: 1.2 (1.0, 1.3)
You *et al.* (2009)	2862	USA	45–85+	Cohort	Self-reported tooth loss	Self-reported stroke	1–8, 14–15	OR for participants having ≥17 missing teeth: 1.27 (1.09, 1.49)
Tu *et al.* (2007)	12 223	Scotland	≤39	Cohort	Tooth loss	Ischemic and hemorrhagic stroke	1, 3–5, 8, 9	HR for those having >9 missing teeth: 1.64 (0.96–2.80)
Abnet *et al.* (2005)	29 584	China	40–69	Cohort	Tooth loss	Fatal stroke	1, 3, 5, 8, 9	RR for those with less than the median age-specific number of teeth: 1.11 (1.01–1.23)
Joshipura *et al.* (2003)	41 380 men	USA	40–75	Cohort	Self-reported periodontitis/ tooth loss	Ischemic stroke	1, 4–11, 16	HR for men with ≤24 teeth: 1.57 (1.24–1.98) HR for men with periodontitis: 1.33 (1.03–1.70)

(*Continued*)

Table 17-3 (*Continued*)

Study	*n*	Country	Age range (years)	Design	Exposure	Outcome	Adjustments[a]	Measure of association
Wu *et al.* (2000)	9962	USA (NHANES I follow-up study)	25–74	Cohort	Gingivitis Periodontitis (clinical) Edentulism	Ischemic stroke	1–10	RR for: gingivitis 1.24 (0.74–2.08); periodontitis 2.11 (1.30–3.42); edentulism 1.41 (0.96–2.06)
Howell *et al.* (2001)	22 071	USA (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	Non-fatal stroke	1, 5, 6, 8–11, 14	RR 1.10 (0.88–1.37)
Morrison *et al.* (1999)	10 368	Canada	35–84	Cohort	Gingivitis Periodontitis (clinical)	Stroke mortality	1, 3, 5–8	RR for: severe gingivitis 1.81 (0.77–4.25); periodontitis 1.63 (0.72–3.67); edentulism: 1.63 (0.77–3.42)

[a] Numbers describe the variables as listed in Table 17-1.
HR, hazard ratio; OR, odds ratio; RR, relative risk; NHANES I: National Health and Nutrition Examination Survey I.

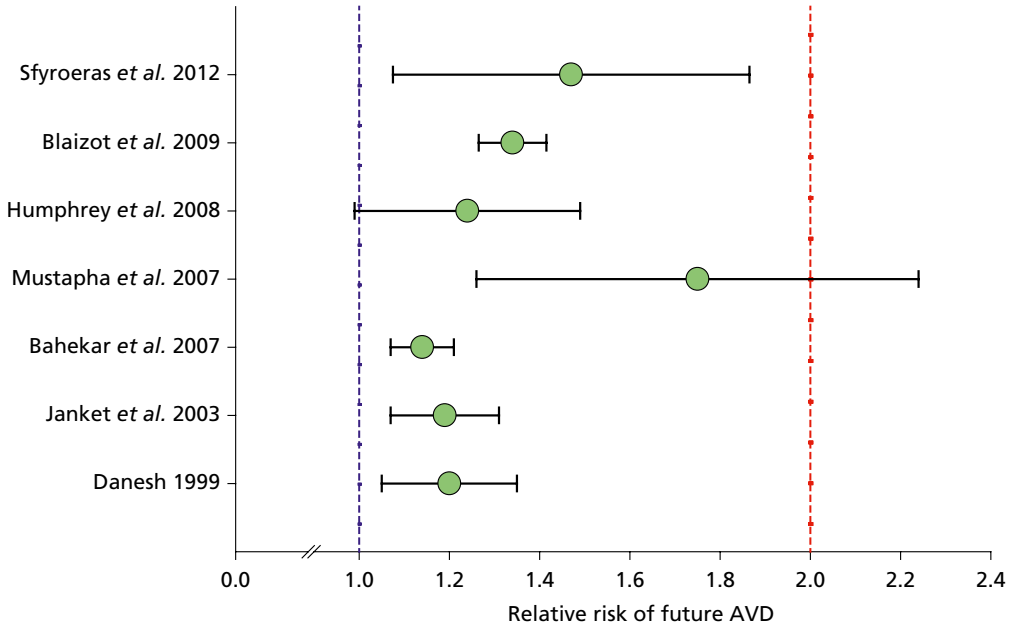

Fig. 17-3 Scatter plot with error horizonal lines of reported adjusted relative risk of observational studies in previous systematic reviews and meta-analysis of the association between periodontitis and atherosclerotic vascular disease (AVD) to date.

trials conducted to date have been largely limited to the study of the effects of periodontal therapy on surrogate markers of AVD or on pathways related to the pathobiology of the disease.

The first intervention study in this area (Ide *et al.* 2004) showed that chronic periodontitis patients undergoing an episode of subgingival scaling experienced changes in their systemic inflammatory status (as assessed by early inflammatory biomarkers such as tumor necrosis factor α and IL-6). In the same year, a randomized trial reported statistically significant reductions in serum IL-6 (median decrease 0.2 ng/L, 95% CI 0.1–0.4 ng/L) and CRP (median decrease 0.5 mg/L, 95% CI 0.4–0.7) in patients with severe generalized periodontitis who received a single-sitting non-surgical periodontal therapy and the use of locally delivered antimicrobials after 6 months and compared with a group who received delayed treatment (D'Aiuto *et al.* 2004). An updated summary of intervention trials on surrogate markers of AVD confirmed limited to moderate evidence that periodontal treatment was associated with reductions of systemic inflammation (reduced CRP and IL-6 serum levels), of blood pressure (reduced systolic blood pressure), and better endothelial function (improved FMD) and subclinical atherosclerosis (reduced IMT) (Table 17-4) (Orlandi *et al.* 2020).

Table 17-4 Summary of the evidence on the effect of periodontal therapy on surrogate markers of cardiovascular diseases.

Effect of periodontal therapy on	Outcome	Number of RCTs since last consensus meta-analysis	Effect	Overall level of evidence
Lipid fractions	Lipids (multiple)	6 RCTs (Caula *et al*. 2014; Kapellas *et al*. 2014; Hada *et al*. 2015; Fu *et al*. 2016; Deepti *et al*. 2017; D'Aiuto *et al*. 2018)	No	Moderate
Blood pressure	Systolic, diastolic	4 RCTs (Hada *et al*. 2015; Zhou *et al*. 2017; D'Aiuto *et al*. 2018; Czesnikiewicz-Guzik *et al*. 2019)	Yes	Moderate
Systemic inflammation	IL-6	3 RCTs (Kapellas *et al*. 2014; Fu *et al*. 2016; Zhou *et al*. 2017)	Yes	Moderate
Systemic inflammation	CRP	5 SR (Ioannidou *et al*. 2006; Paraskevas *et al*. 2008; Freitas *et al*. 2012; Demmer *et al*. 2013; Teeuw *et al*. 2014) 7 RCTs (Bokhari *et al*. 2012; Caula *et al*. 2014; Kapellas *et al*. 2014; Hada *et al*. 2015; Deepti *et al*. 2017; Zhou *et al*. 2017; D'Aiuto *et al*. 2018;Kaushal *et al*. 2019)	Yes	Moderate
Endothelial function	Endothelial function (multiple measures)	2 RCTs (D'Aiuto *et al*. 2018; Saffi *et al*. 2018) 1 SR (Orlandi *et al*. 2014)	Yes	Moderate
Arterial stiffness	Pulse wave velocity	1 RCT (Kapellas *et al*. 2014)	No	Limited
Subclinical atherosclerosis	Common carotid Intima-media thickness	1 RCT (Kapellas *et al*. 2014)	Yes	Limited

RCT, randomized clinical trial; SR, systematic review. (Source: Adapted from Orlandi *et al*. (2020).)

The evidence of the effects of periodontal treatment on vascular surrogate markers of AVD comes, however. from small-sized, intervention studies. A randomized controlled trial involving a total of 120 patients with severe periodontitis, 61 of whom received full-mouth subgingival debridement, completed within a single session and accompanied by extensive application of local antibiotics in all deep periodontal pockets (Tonetti *et al*. 2007), demonstrated a significant improvement in FMD in the test compared with the control treatment group (whole mouth supragingival scaling and polishing in a single session) at a 6-month follow-up examination. A larger and longer intervention study performed in patients suffering from periodontitis and type 2 diabetes confirmed similar benefits in FMD improvement following a standard course of non-surgical and surgical periodontal therapy after 6- and 12-month follow-ups when compared with control therapy (whole mouth supragingival scaling and polishing) (D'Aiuto *et al*. 2018). Similar improvements were reported following non-surgical periodontal treatment in 69 patients with coronary artery disease and severe periodontitis when compared with delayed treatment (Saffi *et al*. 2018).

Promising results have been presented on the beneficial effect of the treatment of periodontitis on arterial blood pressure. In particular, Zhou *et al*. (2017) randomly allocated 107 patients with prehypertension and moderate to severe periodontitis to receive either full-mouth scaling and root planing under local anesthesia or a standard cycle of supragingival scaling and polishing. The authors reported a reduction of systolic BP and diastolic BP levels by 10.3 and 7.2 mmHg, respectively, 6 months following treatment. Further evidence to corroborate these findings came from the first randomized trial using ambulatory blood pressure as a primary endpoint in patients with insufficiently controlled hypertension (Czesnikiewicz-Guzik *et al*. 2019). One hundred and one patients with office blood pressure >140/90 mmHg despite a stable antihypertensive regimen (using at least one medication for over 6 months) and concomitant moderate to severe periodontitis received an intensive or control periodontal

treatment protocol and 2 months after treatment a statistically significant reduction in blood pressure (11.1 mmHg; 95% CI 6.5–15.8) was accompanied by improvements in FMD and inflammatory cellular and biomarkers profiles (Czesnikiewicz-Guzik *et al*. 2019).

In contrast, inconclusive evidence exists on the effects of periodontitis treatment on PWV. Vidal *et al*. (2013) reported an improvement in PWV (13.7 [2.4] to 12.5 [1.9]) 6 months after periodontal treatment in hypertensive patients whilst these findings were not observed in two different clinical trials (Kapellas *et al*. 2014; Houcken *et al*. 2016). Ren *et al*. (2016) randomized 108 patients with moderate to severe periodontitis to receive either supragingival scaling and subgingival instrumentation (test) or supragingival scaling and polishing (control). Participants in the test treatment group showed a significantly decreased PWV after 1 month of an average of -0.58 m/s (95% CI -0.06–1.11).

Likewise, a single-arm study conducted on 35 patients with mild-to-moderate periodontitis reported that non-surgical periodontal therapy resulted in a diminished IMT thickness at 6 and 12 months after treatment completion (Piconi *et al*. 2009). In a subsequent randomized trial, 168 Aboriginal Australians suffering from periodontitis presented with an IMT decrease after 12 months of a single session of periodontal therapy (mean difference of −0.026 mm; 95% CI −0.048–−0.003) (Kapellas *et al*. 2014).

Intervention studies with clinical events

To date there is still insufficient evidence to comment on the effects of periodontal therapy on cardiac events. Consistent observational evidence, however, suggests that several oral health interventions including self-performed oral hygiene habits (toothbrushing) (de Oliveira *et al*. 2010; Park *et al*. 2019), dental prophylaxis (Lee *et al*. 2015), increased self-reported dental visits (Sen *et al*. 2018), and periodontal treatment (Lee *et al*. 2015; Park *et al*. 2019; Holmlund *et al*. 2017) are accompanied by a reduction of AVD events.

Cross-sectional data of The Scottish Health Surveys from 1995 to 2003 comprising 11 869 men and women (mean age of 50 years), was linked to a database of hospital admissions and deaths with follow-up until December 2007 (Information Services Division, Edinburgh) (de Oliveira *et al*. 2010). Participants who brushed less than once a day exhibited the highest incidence of AVD events (HR = 1.7; 95% CI 1.3–2.3) compared with those who brushed twice a day. A retrospective nationwide, population-based study in Taiwan, including 511 630 participants with periodontitis and 208 713 controls was conducted to estimate the incidence rate of AVD events from 2000 to 2015 (Lee *et al*. 2015). Patients with periodontitis who received dental prophylaxis presented with reduced incidence of acute MI (HR = 0.90; 95% CI 0.86–0.95) as opposed to those who received more periodontal treatment (including gingival curettage, scaling and root planing, and/or periodontal flap operation and/or tooth extraction) (HR = 1.09; 95% CI 1.03–1.15). Consistent reductions in the incidence rate of stroke were observed in both the dental prophylaxis (HR = 0.78; 95% CI 0.75–0.91) and active periodontal treatment group (HR = 0.95; 95% CI 0.91–0.99) (Lee *et al*. 2015). In a recent cohort of 8999 patients with periodontitis who received a complete (non-surgical and if needed surgical) periodontal treatment protocol and then followed for more than 30 years, poor responders to the treatment had an increased incidence of AVD events (IR = 1.28; 95% CI 1.07–1.53) compared with good responders (Holmlund *et al*. 2017). Similar benefits were reported in self-reported regular dental care users of the 6736 participants of the ARIC substudy who were followed up for 15 years and exhibited lower risk for ischemic stroke (HR = 0.77; 95% CI 0.63–0.94) when compared with episodic care users (Sen *et al*. 2018). Lastly, the largest prospective population-based trial including 247 696 participants from Korea and free from any vascular disease were followed over 14 years and the study confirmed that one additional toothbrushing episode per day was associated with a reduced incidence of AVD events (HR = 0.91; 95% CI 0.89–0.93) and regular professional cleaning reduced the risk even further (HR = 0.86; 95% CI 0.82–0.90) (Park *et al*. 2019).

To date, only a single, multicenter pilot study has examined the effects of periodontal therapy on cardiac events. The Periodontitis and Vascular Events (PAVE) study (Beck *et al*. 2008; Offenbacher *et al*. 2009b) randomized patients with periodontitis and a history of severe AVD to either community care or a study protocol that consisted of oral hygiene instruction and professional mechanical periodontal therapy. Over a 25-month follow-up period, cardiovascular adverse events occurred with similar frequency and high degree of variation in the community control and the periodontal treatment groups (RR = 0.72, 95% CI 0.23–2.22).

Diabetes mellitus

Biological mechanisms

The role of diabetes mellitus as a risk factor for periodontitis is reviewed in detail in Chapter 18. Newer evidence, however, suggests that periodontitis may represent a risk factor and/or modifier of diabetes onset and progression. This is most evident for type 2 diabetes, whilst the evidence linking periodontitis and type 1 diabetes is mainly based on historical observational and intervention studies performed in the early stages of periodontal medicine.

Inflammation is a known driver of insulin resistance with a role in the initiation and evolution of cardiorenal complications in patients with and without diabetes (Hotamisligil *et al*. 1993).

Previous reports have shown that reduction of inflammation by lifestyle interventions (Schellenberg *et al*. 2013) or drug therapy (i.e. IL-1 antagonists)

(Goldfine *et al*. 2011), improves insulin beta-cell secretory function and decreases blood glucose in patients with diabetes.

Preclinical evidence highlighted how experimental periodontitis in animal models (i.e. ligature-induced periodontitis) is accompanied by an adaptive immune response specifically directed against pathogens and derangements in glucose metabolism including insulin resistance (Pontes Andersen *et al*. 2007; Blasco-Baque *et al*. 2017). As reviewed above, periodontal infections cause elevations of serum pro-inflammatory cytokines and prothrombotic mediators (Loos 2005; Orlandi *et al*. 2020) which, in turn, may result in insulin resistance, may adversely impact metabolic control, and, long-term, may lead or contribute to the development of diabetic complications. This was elegantly confirmed in a cross-sectional survey of 630 patients with both type 1 and 2 diabetes. Presence of severe gingival inflammation was associated with higher levels of bacterial endotoxins and systemic inflammation (Masi *et al*. 2014). Several studies have demonstrated that periodontal therapy can reduce systemic inflammation especially in patients with other comorbidities like diabetes and this evidence was confirmed in a recent systematic review. A meta-analysis of randomized clinical trials confirmed a positive effect of periodontal treatment in reducing biomarkers of inflammation in patients with diabetes and periodontitis (Artese *et al*. 2015). A reduction in inflammatory burden of patients with diabetes could have important implications for metabolic control and might, in part, explain the mechanisms linking periodontitis and increased risk for complications in people with type 2 diabetes.

Epidemiologic evidence

Observational evidence

In one of the first studies that demonstrated periodontitis entails higher risk for diabetic complications, Thorstensson *et al*. (1996) followed 39 pairs of patients with type 1 diabetes, each consisting of a person with severe periodontitis, matched with respect to age, sex, and diabetes duration with a person with no or only mild periodontitis. After a median follow-up of 6 years, a significantly higher incidence of proteinuria and cardiovascular complications, including angina, intermittent claudication, transient ischemic attack, MI, and stroke was found in the patients with severe periodontitis. Evidence from three prospective studies of Pima Indians in the Gila River community in Arizona, a population with a high prevalence of type 2 diabetes, confirmed these preliminary findings. In the first report, Taylor *et al*. (1996) demonstrated that severe periodontitis at baseline conferred increased risk for poor glycemic control (glycated hemoglobin A1c [HbA1c] >9%) after 2 years of follow-up. Subsequently, in the same population but over a median follow-up of 11 years, a diagnosis of severe periodontitis increased the risk of cardiorenal mortality (RR = 3.2; 95% CI 1.1–9.3) (Saremi *et al*. 2005) as well as renal complications (microalbuminuria and end-stage renal disease) (Shultis *et al*. 2007) when compared with no, mild, or moderate periodontitis.

Further evidence of association between periodontitis and dysmetabolic imbalances derives from studies confirming a consistent association between diagnosis of periodontitis and elevated glucose levels (a simple marker of insulin resistance) especially within the context of a cluster of cardiometabolic markers named the metabolic syndrome. This condition is characterized by the co-existence of not only hyperglycemia but also elevated blood pressure, obesity, and dyslipidemia (Alberti *et al*. 2006). A systematic review of 32 cross-sectional studies, eight case–control studies, and three cohort studies concluded that diagnosis of periodontitis was consistently associated with 50% greater odds of metabolic syndrome (OR = 1.46; 95% CI 1.31–1.61) (Gobin *et al*. 2020).

At least five cohort studies explored the association between periodontitis in diabetes-free individuals and the development of type 2 diabetes over time. The first used data from 9296 participants in NHANES I and its Epidemiologic Follow-Up study confirming that participants with severe tooth loss at baseline had an adjusted OR of 1.71 (95% CI 1.19–2.45) for incident diabetes when compared with those least affected (Demmer *et al*. 2008). In contrast, no association between baseline periodontitis and incident diabetes could be demonstrated after multiple adjustments in a 7-year prospective study of 5848 participants without diabetes in Japan (HR = 1.28; 95% CI 0.89–1.86) (Ide *et al*. 2011). Miyawaki *et al*. (2016) analyzed a cohort of 2469 men aged 36–55 years and free from diabetes who were followed over 5-year follow-up period. Self-reported measures of periodontitis were weakly associated with incident diabetes (RR = 1.73; 95% CI 1.14–2.64 for tooth loosening and RR = 1.32; 95% CI 0.95–1.85 for gingival bleeding). Two further studies had been reported following these initial results. In Northern Ireland, 1331 dentate, diabetes-free men underwent a detailed periodontal examination and were followed over a median period of 8 years. Adjusted hazard ratios for incident type 2 diabetes in men with moderate/severe periodontitis compared with those with no/mild periodontitis was 1.69 (95% CI 1.06–2.69) (Winning & Linden 2017). Lastly, Joshipura *et al*. (2018) analysed a cohort of 1206 diabetes free participants who were followed over 3 years for incident glucose intolerance and/or diabetes. Increase in periodontal attachment loss from baseline to follow-up was associated with higher prediabetes/diabetes risk (RR = 1.25; 95% CI 1.09–1.42) and increase in pocket depth was associated with >20% fasting glucose increase (RR = 1.43; 95% CI 1.14–1.79). Collectively, the evidence published to date would support the

notion that periodontitis and its progression could increase the odds of a later diagnosis of type 2 diabetes by a measure ranging from 30% to 70%.

Experimental evidence

Several intervention studies have examined the effect of periodontal therapy on diabetes outcomes including the level of HbA1c, one of the key indicators of metabolic control in diabetes.

Williams and Mahan (1960) reported for the first time that seven out of nine patients with diabetes and periodontitis who underwent nonsurgical and surgical periodontal therapy according to their individual needs showed significant subsequent reduction in the amount of insulin required to maintain acceptable glucose levels. By contrast, a five-arm randomized controlled trial enrolling 113 Native Americans with type 2 diabetes and periodontitis found that participants allocated to treatment arms that included systemic doxycycline as an adjunct to scaling and root planing reduced their HbA1c levels by approximately 10% of their baseline values after 3 months (Grossi *et al*. 1997) (Fig. 17-1).

Almost 20 years after the results of the first intervention study, a large multicenter trial including 514 patients suffering from severe periodontitis and type 2 diabetes and with baseline HbA1c levels between 7% and 9% was published. All participants in the study were randomly assigned to either scaling and root planing or delayed periodontal therapy (Engebretson *et al*. 2013). After 6 months of the treatment, the mean HbA1c levels increased by 0.17% in the test group and by 0.11% in the control group, with no difference between the groups. These inconclusive findings (no difference in HbA1c levels between treatments after 6 months) were later confirmed by another randomized trial including 264 patients with type 2 diabetes and moderate to severe periodontitis (D'Aiuto *et al*. 2018). In this study, participants were randomly allocated to either (1) nonsurgical and, if indicated, surgical periodontal therapy then followed by careful maintenance or (2) supragingival debridement at comparable time points. Twelve months after baseline and after adjustments for baseline HbA1c, age, sex, ethnicity, smoking status, duration of diabetes, and BMI, participants in the test group exhibited a statistically significant greater reduction in HbA1c (average of 0.6%; 95% CI 0.3–0.9) when compared with the control group. In the same study, D'Aiuto *et al*. (2018) reported statistically significant improvements of participants in the test group in both endothelial (improved FMD both at 6 and 12 months) and kidney function (better glomerular filtration rate) and patient reported outcomes (measure of quality of life relevant to diabetes).

Since the first systematic review on the evidence from intervention trials in patients with periodontitis and diabetes (Janket *et al*. 2005), 13 additional reviews with meta-analysis have been published (Darre *et al*. 2008; Teeuw *et al*. 2010; Corbella *et al*. 2013; Engebretson & Kocher 2013; Liew *et al*. 2013,; Sgolastra *et al*. 2013; Sun *et al*. 2014; Wang *et al*. 2014; Simpson *et al*. 2015; Li *et al*. 2015; Teshome & Yitayeh 2016; Cao *et al*. 2019; Baeza *et al*. 2020). Collectively most of the reports, including the most recent Cochrane systematic review, concluded that there appears to be a statistically significant effect of periodontal therapy on HbA1c levels, amounting to about 0.40–0.50% reduction but there is limited evidence on the duration of this effect (Fig. 17-4).

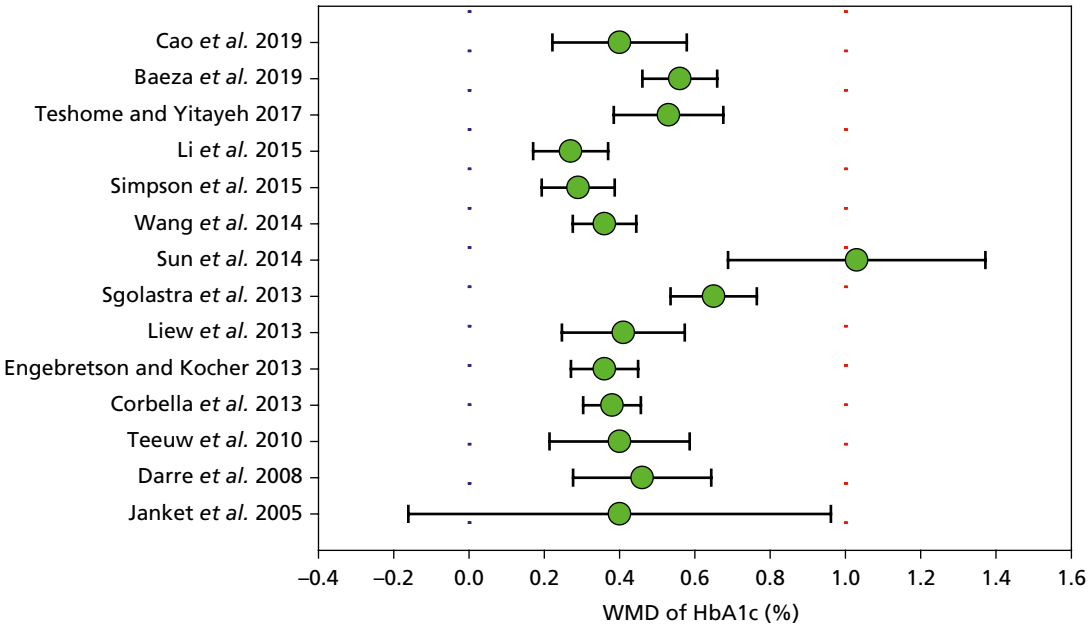

Fig. 17-4 Scatter plot with error horizonal lines of reported adjusted weighted mean differences (WMD) in HbA1c after periodontal treatment in previous systematic reviews and meta-analysis of the association between periodontal treatment and type 2 diabetes outcomes. Please note that the WMDs were originally reported after 6 months of treatment.

Importantly, the magnitude of this effect appears to bear clinical significance within the context of diabetes management: data generated by the United Kingdom Prospective Diabetes Study (Stratton *et al*. 2000) indicate a 35% reduction in the risk of microvascular complications for every percentage point decrease in HbA1c. In addition, an average 0.20% reduction in HbA1c was associated with a 10% reduction in mortality in the general population (Khaw *et al*. 2001). A reduction of 0.5% in HbA1c is comparable with that achieved by adding a second glucose-lowering medication to the management of hyperglycaemia in a patient with diabetes, and hence it is clinically significant. A consensus report endorsed by the respective Federations of Specialist Societies in Periodontology and Diabetes recommended implementation of oral/periodontal assessments as an integral part of diabetes care management (Sanz *et al*. 2018).

Adverse pregnancy outcomes

Biologic mechanisms

Preterm infants are born prior to the completion of 37 weeks of gestation. An estimated 11–13% of pregnancies end in preterm birth (PTB), and this rate appears to be on the rise in several developed countries, despite significant advances in obstetric medicine and improvements in prenatal care utilization (Goldenberg & Rouse 1998; Shapiro-Mendoza & Lackritz 2012). Of interest are the *very preterm infants*, born prior to 32 gestational weeks, the majority of whom require neonatal intensive care due to their increased perinatal mortality, primarily due to impaired lung development and function. The overall contribution of PTB to infant mortality and morbidity is substantial and includes several acute and chronic disorders, including respiratory distress syndrome, cerebral palsy, pathologic heart conditions, epilepsy, blindness, and severe learning disabilities (McCormick 1985; Veen *et al*. 1991).

Preterm infants often weigh less at birth and low birth weight (LBW) (i.e. <2500 g) has been used as a surrogate for prematurity in cases where the exact gestational age at birth is difficult to assess.

Established risk factors for PTB include young maternal age (Scholl *et al*. 1988), multiple gestation (Lee *et al*. 2006), small weight gain during pregnancy (Honest *et al*. 2005), cervical incompetence (Althuisius & Dekker 2005), smoking, alcohol, drug abuse (Myles *et al*. 1998), black race (David & Collins 1997), and a number of maternal infections (uterine tract infections, bacterial vaginosis, chorioamnionitis) (Goldenberg *et al*. 2000; Romero *et al*. 2001). A collective analysis of all established risk factors including obstetric history of PTB as robust markers of future PTB (Mutale *et al*. 1991), however, revealed that approximately 50% of the variance in the incidence of PTB remains unexplained (Holbrook *et al*. 1989).

The possibility that periodontal infections may influence birth outcomes was raised for the first time in the late 1980s (McGregor *et al*. 1988). A subsequent report from Hill (1998) confirmed that amniotic fluid cultures from women with vaginosis rarely contained bacteria common to the vaginal tract, but frequently harbored Fusobacteria of oral origin. A series of experimental studies using common periodontal pathogens in animal models of pregnancy demonstrated that infections from periodontal pathogens caused intrauterine growth retardation, smaller fetuses, and higher inflammation in the amniotic fluid (Collins *et al*. 1994; Boggess *et al*. 2005) . Preliminary clinical evidence confirmed that oral microbes can be identified in the feto-placental unit. However, it is uncertain how pathogens would alter the natural timeline of pregnancy (either via translocation of virulent strains or via increased local relative pathogenic load and by stimulating a neutrophil-driven maternal inflammatory response) (for a comprehensive review of the topic please see Bobetsis *et al*. 2020; Figuero *et al*. 2020).

Epidemiologic evidence

Observational evidence

The first study that reported an association between PTB and periodontitis was a case–control study (Offenbacher *et al*. 1996) of 124 mothers, of whom 93 gave birth to children with a birth weight of <2500 g or prior to 37 weeks of gestation and 46 who delivered infants of normal birth weight at term. Periodontitis, defined as ≥60% of all sites with attachment loss of ≥3 mm, conferred adjusted OR of 7.9 PTB and low weight babies. Twenty years later, a case–control study (Gomes-Filho *et al*. 2016) confirmed that mothers with periodontitis (n = 372) had a sixfold increased likelihood of delivering LBW babies. One of the earlier systematic reviews and meta-analysis published on the association between periodontitis and adverse pregnancy outcomes in case–control studies (Corbella *et al*. 2012) included 17 studies and a total of 10 148 women. The authors reported statistically significant OR for periodontitis and both PTB (OR 1.78; 95% CI 1.58–2.01) and LBW (OR 1.82; 95% CI 1.51–2.20), although the authors cautioned that uncontrolled or inadequately reported confounders may have affected the association demonstrated by the pooled data.

Additional evidence has been reported on the association between periodontitis and other pregnancy outcomes. Longitudinal studies have demonstrated that maternal periodontitis is associated with increased risk for preeclampsia. Periodontitis progression during pregnancy and severe periodontitis at delivery were found to be associated with preeclampsia in a cohort of 1115 healthy pregnant women (Boggess *et al*. 2003). Progression of periodontitis recorded in 1020 pregnant women resulted in an

increased risk for preterm, spontaneous preterm, or very PTBs, independent of traditional risk factors (Offenbacher *et al*. 2006).

A recent overview of systematic reviews including 120 clinical studies grouped in 23 systematic reviews (nine of which had performed a meta-analysis) critically appraised the validity of the published evidence and their conclusions. Seven meta-analyses showed a statistically significant positive association between periodontitis PTB (with ORs and RRs ranging from 1.6 to 3.9). Whereas nine systematic reviews reported on the association between periodontitis and preeclampsia, results from four out of five reviews in which a meta-analysis was performed, confirmed a significant association with ORs/RRs ranging from 2.2 to 2.8. Sixteen systematic reviews reported on the association between periodontitis and LBW with six reviews that performed a meta-analysis resulted in a positive association with ORs/RRs ranging from 1.3 to 4.0. One systematic review investigated the association between periodontitis and small for gestational age suggesting limited evidence on a positive association. Lastly, 17 systematic reviews investigated the association between periodontitis and preterm LBW (a combination of preterm and/or birth weight <2500 g). Seven out of those 17 reviews that performed a meta-analysis reported a significant positive association between periodontitis and preterm LBW with ORs/RRs varying between 2.1 and 5.3. A collective interpretation of these results point towards a prominent role of periodontitis in contributing during pregnancy to the overall risks of PTBs, LBW, and preeclampsia notwithstanding a high percentage (about 11%) of overlap between studies included in different systematic reviews (Daalderop *et al*. 2018).

Experimental evidence

Intervention studies investigating the potential benefit of treating periodontitis during pregnancy with the aim of reducing the incidence of pregnancy complications have had mixed results.

The first published intervention study (Mitchell-Lewis *et al*. 2001) examined a cohort of 213 young, predominantly African-American women who exhibited a particularly high incidence of PTB/LBW (16.5%). Periodontal treatment was associated with a 30% lower incidence of adverse pregnancy outcomes in participants who received the treatment (13.5%) when compared with 18.9% who did not receive the intervention. A subsequent study demonstrated that maternal periodontal therapy reduced the risk of preterm LBW (Lopez *et al*. 2002) confirming a plausible rationale for a number of research groups to plan and conduct larger and multicenter trials on the matter. A few years later, however, two major randomized clinical trials contradicted previous findings of periodontal treatment mitigating risk of PTB (Michalowicz *et al*. 2006, Offenbacher *et al*. 2009a).

Experimental study designs varied across these intervention studies mainly because different active periodontal treatments and controls were chosen. Gazolla *et al*. (2007) for example involved a group of women who "dropped out" of treatment as control therapy whereas Jeffcoat *et al*. (2003) included multiple active treatment groups (including mechanical periodontal treatment with or without systemic administration of metronidazole). Five of the seven studies that were considered to be of higher methodological quality (Jeffcoat *et al*. 2003; Michalowicz *et al*. 2006; Newnham *et al*. 2009; Offenbacher *et al*. 2009a; Macones *et al*. 2010), failed to detect any positive effect of periodontal therapy on pregnancy outcomes, including PTB at <37 or <35 gestational weeks, or LBW of <2500 g or <1500 g. In view of the strong biologic plausibility of the link between maternal periodontal infections and adverse pregnancy outcomes, and of the promising data of the early association studies, at least nine systematic reviews with meta-analyses have been conducted indicating sufficient evidence that periodontal therapy during gestation does result in some improved obstetric outcomes (Polyzos *et al*. 2010; Uppal *et al*. 2010; Chambrone *et al*. 2011; Fogacci *et al*. 2011; George *et al*. 2011; Kim *et al*. 2012; Schwendicke *et al*. 2015; Iheozor-Ejiofor *et al*. 2017; Bi *et al*. 2019). Relative risk reductions reported ranged from 0.6 to 0.9 for PTB and from 0.5 to 1.1 for PBW, confirming a great variation most presumably due to the methodological flaws of the studies included (Fig. 17-5). Further, some preliminary evidence suggests that periodontal treatment during pregnancy significantly decreased risk of perinatal mortality (RR = 0.53; 95% CI 0.30–0.93) (Bi *et al*. 2019).

Interpreting collectively the latest evidence on intervention trials, it is plausible to suggest that performing periodontal treatment is safe during pregnancy and it is associated with a reduced rate of adverse pregnancy outcomes (preterm deliveries and birth weight differences).

Chronic renal disease

Biologic mechanisms

Renal function is commonly measured by means of the glomerular filtration rate (eGFR), which is estimated on the basis of an equation that incorporates the patient's serum creatinine concentration, age, sex, and race (Levey *et al*. 2006). In a healthy adult, eGFR ranges between 100 and 120 mL/min/1.73 m^2 body surface area and any lower values of these estimates define different stages of chronic kidney disease (CKD). Common causes of CKD include diabetes mellitus, glomerulonephritis, and chronic hypertension. Although the prevalence of CKD increases with age, age itself is not regarded as a true risk factor of the disease (Hill *et al*. 2016) as not everyone would develop it despite an average decrease in renal function with age (Lindeman *et al*. 1985).

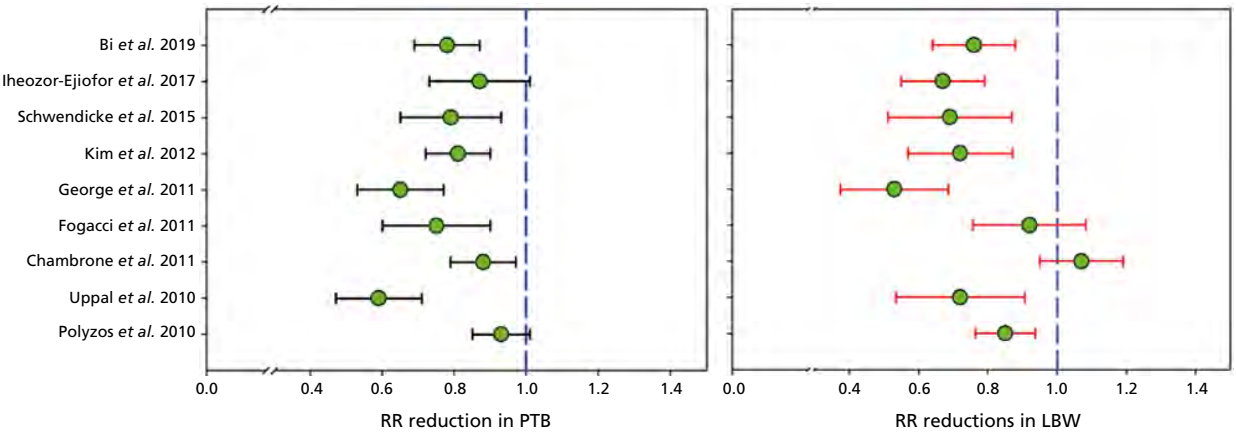

Fig. 17-5 Scatter plot with error horizonal lines of reported adjusted relative risk reductions in adverse pregnancy outcomes (preterm birth [PTB] and low birth weight [LBW]) after periodontal treatment in previous systematic reviews and meta-analysis of the association between periodontal treatment and adverse pregnancy outcomes.

There are various possible causes to explain the link between periodontitis and CKD. Firstly, patients with severe CKD are likely to have an altered immune system because of impaired function of T- and B-lymphocytes as well as monocytes and macrophages (Chatenoud *et al*. 1990; Girndt *et al*. 2016). This could result in a compromised host response to any microbial challenge. In addition, some studies suggested that patients undergoing dialysis are less motivated to maintain good oral hygiene measures because of the intense burden and time-consuming treatment sessions (Borawski *et al*. 2006; Buhlin *et al*. 2007). Confounding diseases like diabetes mellitus and hypertension, which are both major risk factors of CKD, could also further contribute to the severity of periodontitis. A strong association between diabetes and periodontitis could therefore secondarily explain why in patients with CKD, signs of periodontal inflammation and bone loss are observed. Additional confounding variables include age, access to health care or dental care, and renal failure complications (Chen *et al*. 2011a, b).

Evidence supporting the notion that periodontitis triggers a chronic inflammatory response has been reviewed earlier in this chapter. Increased systemic inflammation and oxidative stress burden has been reported in patients with periodontitis and CKD (Ioannidou *et al*. 2011) and it has been directly associated with raised incidence of future CVD events (Arici & Walls 2001; Mathew *et al*. 2008).

Additional evidence on the role of specific periodontitis pathogens, such as *P. gingivalis*, confirmed their presence in epithelial cells, smooth muscle of renal mesangial cells, and neutrophils and macrophages (Kozarov 2012). An increased bacterial load in the systemic circulation is shown to add to the existing inflammatory burden in the renal tissues when examining the association between periodontitis and CKD (Castillo *et al*. 2007; de Souza *et al*. 2007; Stenvinkel 2002; Takeuchi *et al*. 2007).

Epidemiologic evidence

Observational evidence

A series of cross-sectional studies appeared after the year 2000 suggesting a close link between periodontitis and CKD. The first study reported an analysis of data from 5537 participants in the ARIC study confirming that those with either moderate or severe periodontitis had greater odds of eGFR of <60 mL/min/1.73 m^2 when compared with those with no periodontitis or only gingivitis (Kshirsagar *et al*. 2005). Similar estimates were published following the analysis of 6199 participants in the 2001–2004 NHANES study; participants with periodontitis had greater than two-fold higher odds of CKD (Grubbs *et al*. 2011). Evidence of association between exposure to periodontal infections (assessed by IgG antibody levels to specific periodontal pathogens) and impaired renal function was found both in the ARIC (Kshirsagar *et al*. 2007) and NHANES III datasets (Fisher *et al*. 2008). Less conclusive is the evidence reported on the association between periodontitis and kidney function during dialysis with some studies demonstrating that periodontitis was associated with hypoalbuminemia (Kshirsagar *et al*. 2007) and with increased cardiovascular disease- associated mortality (Chen *et al*. 2011a) whereas others reported no association (Castillo *et al*. 2007; Gavaldá *et al*. 2008; Garcez *et al*. 2009; Vesterinen *et al*. 2011).

The first systematic review on the available evidence on the association between periodontitis and CKD concluded that patients with periodontitis had 1.7 greater odds (95% CI 1.4–2.0) of having CKD compared with participants without periodontitis (Chambrone *et al*. 2013). Following up on these results, two separate meta-analyses of cohort studies reported that periodontitis was associated with significant increased risk of incident CKD (RR = 1.73; 95% CI 1.17–2.56) (Deschamps-Lenhardt *et al*. 2019) and of all-cause death when periodontitis was diagnosed (RR = 1.25; 95% CI 1.05–1.50) (Zhang *et al*. 2017).

A summary analysis of cross-sectional surveys expanded on the association between periodontitis and increased odds of CKD (ranging from 1.60 to 1.88) suggesting that these estimates increased with greater severity of periodontitis and accelerated the progression to CKD (OR of association between severe periodontitis and CKD of 2.26; 95% CI 1.69–3.01) (Kapellas *et al*. 2019). This finding was corroborated by Chang *et al*. (2017) who followed 2831 patients over 10 years and reported that periodontal probing pocket depth measures >4.5 mm were associated with faster progression of CKD (HR = 3.1; 95% CI 2.0–4.6).

Experimental evidence

Limited evidence is available on the effects of periodontal treatment on the management of CKD and its complications. A non-randomized trial confirmed that periodontal therapy in 21 predialysis patients and 19 patients without clinical evidence of kidney disease produced improved oral health outcomes, but it was underpowered to show an improvement in renal function (Artese *et al*. 2010). A further study carried out on patients on dialysis found that periodontal therapy was associated with significant reductions in systemic inflammatory biomarkers including hsCRP, IL-6, and serum pro-hepcidin levels (Vilela *et al*. 2011). These results were further confirmed by three additional randomized trials demonstrating that periodontal therapy may not only have a beneficial effect on markers of systemic inflammation, but also renal specific markers such as cystatin C, albumin, and creatinine (Graziani *et al*. 2010; Almeida *et al*. 2017; Grubbs *et al*. 2020). In a recent randomized trial conducted on patients suffering from periodontitis and type 2 diabetes, non-surgical and surgical periodontal therapy was associated with an improvement of kidney function as assessed by eGFR compared with patients who received just scaling and polishing of their teeth over a 12 month period (D'Aiuto *et al*. 2018). The improvement of kidney function was also associated with improved metabolic control, vascular function, and reduced systemic inflammatory burden.

Cognitive decline/dementia

Biologic mechanisms

Alzheimer's disease is the main cause of dementia and one of the great health care challenges of the 21st century. The disease is still defined by the combined presence of amyloid and tau, but researchers are gradually moving away from the simple assumption of linear causality as proposed in the original amyloid hypothesis. The disease is characterized by three clinical phases: a preclinical phase with no symptoms but a distinct pathology, a prodromal phase characterized by cognitive decline and disease-specific lesions. and lastly by the dementia phase. Specific lesions of Alzheimer's disease include neuritic plaques (filaments of beta-amyloid), neurofibrillary tangles (bundles of tau protein), inflammation, and neuronal degeneration. Tau is a crucial component of the neuronal cytoskeleton and its hyperphosphorylation leads to disassembly of microtubules and neuronal functional dysfunction with progressive brain atrophy (Livingston *et al*. 2020).

Hypothetical mechanisms involved in the development of Alzheimer's disease, included (1) amyloid accumulation (Selkoe & Schenk 2003); (2) an uncontrolled inflammatory process affecting neuronal components (McGeer & McGeer 2002); and (3) an infectious hypothesis (Miklossy 2011).

Experimental models of periodontitis including by *P. gingivalis* infection have been linked to increased endotoxemia, brain inflammation, cortical expression of amyloid β42 and β40, and cognitive dysfunction. This concept has been confirmed by several preclinical and clinical studies demonstrating how dysbiotic disorders (including oral dysbiosis) are implicated in Alzheimer's disease pathogenesis (Kamer *et al*. 2009, 2015; Noble *et al*. 2014; Naorungroj *et al*. 2015). Convincing evidence of a possible role of this periodontal pathogen in dementia confirmed that blocking toxic proteases from *P. gingivalis* with drug inhibitors could alter brain colonization and neurodegeneration in an experimental animal model (Dominy *et al*. 2019).

Epidemiologic evidence

Observational evidence

Current evidence consistently suggests that chronic inflammatory diseases increase Alzheimer's disease risk (Kamer 2010). More than 25 observational studies have closely examined the association between periodontitis and cognitive/decline and Alzheimer's disease. Four out of six case–control studies and five out of seven cross-sectional studies reported an association between periodontitis and Alzheimer's disease (Nadim *et al*. 2020). Fourteen cohort studies (seven with prospective and seven with a retrospective design) involving 428 575 participants over a median follow-up of 9 years, concluded that periodontitis or surrogate measures of poor oral health are associated with greater hazard ratios of Alzheimer's disease ranging from 1.06 (95% CI 1.01–1.11) to 2.54 (95% CI 1.30–3.35) (Kamer *et al*. 2020). Similar estimates were reported in cohort studies investigating the association between periodontitis and cognitive decline (Ide *et al*. 2016; Sung *et al*. 2019; Demmer *et al*. 2020). Further in a systematic review and meta-analysis, Leira *et al*. (2017) reported that the association between periodontitis and dementia could be dose dependent with increasing relative risks ranging from 1.86 (95% CI 0.89–3.91) for moderate up to 2.98 (95% CI 1.58–5.62) for severe periodontitis.

Experimental evidence

There is still insufficient evidence on the potential effect of treatment of periodontitis on the onset and progression of Alzheimer's disease. Due to the slow and progressive nature of the disease, it is plausible to hypothesize that any potential benefit in promoting periodontal health in intervention trials would be appropriate if performed during the preclinical and prodromal phase of Alzheimer's disease. A number of logistical and feasibility challenges are faced by researchers who approach this area, but they are not dissimilar, for instance, to those we reviewed earlier in this chapter (larger and long-term studies with ethical considerations of no treatment for periodontitis). Preliminary evidence from Yamamoto *et al*. (2012) suggested that participants (n = 220, ≥65 years of age) who did not attend a dentist regularly had higher hazard ratios for dementia of 1.76 (95% CI 0.96–3.20) when compared with those who had regular dental care (HR 1.44; 95% CI 1.04–2.01). A further small but uncontrolled clinical trial involving 29 patients with mild to moderate Alzheimer's dementia who underwent periodontal treatment, confirmed an improvement in a measure of self-reported and functional cognitive decline (Rolim Tde *et al*. 2014).

Cancer

Biologic mechanisms

Cancer represents still one of the major killers among the non-communicable diseases. Despite great efforts in understanding the pathogenesis of the various forms of cancer, there is still limited evidence on the exact interplay between genetic, environmental, and acquired factors responsible for the development and progression of cancer. Recent evidence suggests that modulating the inflammatory and immune response to specific forms of cancer is set to revolutionize the management and survival rates of the disease. A growing interest in linking chronic infectious/inflammatory diseases like periodontitis and cancer has been reported. The combination of infectious agents and deregulated inflammatory response have been advocated as biological mechanisms linking periodontitis and cancer.

Systemic inflammation for example can increase the risk of development of precancerous and malignant lesions (Siemes *et al*. 2006; Trichopoulos *et al*. 2006; Gunter *et al*. 2011) and cancer development (Federico *et al*. 2007). The presence of severe periodontitis has been claimed to favor the development of phenotypic changes in the mononuclear cell–cytokine system, causing an increased inflammatory response upon exposure to bacterial lipopolysaccharide (Hernichel-Gorbach *et al*. 1994). Diabetes as comorbidity to periodontitis could also increase the risk of cancer development based on the increased inflammatory response and the presence of advanced glycation end product receptor ligands which can directly promote carcinogenesis by stimulating cancer cells and modulating cellular growth in the tumor microenvironment (Logsdon *et al*. 2007). Further, dietary limitations and in particular the assumption of proinflammatory nutrients deriving from tooth loss and masticatory difficulties due to periodontitis have been claimed to increase the risk of cancer development (Mazul *et al*. 2018; Namazi *et al*. 2018).

A variation in bacterial colonization has been observed when comparing oral cancer sites with unaffected areas, suggesting that bacterial microflora may be related to the risk of cancer development (Basith *et al*. 2012; Pushalkar *et al*. 2012). Subgingival bacterial production of endotoxins, metabolic by-products, and enzymes can modify the response of proto-oncogenes and tumor suppressor genes, and potentially interfere with the normal cellular cycle in terms of cellular proliferation and survival (Nwizu *et al*. 2020).

Epidemiologic evidence

Observational evidence

Despite a substantial lack of studies with standardized and comparable methods to speculate about the association between periodontitis and cancer, preliminary evidence suggests a possible link between the two diseases. In a recent systematic review and meta-analysis, 10 studies aimed at investigating the association between periodontitis and total cancer risk were reviewed (Corbella *et al*. 2018). Considering hazard ratios, a statistically significant association of diagnosis of periodontitis was found for all cancers studied (1.14; CI 95% 1.04–1.24) as well as individual cancers; digestive tract cancer (1.34; CI 95% 1.05–1.72), pancreatic cancer (1.74; CI 95% 1.21–2.52), prostate cancer (1.25; CI 95% 1.04–1.51), breast cancer (1.11; CI 95% 1.00–1.23), corpus uteri cancer (2.20; CI 95% 1.16–4.18), lung cancer (1.24; CI 95% 1.06–1.45), hematological cancer (1.30; CI 95% 1.11–1.53), esophagus /oropharyngeal cancer pooled together (2.25; CI 95% 1.30–3.90) and non-Hodgkin lymphoma (1.30; CI 95% 1.11–1.52). Another systematic review confirmed that patients with oral cancer exhibited increased clinical attachment loss, plaque index, bleeding on probing, and radiographic bone loss (Colonia-Garcia *et al*. 2020). Further, limited evidence was available on the possible association between periodontitis and other forms of cancer (i.e. liver, prostatic, hematological, and genitourinary).

Experimental evidence

Limited evidence is available on the potential benefit of improving periodontal health on the onset or progression of a specific form of cancer. Lee *et al*. (2014) found a reduced esophageal cancer risk in males undergoing dental prophylaxis. However, the lack of information regarding the periodontal status

following the treatment and the influence of potential risk factors could have influenced the results. Another study confirmed that the performance of periodontal treatment could reduce the risk of oral cancer (Moergel *et al*. 2013). Although it appears that periodontitis may be related to cancer development, especially in the upper gastrointestinal tract, the causality between periodontitis and risks for all cancers needs further investigation, as multiple methodological and confounding factors exist. Moreover, among the factors that hinder the direct comparison of different studies regarding cancer occurrence in periodontally affected patients, are the different definitions and measurement of periodontitis severity used, the smoking status of the patients, and the relatively scarce number of experimental studies. Nevertheless, the role of oral and systemic inflammation appears of utmost importance to better understand the pathogenetic mechanism behind the potential association between periodontitis and cancer risk.

Conclusion

Somewhat provocatively, it has been stated that modern science tends to *recycle* ideas from the past. This notion certainly applies to some extent to the association between periodontitis and systemic health outcomes. Our views have certainly evolved since the times when the "focal infection" theory prevailed, and our reaction to the potential threat that oral infections may pose to general health are more measured and are geared towards prevention and anti-infective/anti-inflammatory approaches rather than indiscriminate dental extractions. As discussed in this chapter, the proposed associations are not only biologically plausible, but the magnitude of the biologic effects of periodontal diseases on general health outcomes is gradually being refined. It is increasingly evident that periodontal treatment results in lower levels of systemic inflammation, at least in patients who already have another comorbidity (i.e. diabetes). This impact on the host could well represent the main mechanism through which periodontitis influences the onset and progression of several chronic diseases.

Drawing any firm conclusions on whether periodontitis causes other non-communicable diseases is influenced by the limited data on long-term benefits of reduction of new clinical events or complications. This situation is particularly true for chronic diseases, such as periodontitis, that require long-term management but that are predominantly driven by a fine interplay between patients' compliance/behavior and effective dental and periodontal care. Larger and longer clinical trials will be eventually required to demonstrate whether or not periodontitis is a risk factor for poor systemic health outcomes. Ongoing research will hopefully clarify these issues in the near future. It is important to note, however, that we have not reviewed a plethora of studies linking periodontitis with other non-communicable diseases (i.e. inflammatory diseases, arthritic diseases, pulmonary infections and diseases. and many more); hence we urge the reader not only to be aware of these associations but to approach and critique the evidence available with an open-minded spirit.

Expert recommendations from consensus workshops on the association between periodontitis and systemic health outcomes have been published with the aim of easier interpretation of the published evidence for oral health professionals. There are some common motifs in these clinical recommendations such as; (1) to inform and communicate with patients that periodontitis is closely interlinked with other comorbidities and in particular it does share several of the common risk factors responsible for most of these non-communicable diseases; (2) to provide oral health education and a personalized oral hygiene regime as part of an oral examination that includes a comprehensive periodontal evaluation consisting of full-mouth probing and bleeding scores; (3) if no periodontitis is diagnosed, patients should be placed on preventative programmes with regular monitoring (at least once a year) whereas if periodontitis is diagnosed, they should be managed as soon as their systemic health status permits. Appropriate and effective mechanical non-surgical periodontal therapy should be provided as well as dental rehabilitation to restore adequate mastication for proper nutrition. Oral health professionals should also be weary of and diagnose/manage other common oral diseases, especially in high-risk patients (i.e. with diabetes or with immune-suppression disorders) including dry mouth, burning mouth, candida infections, and dental caries.

If a patient with periodontitis presents with established cardiovascular disease, the patient should be informed of the potential risk of suffering future additional cardiovascular complications and they should actively manage their cardiovascular risk factors (such as diabetes, obesity, smoking, hypertension, hyperlipidaemia, and hyperglycaemia). Lastly their periodontitis should be managed as soon as their cardiovascular status permits, and this should be discussed with the relevant general or specialist medical practitioner in charge of the patient's care (Sanz *et al*. 2020).

Patients with diabetes should be advised that they have an increased risk for gingivitis and periodontitis. They should also be told that if they suffer from periodontitis, their glycaemic control may be more difficult to achieve, and they are at higher risk of other complications, such as eye, kidney, and cardiovascular diseases. Initial mechanical periodontal therapy should be provided as soon as feasible, as this may help to improve glycaemic control (Sanz *et al*. 2018).

If the oral health professional is dealing with a female patient during pregnancy, all of the above would apply as soon as the stage of pregnancy has been confirmed. The patient should be made aware

of the potential association between the presence of periodontitis and adverse pregnancy outcomes. It is important to emphasize that all preventive, diagnostic, and therapeutic oral procedures are safe throughout pregnancy and that these measures are effective in improving and maintaining oral health. In particular, non-surgical periodontal therapy (scaling and root surface instrumentation) and extractions are safe during pregnancy, and especially during the second trimester of gestation (Figuero & Sanz 2020).

All the evidence to date underscores that the oral cavity is an integral part of the human body, and that "health" must encompass oral – and periodontal – health as well. Periodontal medicine has provided a unique opportunity for oral health professionals and researchers to expand their investigative sphere, interact fruitfully with colleagues in medicine, and acquire more knowledge.

Irrespective of the definitive conclusions of these research efforts, their byproducts may prove to be just as important as the elucidation of the research task *per se*.

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Chapter 18

Periodontitis and Systemic Diseases (Cardiovascular Disease and Diabetes): Biological Perspectives for Oral/Periodontal Implications

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Introduction

The mouth was recognized as a site of infection in the human body since ancient times. In modern medicine, "focal infection" was defined to describe this observation (Miller 1891a). At the beginning of the nineteenth century, when dentistry was becoming an independent discipline with only a handful of dental schools in the world, the focal infection theory was a revolutionary thought. It highlighted the oral cavity as a place where bacteria originated from and disseminated to other sites of the body, eventually causing disease. With this theory, the human body was connected, and the oral cavity was linked to overall health. Dental and oral diseases were seen as the root cause for systemic inflammation; thus, elimination of oral inflammation was a prerequisite to prevent/treat systemic diseases. Ironically, this approach has led to serial extractions of teeth as a "cure" for "gum diseases" and elimination of the infectious "foci" from the body (Miller 1891b; Hale 1931) instead of increased awareness of the prevention of oral diseases and care for oral health. As a result, extensive and unnecessary extractions were performed where edentulism and replacing the permanent teeth with dentures, "the third set of teeth", became rampant. The focal infection concept was abandoned, and the oral cavity and the rest of the body were once again disconnected.

After two world wars and global turmoil, the oral and systemic health link was revisited. Leonard

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

(1946) described that patients with periodontal disease could have systemic problems. In their landmark publication, Karshan *et al*. (1946) linked systemic abnormalities in blood chemistry to periodontal diseases and noted that this link could be bidirectional. In a symposium focused on periodontal disease and systemic health in 1949, pregnancy, diabetes, and leukemia were recognized as systemic diseases with possible associations with periodontal diseases. The first reference to the link between cardiovascular diseases and periodontal diseases was made in 1970 (Brasher & Rees 1970). To date, more than 5000 publications in the English language have reported evidence on the association between oral and systemic health.

While most of the early work was focused on the impact of diet on periodontal health, histological data from animal studies suggested that the link between oral and systemic disease processes was highly complex (Shklar 1974). More than 50 systemic diseases and conditions have been associated with various forms of periodontal diseases either through shared pathways of inflammation, microbial involvement, or a combination of infecto-inflammatory mechanisms. The appreciation of the complexity of periodontal disease pathogenesis as a result of oral immunology, a new scientific field, and recognition of inflammatory pathways of disease in the 1980s paved the way for the understanding of the periodontal–systemic disease link. In this complicated relationship, systemic conditions increase the risk of incidence, severity, and progression of periodontal diseases. In turn, periodontal diseases may negatively impact systemic health. Thus, there exists a bi-directional link between systemic and periodontal diseases. This observation was first coined for the diabetes–periodontal disease link (Taylor 2001) and is now increasingly applied to other systemic diseases.

We will focus on two systemic diseases and present the biological plausibility of their connection to periodontal diseases: diabetes and cardiovascular diseases. In addition to affecting human populations globally, diabetes and cardiovascular diseases have well-established associations with disruptions in periodontal health. Thus, the knowledge gained applies to the understanding of a generalizable link between periodontal diseases and systemic pathologies. We will refer to the atherosclerotic forms of coronary heart disease (angina pectoris, myocardial infarction), ischemic stroke, and peripheral arterial diseases, which all present with inflammatory pathogenesis.

Plausibility of periodontal disease as a risk factor for diseases at distant tissues

The original hypothesis of how periodontal diseases and systemic diseases could be connected proposed three mechanisms: metastatic infections, dissemination of bacterial toxins, and immunological injury (Thoden van Velzen *et al*. 1984). A metastatic spread of microbes (and their products) or inflammatory mediators or both with an unclear immunological injury were suggested to mediate the local tissue disturbances in the periodontium to the distant organs. This approach presenting a linear plausibility, is overly simplistic. Complex diseases that involve both the infection and inflammation consist of a series of highly complex microbiological and immune mechanisms. Whereas circulation can transport the microbes between organs, colonization and pathological consequences of microbial infections at "non-origin sites" are much more complicated processes. Indeed, systemic bacteremia as a result of periodontal infection is rare. To date, only certain species of periodontal bacteria have been recovered from other organs. The underlying reason for the colonization of certain periodontal bacteria of specific extraoral sites while other species cannot is poorly understood. With the advancement of modern molecular microbiological techniques such as pan-metagenomics, we also recognize the complexity of microbe–microbe interactions and appreciate the highly sophisticated spatial organization and site-specificity of microbial communities. Thus, free and random migration of one species from one body site to another is possible but does not necessarily explain the colonization and habitat-building of oral bacteria in non-oral sites.

The concept of inflammatory metastasis is even more complicated. In theory, the inflammatory mediators originated from periodontal inflammation in local tissues can get into the systemic circulation and reach other parts of the body. Cellular and molecular mechanisms of disease can be associated with the levels of these mediators. However, this simplistic view dismisses the complexity of tissue architecture and specificity in different organs. Inflammation is an active process that requires receptor–ligand interactions to progress and resolve and, therefore, protect the host from damage. There is a redundancy of cytokines, chemokines, lipid mediators, and other soluble factors produced from multiple sources and several cell types. Increasing evidence suggests that many cell types, including those that are not immune system cells, are capable of producing the inflammatory mediators, which complicates the linearity of the inflammatory spread paradigm. The inflammatory process is not linear or sporadic; it is continuous and involves multiple overlapping processes and phases with the goal of survival of the organism. Therefore, immunologic dissemination of cellular or soluble structures spreading the inflammation requires a complex mechanism to be associated with the disease process elsewhere in the body.

In the light of technological advances of the last decade and with the help of -omics, the modern view of periodontal disease pathogenesis and its connection to systemic diseases requires a holistic approach. We now recognize the importance of a commonality of similar pathways of diseases that are now

called comorbidities. All clinical forms of periodontal diseases involve an intimate interaction between the specialized microbiome communities and host responses to these communities. Understanding the role of infecto-inflammatory stimulation of the immune cells and non-immune cells of the periodontium in the oral–systemic link, therefore, has led to a paradigm shift (Hasturk & Kantarci 2015).

If one sees the human body as a single entity, a local disruption of the homeostatic balance cannot be merely observed as an isolated phenomenon. The cells and mediators of the inflammatory response are unlikely to remain confined to the organ system in question. Oral tissues, being a niche for one of the most diverse human microbiomes, are never sterile. Commensal species in oral biofilms always have the potential of becoming pathogenic. The evolutionary interaction between the host and the microbiota has led to the development of a highly specialized host response in periodontal tissues where the epithelia and vasculature demonstrate considerable anatomical differences compared with the rest of the body. As a function of this complex interaction, the immune cells travel to distant organs through the systemic circulation. The immune system cells can be challenged by periodontal bacteria and transmit the inflammatory response to other organs (Hayashi *et al*. 2010). Dendritic cells, which are traditionally seen as the "presenters" of antigens, can also serve as "transporters" of bacteria and their virulence factors (Miles *et al*. 2014). The concept of a "mobile oral microbiome" may involve the host's immune system for migration and colonization of the oral resident microbial species to distant organs (Han & Wang 2013).

Plausibility of systemic dissemination of oral bacteria

Periodontal diseases are associated with complex microbiomes. Each microbiome in the oral cavity is distinct. Supra- and subgingival microbiomes are directly associated with periodontal diseases. The other mucosal surfaces (e.g. tongue dorsum) may serve as niches for microbial communities that can spread between different ecological habitats of the oral cavity. Oral bacterial species can enter the circulation following brushing and flossing or professional interventions such as scaling, tooth extraction, and periodontal probing. Although rare, a higher risk of bacteremia may be associated with gingival inflammation and periodontal diseases (Tomas *et al*. 2012; Balejo *et al.*, 2017). Thus, systemic dissemination of microbial species is plausible, supporting the theory that periodontal disease-associated microbes can metastatically cause systemic pathologies in distant organs.

In principle, all microbial organisms and their products can travel throughout the body via the circulation. Bacteremia, which involves the presence of bacteria in the blood and its compartments, results in sepsis. Since bleeding is a common sign and symptom of periodontal inflammation, every time the periodontal pocket bleeds, microbial communities or single species can potentially enter the blood circulation. Circulating microorganisms and their products can be the result of disease activity or due to a mechanical injury by periodontal procedures such as probing or scaling. There is conflicting data on how many bacteria can be found in the systemic circulation following an active burst of periodontal disease, after bleeding on probing, or due to mechanical instrumentation (Lockhart *et al*. 2004; Lockhart *et al*. 2008; Hirschfeld & Kawai 2015). The lack of consensus to this end may be the result of differing sensitivities of detection methods for bacteria and the timing of the bacteremia (Bahrani-Mougeot *et al*. 2008). While bacteremia is an accepted phenomenon (Kinane *et al*. 2005; Crasta *et al*. 2009), it, therefore, remains unclear whether sepsis/septicemia could be the result of periodontal infection or instrumentation.

Nevertheless, periodontal bacteria have been recovered from distant organs and were associated with pathological processes. For example, *Fusobacterium nucleatum* is commonly linked to various forms of cancer (e.g. pancreatic or colon carcinoma) and found in the amnion and placenta associated with adverse pregnancy outcomes. Other periodontal pathogens and their virulence factors (e.g. proteases) were also isolated from distant organs such as the aorta (Deshpande *et al*. 1998; Yumoto *et al*. 2005; Takahashi *et al*. 2006) and brain (Miklossy 2011; Poole *et al*. 2015; Laugisch *et al*. 2018). Cardiovascular lesions have been shown to harbor *Porphyromonas gingivalis* and its virulence factors (Cairo *et al*. 2004; Marcelino *et al*. 2010; Nichols *et al*. 2011; Figuero *et al*. 2014; Range *et al*. 2014; Velsko *et al*. 2014; Ziver *et al*. 2014; Szulc *et al*. 2015; Velsko *et al*. 2015; Kannosh *et al*. 2018; Joshi *et al*. 2019). Recently, gingipains from *P. gingivalis* were detected in the brains of patients with Alzheimer's disease (Dominy *et al*. 2019). The list of periodontal bacteria that can colonize non-oral and distant sites of the body is increasing parallel to the advancement of microbiological detection techniques. The animal models support these human clinical observations. In addition to the bacteria, their products, such as lipopolysaccharides, may be derived from the periodontal microbiota and enter the circulation, presenting a potentially plausible mechanism through which periodontal bacteria can be associated with systemic diseases. How this dissemination takes place and whether the severity of periodontal diseases is associated with the spread of the bacteria is, however, not straightforward. It is also unclear how the periodontal bacteria colonize specific distant organs. An important question is the number of bacteria entering local circulatory routes in local tissues and traveling through the systemic circulation. How many bacteria enter the circulation, and how many are required to cause disease elsewhere in the body? Which organs are more susceptible to

oral bacteria, and why? Regardless of the number of bacteria, a healthy immune system can eliminate and eradicate the invaders quite efficiently. However, is a dysfunctional immune response a prerequisite for the initiation and progression of inflammatory diseases due to migrating bacteria? Is the detection of oral/periodontal bacteria in a distant organ associated with a non-septic transmission of microbial species that are linked to a failed immunologic clearance? These questions need to be addressed.

The duration of bacteremia until the clearance is also critical. Infectious diseases such as tuberculosis and viral infections (e.g. HIV) can lead to a latency of infection, which is essential for the disease outcome. Days to weeks may be required before a full-blown infection and mounting the consequent host response. For oral bacteria disseminating to other parts of the body, this knowledge is limited. According to Koch's postulates, a single species can cause a systemic disease if enough time lapses between the inoculation and infection. This concept has been illustrated in animal models when species animals were inoculated with periodontal bacteria (Gradmann 2014; Kantarci *et al*. 2015). In humans, however, ethical concerns prevent direct inoculation and experimental transfer of periodontal pathogens. Even when interindividual transfer is possible between spouses (Dowsett *et al*. 2002; Van Winkelhoff & Boutaga 2005), there is no clear evidence that either periodontal infections or systemic infections can be attributed to the periodontal microbiota that is introduced. A modification of Koch's postulates was presented by Socransky and Haffajee (1992) to address these limitations.

Another critical factor is the colonization capacity of oral species on non-dental and non-oral surfaces. *in vitro;* models demonstrated that all cell types and structures of the human body could present favorable environments for colonization of individual or multiple oral species under controlled environmental conditions in the laboratory. However, *in vivo;* studies in humans and animals suggest a site-specificity. Periodontal species or their genetic material were found in cardiovascular tissues (Deshpande *et al*. 1998), suggesting that vessel walls can be potential growth sites for pathogenic periodontal microbes such as *Porphyromonas gingivalis*. Likewise, bridging species such as *Fusobacterium nucleatum* have been found in amniotic fluid (Han *et al*. 2004). This area of research needs further exploration, especially in the context of artificial surfaces generated for the repair of different organs and how periodontal species can colonize these.

Inflammatory processes as a link between periodontal and systemic diseases

Clinical and progressive causality between inflammatory diseases cannot be tested in humans; thus, preclinical *in vivo;* systems, *in vitro;* models, and therapy studies are needed. Based on well-designed epidemiological studies, people with periodontal diseases present a higher risk for systemic inflammation, possibly due to an inflammatory predisposition (Holtfreter *et al*. 2013; Boylan *et al*. 2014). Periodontal disease is a chronic inflammation and shares common mechanistic pathways with other systemic inflammatory diseases. There are co-morbid associations between periodontitis, diabetes, and cardiovascular diseases (Sanz *et al*. 2013; Tonetti *et al*. 2013; Chapple & Wilson, 2014; Payne *et al*. 2015).

Periodontal inflammation presents highly intertwined molecular pathways of cellular and non-cellular components and immune and non-immune processes that maintain periodontal health. A healthy periodontium is resistant to microbial intrusion. The epithelial lining of the sulcus wall presents a multilayer barrier to commensal microbes residing in periodontal space. Even in the absence of disease, there is an inflammatory response against microorganisms. At this stage of the homeostatic inflammatory process, the key players are epithelial cells, endothelial cells, complement proteins, neutrophilic granulocytes, and tissue-resident macrophages. Under these "healthy" conditions, the epithelial lining of the sulcus prevents or minimizes bacterial infiltration; vasculature allows balanced extravasation of neutrophils, which will eliminate the microbial organisms and their products through a precise phagocytic and killing mechanism. Neutrophils are short-lived; they are cleared by apoptosis by the other neutrophils and tissue-resident macrophages through a process that ensures the balance of the inflammatory response regulated by cytokines and lipid mediators or inflammatory activation and resolution to prevent tissue damage. Under normal conditions, the resolution of inflammation is an active process and requires a well-orchestrated immune response (Kantarci *et al*. 2006; Hasturk 2012b).

Progression of health to disease in periodontal tissues is a result of unresolved inflammation that becomes chronic. Antigen-presenting cells and lymphocytes join phagocytes, endothelial cells, and fibroblasts gain proinflammatory characteristics, and there is a continuous propagation of neutrophilic and monocytic infiltration to the periodontal tissues. The epithelial lining of the periodontal pocket serves as a gateway for microorganisms leaving the periodontal space and entering the body. Epithelial cells stimulated by the periodontal bacteria recruit an increasingly higher number of neutrophils, a process regulated by chemokines such as interleukin-8 (IL-8). Neutrophil priming results in preactivation of these non-specific immune cells; upon an additional stimulus (e.g. lipopolysaccharides and various microbial factors), primed neutrophils respond with an increased function. Neutrophils have been demonstrated to be primed in various forms of periodontal diseases (Fredriksson *et al*. 2003; Kantarci *et al*. 2003; Matthews *et al*. 2007; Wright *et al*. 2008). The priming of neutrophilic granulocytes can be due to genetics, microbial stimuli, hyperglycemia, smoking, and various other

factors. Primed neutrophils, in turn, will respond to secondary stimuli producing increased levels of reactive oxygen radicals and enzymes. These substances are typically produced to eliminate the bacteria, viruses, and apoptotic cells and return to baseline levels when inflammation resolves. Excessive neutrophil function results in neutrophil-mediated tissue injury of the host. One of the fundamental mechanisms through which neutrophils can link inflammatory processes of distant organs is the transmission of the uncleared bacteria and their products to escape the immune surveillance of the host. This mechanism is referred to as the "Trojan horse" effect (Laskay *et al*. 2003; Eruslanov *et al*. 2005; Fexby *et al*. 2007; Thwaites & Gant 2011; Gutierrez-Jimenez *et al*. 2019; McDonald *et al*. 2020) and would explain how the oral bacteria can be recovered from other sites of the human body.

Chronic and unresolved inflammation also leads to a "leaky" epithelium. A pathological transformation of the epithelial barrier is a critical component of allowing the gut microbiome to disseminate to the other parts of the body, including the brain. It is not entirely clear whether the same modification of the periodontal pocket epithelium takes place and if there are any specific changes inherent to the periodontium; however, this mechanism presents a plausible link between local and systemic diseases through an infecto-inflammatory pathway.

Monocyte infiltration to the diseased periodontal tissues has profound repercussions. Similar to the neutrophils, a preactivation/priming can be seen in monocytic cells. Monocytes differentiate into tissue-resident macrophages with a wide array of functions and a longer life. Macrophage-mediated tissue damage is a critical component of the periodontal pathology. M1-type macrophages, which are involved in the activation of tissue inflammation, are increased, secrete cytokines, tissue-degrading enzymes, and lead to increased activation of the lymphocytic infiltration. M1-macrophages lead to tissue damage through the activation of osteoclastic bone loss, fibroblastic matrix metalloproteinase production, and the endothelial cell activation–pathological process that creates a favorable environment for bacterial invasion. Monocyte-mediated tissue inflammation as a hallmark of hyperglycemia in diabetes and atherosclerosis in cardiovascular diseases is a highly plausible link between periodontal disease and systemic diseases.

A net outcome of increased phagocyte activation is the expansion of immune response to T-cell mediated tissue damage. T-helper 17 (Th17) cells are critical for immunity-driven tissue destruction. This process is referred to as osteoimmunology and includes bone loss as a result of the immune response (Alvarez *et al*. 2019). In addition to the T cells, B-cells were demonstrated to play an active role in the inflammation where the periodontal disease may exacerbate the systemic impact on distant organs (Shin *et al*. 2009; Jagannathan *et al*. 2010).

Biological plausibility of a link between periodontal diseases and cardiovascular diseases

Vascular diseases and their ischemic complications such as myocardial infarction, peripheral vascular diseases, and stroke, lead to morbidity and mortality in cardiovascular tissues. Atherosclerosis is characterized by vascular inflammation and subintimal lipid accumulation. Atherosclerotic plaques may appear early in life and advance to severe, symptomatic "vulnerable" plaques. Rupture of lipid-rich and inflamed coronary plaques triggers thrombosis as in an atherothrombotic event, which can lead to the acute coronary syndrome and sudden ischemic death. Infections and other inflammatory diseases, including HIV and type 2 diabetes, increase the risk for atherosclerotic changes and rupture. As a noncommunicable disease, periodontitis has been shown to impart excess risk for atherosclerosis. The link between periodontal and cardiovascular diseases may involve the metastatic microbial dissemination, inflammatory mediators, and their combination through a dysfunctional endothelium (Tonetti *et al*. 2013; Sanz *et al*. 2019). Low-grade and chronic systemic inflammation is a plausible mechanism through which cardiovascular diseases and periodontal diseases are linked (Carrizales-Sepulveda 2018). This association is bi-directional, where factors involved in the development of cardiovascular diseases also underlie periodontal inflammatory changes. In turn, periodontitis, both as infection and a profound source of inflammatory mediators, leads to the exacerbation of cardiovascular complications. There is a clear epidemiological association between periodontal and atherosclerotic cardiovascular diseases (Dietrich *et al*. 2013). An increased risk of atherosclerotic vascular disease amongst individuals with chronic periodontitis is independent of other established cardiovascular risk factors. In a population-based study from Korea that longitudinally evaluated the risk exposure from untreated oral conditions including periodontal disease and caries, the risk of cardiovascular events, cardiac death, myocardial infarction, stroke, and cardiac failure, was significantly higher, supporting the critical role of periodontal health in patients with cardiovascular risk (Park *et al*. 2019). Figure 18-1 shows the biological plausibility of the link between periodontal and cardiovascular diseases.

Microbial factors

Endothelial cells and their functional roles in vascular integrity are critical for cardiovascular health. Disruption of endothelial function is an early indicator of cardiovascular disease (Vita & Loscalzo 2002; Pober *et al*. 2009; Kolattukudy & Niu 2012). While uncontrolled inflammation is detrimental to endothelial function, the infection can also cause endothelial dysfunction (Vita & Loscalzo 2002; Vaudo *et al*. 2008).

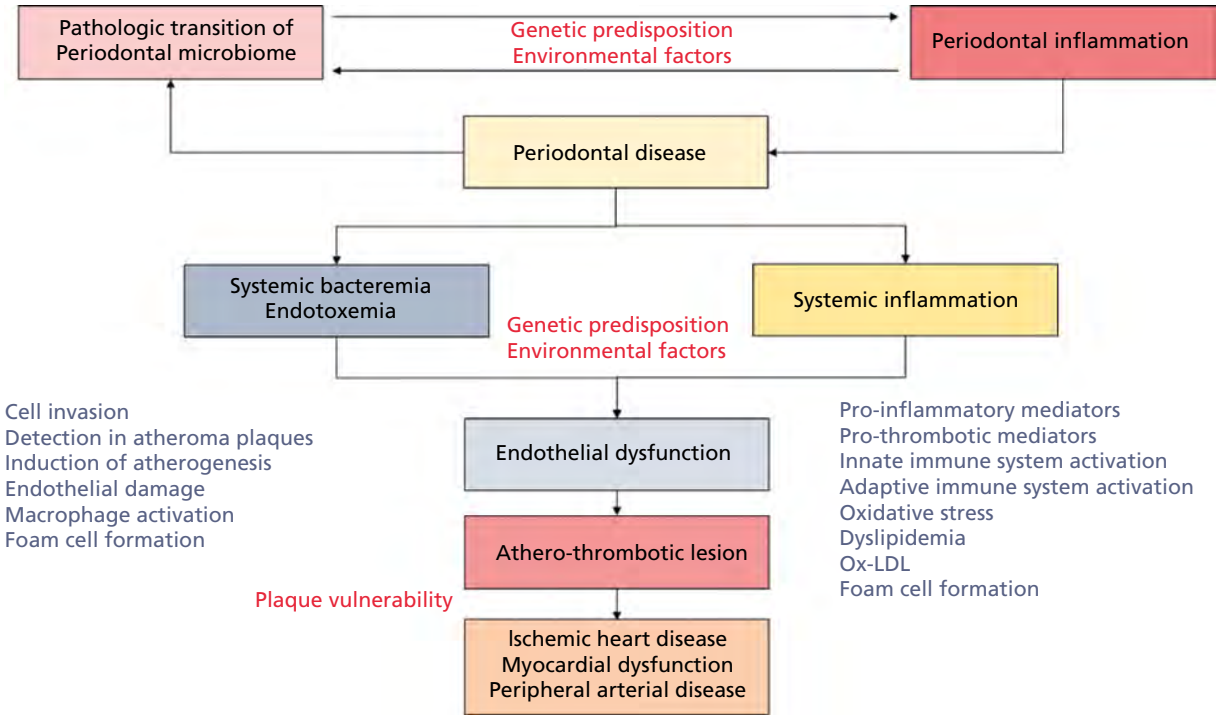


Fig. 18-1 Plausibility of the biological link between periodontal diseases and cardiovascular diseases. Ox-LDL, oxidized low-density lipoprotein.

Fusobacterium nucleatum activates the endothelial cells and promotes an inflammatory phenotype disrupting the vessel-formation capacity of these cells through a hypoxia-mediated mechanism (Mendes *et al*. 2016; Mendes *et al*. 2018). Therefore, an infectious etiology is a potential co-factor for the development of cardiovascular diseases, based on the discovery of co-localization of bacteria in atheromas. An infectious agent can also cause activation of the innate immune system and accelerate atherosclerosis (Richardson *et al*. 1997a, b). Hence, infectious agents (e.g. *Chlamydia pneumonia*) might be an indirect etiological factor for cardiovascular disease providing the necessary inflammatory stimulus (Kuo *et al*. 1993).

Following reports of *Chlamydia* infections to be a risk factor for coronary artery disease in a cardiovascular disease cohort, periodontal infections were strongly associated with the development of atherosclerosis (Mattila 1993). Pathogens from the oral cavity can invade the gingival epithelium and the vascular endothelium and enter atherosclerotic plaque via the bloodstream, which could promote an inflammatory response within the vessel wall or some oral pathogens that produce toxins with proatherogenic action or autoimmune reaction.

Periodontal bacteria are present and cultivable from atheromas (Kozarov *et al*. 2005; Dolgilevich *et al*. 2011). In addition to the periopathogenic species of bacteria, their virulence factors and nucleic acids were isolated from atheroma lesions. There is also a higher association of periodontal microbial invasion of the vascular lesions in patients with periodontitis (Armingohar *et al*. 2014; Mahendra *et al*. 2013). Not only the migration but also the colonization of periodontal species such as *P. gingivalis* and *A. actinomycetemcomitans* in atherothrombotic lesions is plausible. Using 454 pyrosequencing of 16S rRNA, bacteria from the oral cavity and gut were shown to correlate with disease markers of atherosclerosis, specifically atherosclerotic plaque and plasma cholesterol (Koren *et al*. 2011). *Streptococcus* was strongly positively correlated with high-density lipoprotein (HDL) cholesterol and ApoAI (a significant component of HDL), whereas *Neisseria* was strongly negatively correlated with these markers. *Fusobacterium* abundance was positively correlated with low-density lipoprotein (LDL) cholesterol and total cholesterol. Similarly, members of the *Erysipelotrichaceae* and *Lachnospiraceae* families in the gut also positively correlated with LDL cholesterol and total cholesterol.

Analysis of thrombi collected by aspiration during interventions on the coronary arteries of patients who had a myocardial infarction showed 19.7% *A. actinomycetemcomitans*, 3.4% *P. gingivalis*, and 2.3% *T. denticola*. Antibody levels against four major periodontal pathogens, *P. gingivalis, A. actinomycetemcomitans, T. forsythia,* and *T. denticola*, are related to an increased relative risk of myocardial infarction. Clinical studies particularly suggested a direct relationship between the severity of periodontal conditions and left ventricular hypertrophy. *A. actinomycetemcomitans* and *Aggregatibacter aphrophilus* are implicated in 1–3% of all infective endocarditis. Other studies highlighted the critical role of oral *Streptococci* in the development of myocardial infarction. *Streptococcus sanguinis (S. sanguinis)*, a commensal bacterium, profuse in periodontitis, is recognized as an origin of infective endocarditis. Its fimbriae and adhesin facilitate its initial

attachment on the tooth. Then, the production of glucans and eDNA promotes the maturation of *S. sanguinis* biofilm. After accessing the heart, *S. sanguinis* must then adhere to the endocardium. Considering the impact of biofilm formation on adhesion in the oral cavity, it would be conceivable that biofilm formation might be significant for adhesion to endocardial surfaces as well. Indeed, endocarditis is frequently regarded as a model of a biofilm-mediated disease. However, studies have demonstrated that *S. sanguinis* endocarditis causation is not dependent upon biofilm formation. Therefore, in contrast to this situation in the oral cavity, there is no evidence that biofilm formation is important for *S. sanguinis* in the cardiac environment to infective endocarditis (Hashizume-Takizawa *et al*. 2019).

Control of chronic inflammation caused by periodontitis may positively impact the treatment of myocardial hypertrophy, decreasing the risk of acute myocardial infarction. The risk of stroke, described by a meta-analysis of cohort studies, was significantly increased by the presence of periodontitis. Periodontal diseases were significantly correlated with cardioembolic and thrombotic stroke subtypes. Regular dental care utilization was associated with a lower adjusted stroke risk. Pussinen and colleagues have established that *P. gingivalis* may especially be correlated with stroke (Pussinen *et al*. 2007).

Preclinical animal models support human clinical observations. For example, experimental periodontitis induced by a human pathogen (*P. gingivalis*) in mice, rabbits, and pigs led to atheroma formation (Schenkein & Loos 2013; Hasturk *et al*. 2015). *P. gingivalis* can intensify atherosclerosis through the activation of endothelial cells producing specific adhesion molecules that allow macrophage diapedesis and subsequent conversion to foam cells and further atheroma progression. *P. gingivalis* increases the progression of inflammatory plaque accumulation in the arteries with the accumulation of inflammatory mediators and cholesterol esters. Infection with *P. gingivalis* after myocardial infarction in mice enhanced myocardial high mobility group box 1 (HMGB1) expression. HMGB1 is a nuclear protein released from necrotic cells and capable of inducing the inflammatory response. There is a possible relationship between periodontal diseases and postinfarction myocardial inflammation through HMGB-1. Infection with *P. gingivalis* during myocardial infarction generates a prejudicial part in the recuperation procedure of the infarcted myocardium by penetration and invasion of *P. gingivalis* into the myocardium, thus favoring programmed cell death and the MMP-9 action of the myocardium, which successively produces cardiac rupture. Experimental periodontitis in rats was associated with impaired endothelial function in gingival tissues showing that periodontal diseases may generate the disruption of vascular function in oral microcirculation. Other periodontal bacteria species (*Treponema denticola*, *Tannerella forsythia*, and *Fusobacterium nucleatum)* can also cause atheromatous changes (Velsko *et al*. 2014, 2015). Although these studies do not necessarily support that the bacteria directly leads to atheroma formation, they suggest a critical role for human periodontal pathogens in cardiovascular disease pathology.

Other information gained from animal studies is the genetic susceptibility of the individual. Human pathogen-induced periodontal disease requires apolipoprotein E (ApoE) and toll-like receptor (TLR) signaling for atheromatous consequences. Activation of these pathways by the periodontal bacteria and their various components that mediate virulence results in atherothrombotic progression, adhesion, and oxidative stress production by the aortic endothelial cells.

Strain differences within a species may also influence the virulence and their atherogenic capacity (Progulske-Fox *et al*. 1999). *in vitro;* studies demonstrated that the *P. gingivalis* 381-induced gene expression in human coronary artery endothelial cells was fimbriae-dependent and mediated through TLRs (Chou *et al*. 2005; Yumoto *et al*. 2005). *P. gingivalis* W83, which does not express fimbriae, but expresses capsule, induced a substantially lower inflammatory cell response in human coronary artery endothelial cells (Rodrigues *et al*. 2012). On the other hand, another capsule-positive strain, *P. gingivalis* A7436, which also expressed type IV fimbriae, induced a moderate inflammatory response in human coronary artery endothelial cells. *in vivo;* work showed that both W83 and A7436 accelerated atherosclerosis in ApoE-null mice (Li *et al*. 2002; Maekawa *et al*. 2011). The induction of periodontal disease by *P. gingivalis* A7436 strain in an accelerated atherosclerosis model in rabbits has been shown to provoke the atherosclerotic changes and result in a more severe form of the atherosclerotic lesion (Hasturk *et al*. 2015). Collectively, these studies showed that while endothelial dysfunction was critical, additional atherosclerotic properties can be attributed to human oral bacteria independent of their surface characteristics and virulence.

The periodontal bacteria can lead to C-reactive protein (CRP) generation by local vessels in the inflamed periodontium that can cause systemic dissemination of the bacteria by the macrophages, which eventually may become foam cells and involved in atheroma formation. Periodontal bacteria may then be detected in atheroma plaques. TLRs (particularly TLR-2, TLR-4, and TLR-9) are involved in this pattern recognition of periodontal bacteria and their products (e.g. lipopolysaccharide, lipoteichoic acid) and the activation of endothelial cells and macrophages. This theory also supports the lack of finding that periodontal diseases, even at their most severe levels of bacterial burden, do not lead to sustained bacteremia or sepsis. However, periodontal bacteria were detected in atheroma plaques in parallel with the antibody levels against periodontal bacteria in the systemic circulation. IgG levels against *P. gingivalis* had been shown to have a strong association with carotid intima/media

thickening (Beck *et al*. 2005; Champagne *et al*. 2009). A similar response was seen in a study that was done in Finland for *A. actinomycetemcomitans* (Pussinen *et al*. 2005). A meta-analysis of data demonstrated the impact of this link (Mustapha *et al*. 2007). A model for the microbial etiology of atheromatous plaque formation was presented (Kebschull *et al*. 2010; Pollreisz *et al*. 2010). Accordingly, vascular endothelial cells can be invaded by fimbriated pathogens such as *P. gingivalis* (Khlgatian *et al*. 2002; Chou *et al*. 2005; Takahashi *et al*. 2006). Meanwhile, *P. gingivalis* and other periodontal pathogens can induce apoptosis of endothelial cells and smooth muscle cell proliferation in the intima and neointima formation. Plaque rupture can therefore be induced by pathogen-mediated extracellular matrix degradation by endothelial cells, macrophages, T cells, and plasma cells, leading to exposure of prothrombotic plaque components and subsequent vessel occlusion.

Host factors

Local inflammation can lead to systemic and vascular inflammation (Libby & Hansson 2015), possibly through a process that involves an elevated host response, both affecting the innate and acquired arms of the immunity. Periodontitis presents a risk factor for cardiovascular disease as a common determinant of susceptibility. While *P. gingivalis* can induce periodontal inflammation and can increase co-existent atherosclerosis in cholesterol-fed rabbits, *P. gingivalis* was not detectable in the atheroma tissues (Jain *et al*. 2003). Periodontal disease accelerated atherogenesis, changes in the arterial layers, intima, and media, causing smooth muscle cell proliferation leading to medial fibrosis, macrophage infiltration, and necrotic core formation with increased intimal thickness and fibrous cap formation (Hasturk *et al*. 2015). These observations indicate that local inflammatory diseases, in this case, periodontal disease, can accelerate the initiation and progression of another disease in a distant organ.

Several molecules associated with inflammation and host response to microbial challenge have been suggested to play a role in the link between periodontal diseases and cardiovascular diseases (Van Dyke & van Winkelhoff 2013). The most studied molecules are cell- and cytokine-mediated markers of inflammation such as CRP, fibrinogen, inflammatory cytokines, and lipid mediators. These molecules are both involved in the pathogenesis of periodontal diseases and atherothrombogenesis at a "low-level inflammation" (Danesh *et al*. 2000a, b; Danesh & Pepys 2000). Animal studies provide mechanistic insight to this link where experimental periodontitis has been demonstrated as a contributing factor to the incidence and progression of atherosclerotic plaque development (Jain *et al*. 2003; Gibson *et al*. 2004; Hasturk *et al*. 2015). The atheroma plaque also becomes an active source of inflammatory progression with activated immune cells and their production of inflammatory cytokines (interferon, interleukin-1, interleukin-6, and TNF-α). The same cytokines are produced by the adipose tissue, which further contributes to atherogenesis and metabolic syndrome (Hansson 2005). Proinflammatory cytokines produced by the atheroma plaques increase CRP, serum amyloid A, and fibrinogen, exacerbating systemic inflammation. The circulating levels of CRP were significantly elevated by the presence of periodontitis (Hasturk *et al*. 2015). Figure 18-2 shows the impact of experimental periodontitis in a rabbit model and how it can lead to the initiation and progression of atheroma formation. Notably, the resolution of the inflammation prevents periodontal disease and atheromatous plaque disruption, further emphasizing the role of inflammation in the periodontal–cardiovascular disease link.

CRP is an inflammatory mediator produced by the liver. Cytokines such as IL-6 stimulate CRP production. CRP, in turn, opsonizes the bacteria to be presented and eliminated by the cells, which express the receptors for CRP. Neutrophils and macrophages respond to CRP through a ligand-receptor activation. During this process, the complement cascade is involved in phagocyte-mediated and CRP-induced bacterial killing. Atheroma formation has been closely linked to elevated CRP levels, foam cell formation, macrophage activation, and an inflammatory process on the vessel walls impacting the endothelia. As noted, endothelial cells are critical for the periodontal–cardiovascular disease link. Local production of CRP by endothelial cells contributes to local inflammation and increases hepatic CRP production. This observation is also important to demonstrate that any local inflammatory process can lead to CRP production, making it plausible that periodontal diseases can contribute to systemic circulatory CRP levels.

CRP is involved in the elimination of oxidized or enzymatically modified LDL (ox-LDL) cholesterol through opsonization. This process is critical for controlling the levels of ox-LDL and prevents the impact of high-fat intake and obesity. CRP-mediated oxo-LDL elimination involves macrophage phagocytosis and complement activation. In chronic inflammation where CRP is produced in high levels and with the abundance of ox-LDL, this protective process results in foam cell formation and atheromatous changes on the vessel walls.

Periodontal treatment reduces the markers of inflammation and restores endothelial dysfunction in patients with cardiovascular diseases (D'Aiuto *et al*. 2007; Tonetti *et al*. 2007; Teeuw *et al*. 2014), further suggesting a profound role for the systemic inflammation as a plausible mechanism through which periodontal diseases can modulate the cardiovascular diseases. One interesting observation from these studies was the role of not only the macrophages but also neutrophils, potentially both types of phagocytes regulating the endothelial cell function. It is also plausible that the primed/preactivated neutrophils may play a

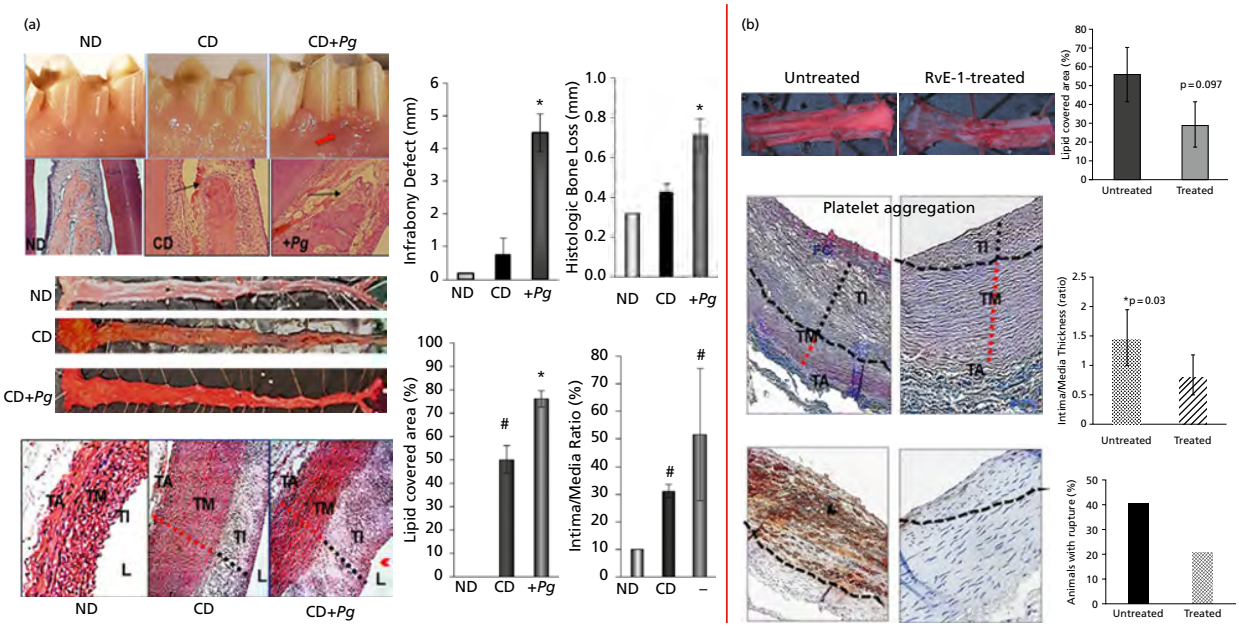


Fig. 18-2 The impact of experimental periodontitis in a rabbit model and how it can lead to the initiation and progression of atheroma formation (Panel A). The resolution of the inflammation prevents periodontal disease and atheromatous plaque disruption (Panel B). (Hasturk *et al*. 2015). CD, cholesterol diet; FC, fibrous cap; L, lumen; ND, normal diet; Pg, experimental periodontitis with *Porphyromonas gingivalis*; TA, *tunica adventitia*; TI: *tunica intima*; TM: *tunica media*.

critical role in the link between periodontal and cardiovascular diseases. While this issue has been well characterized for aggressive and chronic forms of periodontitis, there are no currently available studies demonstrating the impact of this hyperactivation has any mechanistic impact. This mechanism highlights the role of phagocyte activation in disrupting the endothelial cell function and possibly the integrity of endothelium similar to the periodontal pocket epithelium and leading to a "leaky" lining of the vessel walls. Another interesting observation was that the comorbidities in patients with cardiovascular diseases such as diabetes were also positively impacted by periodontal treatment, further emphasizing the inflammatory resolution of the periodontal lesion and its systemic impact.

Another plausible and emerging mechanism is the activation and aggregation of the platelets (Laky *et al.* 2018). Platelets play a significant immunomodulatory role. They are directly involved in the activation of inflammation and its resolution through cell-cell interactions with leukocytes, particularly with neutrophils. Specific integrins regulate platelet-leukocyte cross-talk. For example, CD62L (P-selectin) on platelets and its ligand (glycoprotein ligand-1; PSGL-1) on leukocytes are critical for platelet function. Likewise, platelet-neutrophil interactions through lipoxygenase cross-talk regulate the resolution of inflammation through the production of lipoxins. Another platelet function during the atherosclerotic process is regulated by GPIIb/IIIa-mediated fibrinogen activation and binding of the platelets to other platelets. CD40L is a modulator of reactive oxygen radical production by the platelets and the atherogenesis. Periodontal treatment restores the platelet function, which furthers emphasizes the impact of periodontal inflammation on the atherogenesis process, vascular function, and systemic inflammation.

Summary

Figure 18-3 summarizes the phases of atherosclerosis, atherothrombosis, and cardiovascular events that the periodontal pathogens and periodontal inflammatory mechanisms can modulate. Inflammation initiates atherosclerosis and destabilizes the atheromatous plaques in the vascular intima leading to plaque rupture. Thrombosis results in infarcts and major cardiovascular events. The vulnerability of atheroma plaques is associated with the inflammatory load. Activation of the inflammatory process around the atheroma plaques results in fibrous cap disruption and plaque rupture. This process, combined with the microbial factors, involves TLR2 activation, the release of pro-inflammatory mediators, and the up-regulation of cell adhesion molecules. A gradient of chemokines recruits monocytes (e.g. monocyte chemoattractant protein 1); monocytes chemotactically migrate into the subendothelial space, transform into macrophages, and subsequently into foam cells

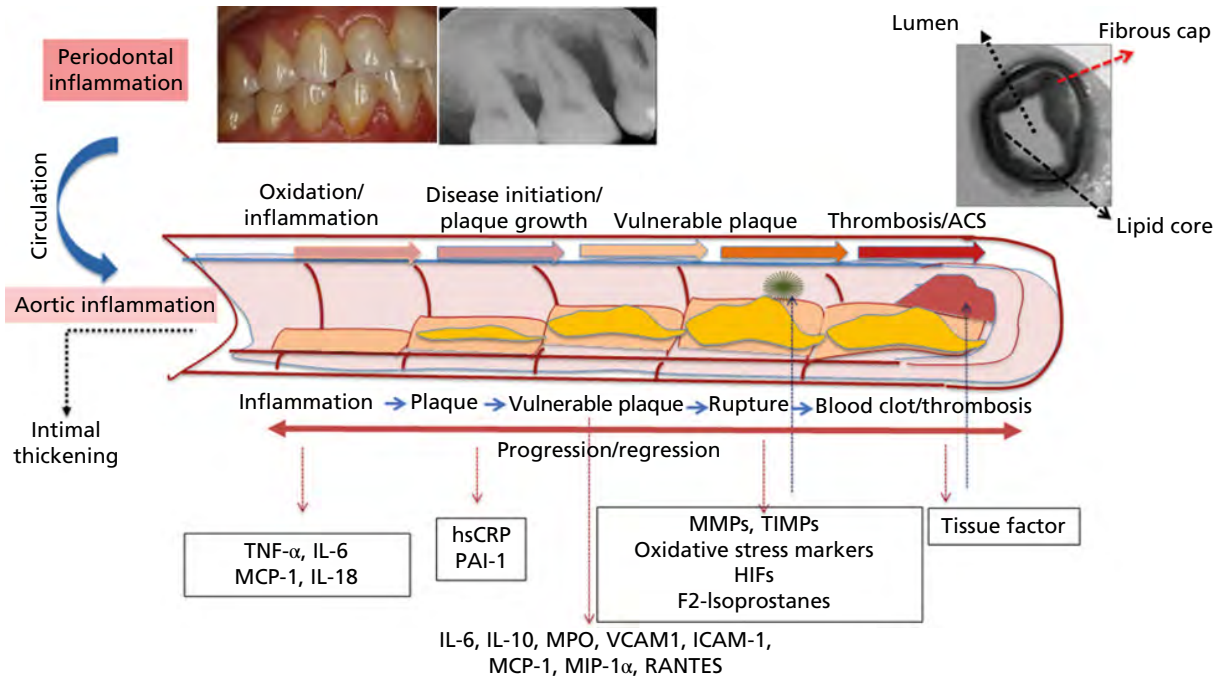


Fig. 18-3 The phases of atherosclerosis, atherothrombosis, and cardiovascular events that the periodontal pathogens and periodontal inflammatory mechanisms can modulate. ACS, acute coronary syndrome; HIFs, hypoxia inducible-factors; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion protein-1; IL-6, interleukin-6; IL-18, interleukin-18; IL-10, interleukin-10; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein 1 alpha; MMPs, matrix metalloproteinases; MPO, myeloperoxidase; PAI-1, plasminogen activator inhibitor-1; RANTES, regulated upon activation, normal T Cell expressed and presumably secreted; TIMPs, tissue inhibitor of metalloproteinases; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion protein-1.

after uptake of oxidized LDL (ox-LDL). Apoptosis of LDL-rich macrophages results in the accumulation of lipids in the subendothelial space. Extracellular matrix build-up leads to the formation of a fibrous cap covering the plaque. Denudation of the fibrous cap and its prothrombotic components occurs after endothelial cell apoptosis.

Biological plausibility of a link between periodontal diseases and diabetes

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia occurring over a prolonged period. As a global epidemic, diabetes affects more than 450 million people worldwide. Complications of diabetes significantly affect the quality of life, longevity, and health care costs across both the developed and developing world. Diabetes mellitus, especially if poorly controlled, can increase the risk for periodontal disease and worsen the course of the disease, ultimately resulting in tooth loss. The impact of diabetes on periodontal tissues through hyperglycemia and inflammatory pathways triggering bacteria-induced inflammation are well-described. Periodontal diseases are considered as one of the complications of diabetes (Loe 1993). Although the original observation has been categorically linked to diabetes, it is the uncontrolled glycemia in patients with diabetes that presents with periodontal disease and tissue breakdown. This observation further supports the impact of chronic hyperglycemia on the entire body, including the periodontal tissues. The mechanism that links diabetes and periodontal disease are similar to the other organs, including microangiopathy, altered collagen metabolism, and altered host inflammatory response.

Although periodontal disease and diabetes are distinct diseases affecting different organs with unique etiologies, they share a common mediator of unresolved inflammation. To this end, a chronic and unresolved inflammation presents the strongest plausibility for the detrimental effects of inflammatory events that could also link periodontal disease to diabetes. Consequently, in the case of diabetes–periodontal disease connection, the inflammatory axis is more predominant than the plausibility of a microbial etiology. Periodontal microorganisms have also been associated with increased inflammation, and therefore thought to be a contributory factor in the link to diabetes (Chapple *et al*. 2013). The reciprocal nature of the bidirectional relationship also exists between diabetes and periodontal disease, where in individuals with diabetes, periodontitis can adversely affect glycemic control and increase risk for complications such as cardiovascular disease, retinopathy, and kidney disease. Figure 18-4 summarizes the plausible link between periodontal disease and diabetes and how diabetes can affect periodontal diseases.

Host factors

Hyperglycemia has both acute and chronic effects. Acute-phase proteins and reactive oxygen radicals are responsible for increased systemic inflammation. Chronic hyperglycemia results in metabolic dysregulation and leads to several pathological events such as metabolic syndrome, obesity, and diabetes. The outcomes of chronic hyperglycemia and a dysregulated metabolic control of excessive glucose

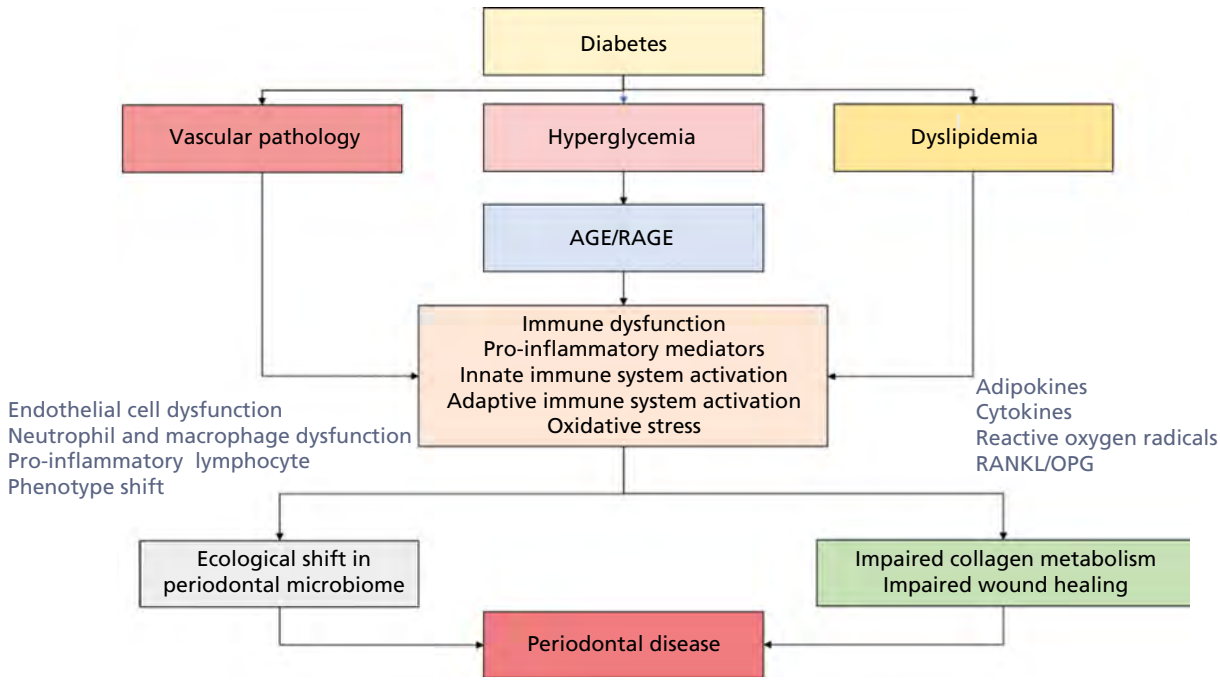


Fig. 18-4 Plausibility of the biological link through which diabetes impacts periodontal health. AGE, advanced glycation end-products; OPG, osteoprotegerin; RAGE, receptor for AGE; RANKL, receptor activator of nuclear factor kappa-B ligand.

are closely related. As one of the ancient diseases of humankind, diabetes mellitus is caused by defective insulin secretion or insufficient insulin production, or both. Unregulated insulin metabolism, in turn, leads to hyperglycemia and dysregulated protein and lipid metabolism. Type 1 diabetes is due to defective insulin production by the pancreatic islet cells and accounts for 5% of patients diagnosed with diabetes. Type 2 diabetes is a chronic disease where insulin production is insufficient to metabolize glucose levels and is closely associated with metabolic syndrome and obesity. Type 2 diabetes accounts for 90–95% of cases of diabetes. Both types 1 and 2 diabetes present with hyperglycemia, poor metabolic control, and macro- and microvascular defects that affect the entire body.

The majority of evidence on how diabetes affects periodontal health comes from patients with type 2 diabetes. Limited but strong data also link type 1 diabetes and periodontal disease. In both forms, chronic and uncontrolled hyperglycemia leads to altered collagen metabolism, vascular response, lipid metabolism, and formation of advanced glycation end products (AGEs). Receptors for AGE (RAGE) are ubiquitous and are expressed in almost all cell types, including the stromal and immune cells. Periodontal diseases can disrupt metabolic health and exacerbate diabetic complications. During this process, periodontal inflammation increases endothelial and immune cell activation. Neutrophils are primed by hyperglycemia and AGEs. A similar process has been shown for macrophages (Yalda *et al*. 1994; Salvi *et al*. 1997a, b). Hyperglycemia caused gingival and periodontal ligament fibroblasts to present with a decreased collagen production and increased collagenolytic activity (Ramamurthy & Golub 1983; Sasaki *et al*. 1992; Yu *et al*. 2012). Similar to neutrophils and macrophages, a hyperinflammatory phenotype of oral epithelial cells has also been associated with diabetes (Amir *et al*. 2011). B cells gain proinflammatory characteristics in patients with diabetes.

Cytokines such as TNF-α are produced at high levels. The disrupted epithelial lining of the periodontal pocket presents a gateway for pathogenic periodontal microbiota, and microbial products further aggravate inflammation. Specifically, TNF-α is linked to defective lipid metabolism, insulin deficiency, and inactivation. Thus, AGEs are critical for the biological plausibility of the link between periodontal diseases and diabetes. AGEs are produced as a result of chronic hyperglycemia and by irreversible non-enzymatic glycation of proteins and lipids. RAGE belongs to the immunoglobulin superfamily and acts as a multiligand signaling receptor (Schmidt *et al*. 1992). Hyperglycemia leads to an increase in RAGE expression, where RAGE mediates the inflammatory complications of diabetes.

In periodontal tissues, RAGE expression has been demonstrated, and its role in alveolar bone loss has been established by treatment with the soluble RAGE competitively binding to RAGE and preventing the effects of AGE (Lalla *et al*. 1998, 2000a,b). AGE proteins were detected in saliva samples from patients with diabetes. Serum AGE levels were associated with the extent of periodontitis in type 2 individuals in parallel with glycated hemoglobin (HbA1c) levels (Karima *et al*. 2005). Further confirmation for the role of RAGE came from studies involving other animal models and human tissues. The receptor-ligand interactions between the RAGE and AGEs result in an unresolved and chronic inflammation, delayed wound healing, impaired bone healing, and destruction of periodontal tissues in diabetes (Santana et al. 2003; Taylor *et al*. 2013). When AGEs bind to RAGE, cellular phenotype and function are critically impacted, and various signaling pathways can be activated. For example, in osteoblasts, the p38-JNK axis is involved, and AGE-RAGE signaling activates caspase three and caspase 8-mediated apoptosis (Alikhani *et al*. 2007). RAGE activation also leads to cross-talk between other receptors that are critically involved in immune cell responses during inflammation. In patients with diabetes, increased expression of TLR2, TLR4, and TLR9 were reported in periodontal tissues. These receptors are critical for the recognition of periodontopathogens and their virulence factors (e.g. LPS). TLR-4 has a significant role in proinflammatory cytokine production by myeloid cells (Bagchi *et al*. 2007). RAGE-TLR cross-talk, mainly TLR-4, can thus stimulate cytokine production (e.g. IL-1b, IL-6, and TNF-α) and augments inflammation through the activation of multiple cell types. As TLRs are also expressed on almost all cell types, RAGE-TLR cross-talk leads non-traditional immune cells to adopt a proinflammatory phenotype in diabetes. For example, circulating TLR-4-positive human B lymphocytes were able to recirculate and promote systemic inflammation in patients with diabetes, presenting a plausible mechanism through which periodontal diseases and antibody responses against periodontopathogens can exacerbate diabetic complications (Wright *et al*. 2008; Shin *et al*. 2009; Jagannathan *et al*. 2010).

AGE-induced oxidative stress is an essential mechanism in the AGE-mediated inflammatory process and tissue damage in the periodontium. Increased inflammation and other pathologic consequences of AGE–RAGE interactions, such as oxidative stress, create a vicious circle for chronic propagation of further AGE formation. Several cell types, including neutrophils and macrophages of the immune system and fibroblasts and endothelial cells of the tissues, contribute to oxidative stress and reactive oxygen radical formation in periodontal tissues during inflammation (Chapple *et al*. 1996; Karima *et al*. 2005; Ding *et al*. 2007; Graves & Kayal 2008; Allen *et al*. 2011). In patients with diabetes, periodontal disease severity is correlated with the neutrophil oxidative burst (Karima *et al*. 2005). Hyperglycemia leads to a hyperactive neutrophil phenotype, which is a primary source of reactive oxygen species. Oxidative

burst and reactive oxygen species lead to the activation of proinflammatory pathways, lipid peroxidation, and insulin resistance in patients with diabetes and periodontal disease (Allen *et al*. 2011; Bastos *et al*. 2012). Hyperglycemia may lead to oxidative stress via several pathways with subsequent effects on inflammatory responses (Graves & Kayal 2008). The mechanism through which proinflammatory cytokine production in response to reactive oxygen species in diabetes involves signaling through MAP kinase, NF-KB, and the NALP3 inflammasome (Graves & Kayal 2008). This mechanism is also critical for understanding alveolar bone loss in patients with diabetes as the Wnt signaling and FoxO transcription factor regulate osteoblast activity. Another net effect of diabetes and hyperglycemia is the increased levels of leptin, which also contributes to oxidative stress.

Levels of CRP, TNF-α, and IL-6 in systemic circulation are elevated in periodontal diseases (Bretz *et al*. 2005; Engebretson *et al*. 2007; Paraskevas *et al*. 2008), posing a plausible link to diabetes. Patients with diabetes and periodontitis exhibit an imbalance in circulating levels of proinflammatory markers (reduced IL-10, IL-4, and adiponectin and increased CRP) (Genco *et al*. 2020). Another level of evidence suggests that there is a correlation between HbA1c and CRP in patients with periodontitis (Demmer *et al*. 2010). Thus, chronic dysregulation and imbalance of peripheral cytokine networks is a central mechanism in the pathogenesis of diabetes and the link with periodontal disease (Kolb & Mandrup-Poulsen 2010), highlighting the importance of the chronicity of inflammation and the risk it poses in susceptible individuals. Periodontal therapy reduces HbA1c, and circulating cytokines (TNF-α) and CRP in people with diabetes (Artese *et al*. 2015; Genco *et al*. 2020).

Human and animal studies have also reported increased levels of IFNγ and macrophage inhibitory proteins (MIP-1, MIP-2), and monocyte chemotactic protein-1 (MCP-1) in people with diabetes and periodontal disease. As diabetes is associated with delayed and impaired wound healing and, therefore, could be linked to the severity of periodontitis, one plausible mechanism may be through an exacerbated and unresolved periodontal inflammation. Indeed, diabetes increases the RANKL-mediated osteoclastic activity, MMP-mediated connective tissue degradation, and reduced levels of collagen and extracellular matrix proteins, all of which will contribute to increased tissue degradation and disrupted wound healing.

Osteoimmunological mechanisms can be activated by diabetes and lead to periodontal destruction (Jiao *et al*. 2015; Graves *et al*. 2020; Huang *et al*. 2020). Osteoclastic bone resorption is regulated by Th17 cells, which also produce RANKL and IL-17. There is also an association between glycemic control and IL-4 and IL-17 levels in gingival crevicular fluid (GCF) samples from patients with diabetes and periodontitis. Patients with poorly controlled diabetes present with elevated Th17 and Treg cells in periodontal tissues, suggesting a mechanism for diabetes-induced periodontal tissue loss. In line with these findings, RANKL levels were shown to be increased in periodontal tissues and GCF samples of patients with diabetes. This mechanism is regulated by the AGE–RAGE axis. A recent study that applied a single cell analysis approach revealed fundamental differences in immune cell function in periodontal tissues of periodontitis patients with type 2 diabetes and periodontal tissues of patients without diabetes, which may account for the increased risk and severity of periodontal disease in subjects with type 2 diabetes (Belkina *et al*. 2020).

Microbial factors

Periodontal diseases as infectious diseases can adversely impact diabetes and its control. This mechanism is summarized in Fig. 18-5. As periodontal diseases lead to the dissemination of oral bacteria into the circulation, there is also a consensus that periodontal microbiota directly impacts the diabetic state or glycemic control. Previous studies investigating the role of oral microbiota demonstrated that the abundance of oral microorganisms increases in diabetes mellitus. There is limited evidence that diabetes has any significant impact on the composition or the amount of oral microbiota, and a diabetic periodontal microbiome is different from other types of periodontitis (Chapple *et al*. 2013; Taylor *et al*. 2013). While hyperglycemia potentially modifies the environment for the periodontal bacterial species and therefore their composition and virulence would change, further studies are needed to identify the impact of diabetes, metabolic syndrome, and mechanistic links on the periodontal microbiome. The impact of periodontal microbiota on diabetes or glycemic control is addressed in a limited number of studies. *P. gingivalis* has been shown to modulate the glycemic control in patients with diabetes (Makiura *et al*. 2008).

Studies based on traditional methods such as checkerboard DNA–DNA hybridization and PCR showed limited detection of a small number of selected species in patients with diabetes compared with patients without diabetes. Table 18-1 summarizes the recent studies reporting the diversity in the periodontal microbiome in the presence of type 2 diabetes. Although few, these studies, utilizing the newer high-throughput and genomic technologies, have revealed new information regarding the complex relationship between diabetes and periodontal disease. 16S rRNA sequencing or 16S rDNA pyrosequencing overall showed a reduced microbial diversity in the subgingival microbiome of subjects with type 2 diabetes compared with those healthy controls or in patients without diabetes with periodontitis. Studies utilizing metagenomic shotgun sequencing revealed functional clues to the microbiome analysis

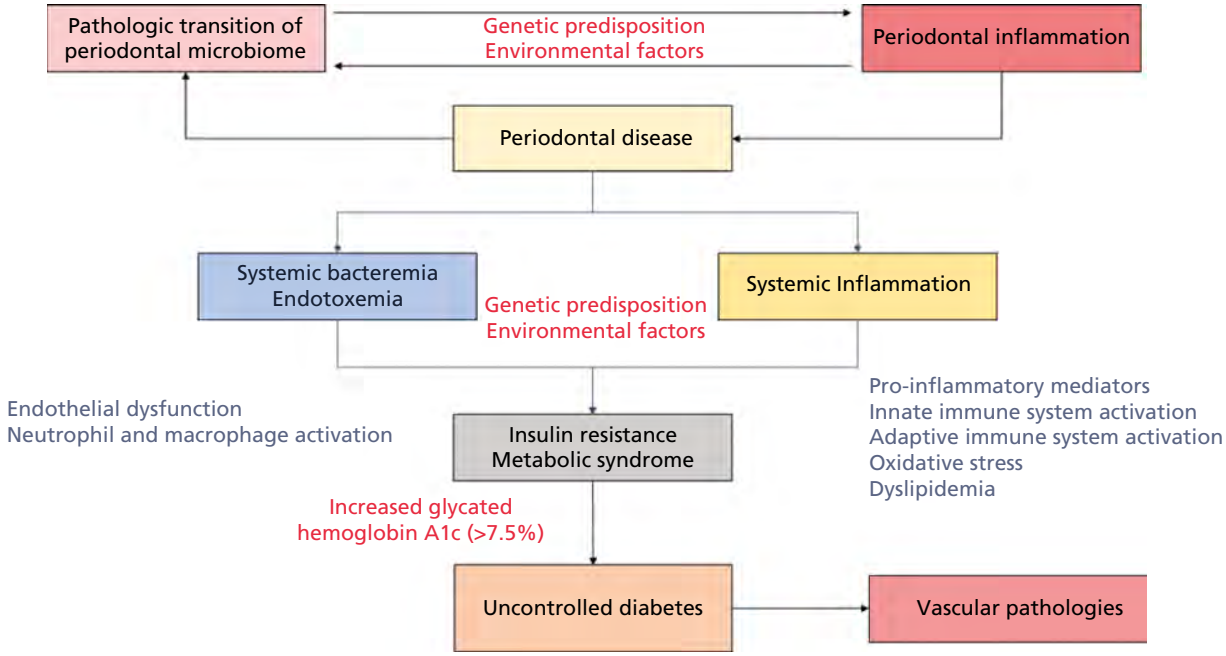


Fig. 18-5 Plausibility of the biological link through which periodontal diseases modify diabetes.

Table 18-1 Studies reporting reduced diversity in the periodontal microbiome in the presence of type 2 diabetes.

Author	Year	Study title	Study design	Analytical method	Main finding
Casarin *et al.*	2013	Subgingival biodiversity in subjects with uncontrolled type-2 diabetes and chronic periodontitis	12 subjects with uncontrolled (HbA1c >8%) type 2 diabetes and 11 non-diabetic subjects with severe generalized chronic periodontitis	16S rRNA	*Overall: subjects with uncontrolled type 2 diabetes and chronic periodontitis presented significant dissimilarities in subgingival biodiversity compared with subjects without diabetes.* Higher percentages of total clones of TM7, *Aggregatibacter, Neisseria*, *Gemella*, *Eikenella*, *Selenomonas*, *Actinomyces*, *Capnocytophaga*, *Fusobacterium*, *Veillonella*, and *Streptococcus* genera, and lower percentages of *Porphyromonas*, *Filifactor*, *Eubacterium*, *Synergistetes*, *Tannerella*, and *Treponema* genera were found in subjects with diabetes than in subjects without diabetes (P <0.05). *Fusobacterium nucleatum*, *Veillonella parvula*, *V. dispar*, and *Eikenella corrodens* were detected significantly more often in subjects with diabetes than in subjects without diabetes.
Zhou *et al.*	2013	Investigation of the effect of type 2 diabetes mellitus on subgingival plaque microbiota by high-throughput 16S rDNA pyrosequencing	Non-diabetic and type 2 diabetes diabetic subjects with or without periodontitis. Total n = 31	16S rDNA 454 pyrosequencing (V1–V3 region)	*Overall: type 2 diabetes could alter the bacterial composition in the subgingival plaque*. Comparing periodontally healthy samples with periodontitis samples identified 20 health-associated and 15 periodontitis-associated operational taxonomic units (OTUs). In healthy subjects, the abundances of *Prevotella*, *Pseudomonas*, and *Tannerella* genera and nine OTUs were significantly different between subjects with diabetes than in subjects without diabetes. In periodontitis subjects, the abundances of three phyla (Actinobacteria, Proteobacteria, and Bacteriodetes), two genera (*Actinomyces* and *Aggregatibacter*), and six OTUs were also significantly different between patients with diabetes and patients without diabetes. Type 2 diabetes could alter the bacterial composition in the subgingival plaque.
Ganesan *et al.*	2017	A tale of two risks: smoking, diabetes and the subgingival microbiome	Non-smoking normoglycemic and hyperglycemic individuals, and smoking normoglycemic and hyperglycemic individuals with	16S rDNA pyrosequencing (V1–V3 region)	*Overall: smoking and hyperglycemia impact the subgingival microbiome in distinct ways; if these perturbations intersect, their synergistic effect is greater than each effect separately*. Periodontally healthy patients who smoked without diabetes presented similar subgingival microbiome as the subjects without diabetes with periodontitis. Patients with diabetes were dominated by species

Table 18-1 (*Continued*)

Author	Year	Study title	Study design	Analytical method	Main finding
			severe generalized periodontitis (*n* = 25/group) in addition to 75 periodontally healthy subjects		*Fusobacterium*, *Parvimonas*, *Peptostreptococcus*, *Gemella*, *Streptococcus*, *Leptotrichia*, *Filifactor*, *Veillonella*, *TM7* and T*errahemophilus* clustering based on HbA1c levels. Patients who smoked with periodontitis evidenced a robust core microbiome dominated by anaerobes. Patients with diabetes and patients with diabetes who smoked were microbially heterogeneous and enriched for facultative species.
Long *et al*.	2017	Association of oral microbiome with type 2 diabetes risk	98 subjects with incident type 2 diabetes, 99 obese patients without diabetes. and 97 normal weight patients without diabetes	16S rRNA sequencing	*Overall: oral microbiome may play an important role in diabetes etiology*. *Actinobacteria* was significantly less abundant among patients with type 2 diabetes than among the controls. *Actinomyces* and *Atopobium* were associated with 66% and 72% decreased risk of diabetes. *Mobiluncus*, *Corynebacterium* and *Bifidobacterium* were less abundant in patients who were obese without diabetes compared to normal weight individuals without diabetes.
Longo *et al*.	2018	Glycaemic status affects the subgingival microbiome of diabetic patients	21 type 2 diabetes subjects with chronic periodontitis divided into two groups: HbA1c ≥8% and HbA1c <7.8%	16S rRNA sequencing (V5–V6 region)	*Overall: glycemic status modulates subgingival biofilm composition*. Controlled type 2 diabetes presented greater diversity than uncontrolled type 2 diabetes. Uncontrolled type 2 diabetes favored fermenting species associated with propionate/succinate production and unfavored butyrate/pyruvate forming species. Higher abundances of *Anginosus* and *Streptococcus agalactiae* were found in uncontrolled type 2 diabetes. Uncontrolled type 2 diabetes present with altered subgingival microbiome with invasive profile.
Farina *et al*.	2019	Whole metagenomic shotgun sequencing of the subgingival microbiome of diabetics and non-diabetics with different periodontal conditions	12 subjects in four study groups based on the presence/absence of poorly controlled type 2 diabetes mellitus and moderate–severe periodontitis	High-resolution whole metagenomic shotgun sequencing	*Overall: whole metagenomic shotgun sequencing was extremely effective in the detection of low-abundant taxon*. The presence of type 2 diabetes and/or periodontitis were associated with a tendency of the subgingival microbiome to decrease in richness and diversity. The presence of type 2 diabetes was not associated with significant differences in the relative abundance of one or more species in patients either with or without periodontitis. The presence of periodontitis was associated with a significantly higher relative abundance of *Anaerolineaceae bacterium* oral taxon 439 in subjects with type 2 diabetes
Saeb *et al*.	2019	Relative reduction of biological and phylogenetic diversity of the or al microbiota of diabetes and prediabetes patients	15 type 2 diabetes patients, 10 impaired glucose tolerance subjects, and 19 control subjects	16S rRNA sequencing	*Overall: a clear reduction of the biological and phylogenetic diversity in oral microbiota of subjects with diabetes and prediabetes was found compared with oral microbiota in normoglycemic subjects*. The group with diabetes exhibited reduction of species and diversity but the highest evenness value and the highest microbiota bacterial pathogenic content.
Shi *et al*.	2020	The subgingival microbiome associated with periodontitis in type 2 diabetes mellitus	Type 2 diabetes patients (*n* = 15) compared with subjects without diabetes (*n* = 16)	Metagenomic shotgun sequencing	*Overall: patients with type 2 diabetes are more susceptible to shifts in the subgingival microbiome toward dysbiosis, potentially due to impaired host metabolic and immune regulation*. In periodontitis state, the shift in subgingival microbiome from the healthy state was less prominent in type 2 diabetes compared with subjects without diabetes, despite similarity in disease state. Presence of pathogenic species in relative abundance correlated with periodontitis state, but also in the healthy state in type 2 diabetes. A set of microbial marker genes were associated with the clinical states.

and concluded that type 2 diabetes subjects are more susceptible to dysbiosis in subgingival microbiome possibly due to impaired host metabolic and immune regulation. With this approach, an oral taxon that predicted the presence of periodontitis in subjects with type 2 diabetes was detected (Casarin *et al*. 2013; Zhou *et al*. 2013; Ganesan *et al*. 2017; Long *et al*. 2017; Longo *et al*. 2018; Farina *et al*. 2019; Saeb *et al*. 2019; Shi *et al*. 2020). Despite powerful analyses, the results from these studies warrant confirmation from larger and longitudinal studies.

Summary

Diabetes may be associated with an altered inflammatory process that is referred to as "diabetic periodontitis", although there is no consensus on this definition and recognition of patients with diabetes present with a distinct periodontal disease phenotype. It is clear, however, that the severity of periodontitis increases the inflammatory burden in patients with diabetes. A diabetic person experiences a challenge in controlling his/her glycaemia, suffering from oral complications of periodontal disease, e.g. mastication, abscesses, loose teeth, bad breath, esthetic outcomes, increased risk for adiposity, systemic inflammation, cardiovascular disease, kidney disease, and ocular complications (Fig. 18-6). Diabetic control gets worse with increased severity of periodontitis (Karima *et al*. 2005), which increases the systemic inflammatory markers (e.g. CRP) while decreasing the anti-inflammatory cytokines (e.g. IL-10). Clinical cases demonstrate the adversity periodontitis presents in patients with diabetes (Figs. 18-7, 18-8, 18-9).

There are critical modifying factors such as the duration of diabetes, and therefore exposure to hyperglycemia, AGEs, and chronic micro- and macrovascular defects, age of onset, lipidemia, and type of

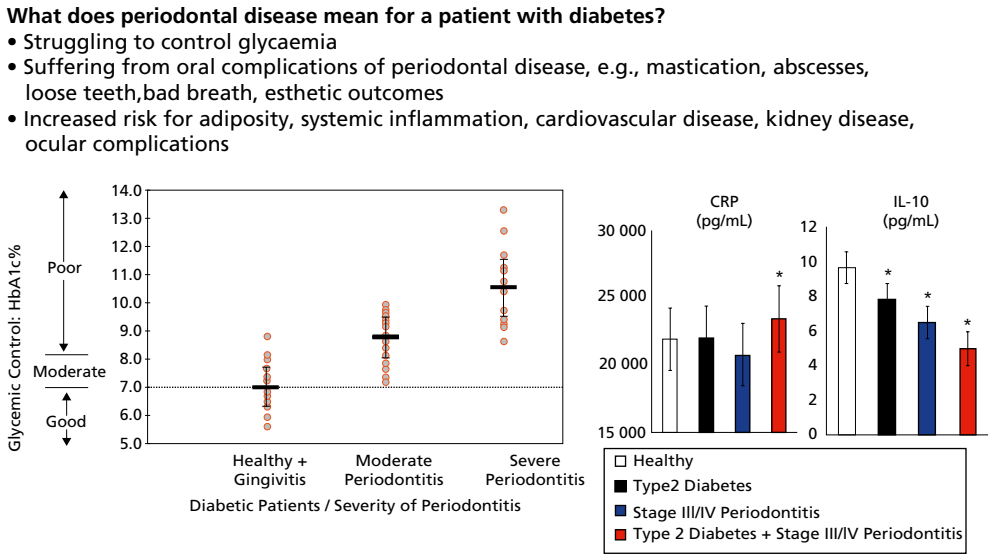


Fig. 18-6 Diabetic control and the severity of periodontitis. CRP, C-reactive protein; interleukin-10, IL-10

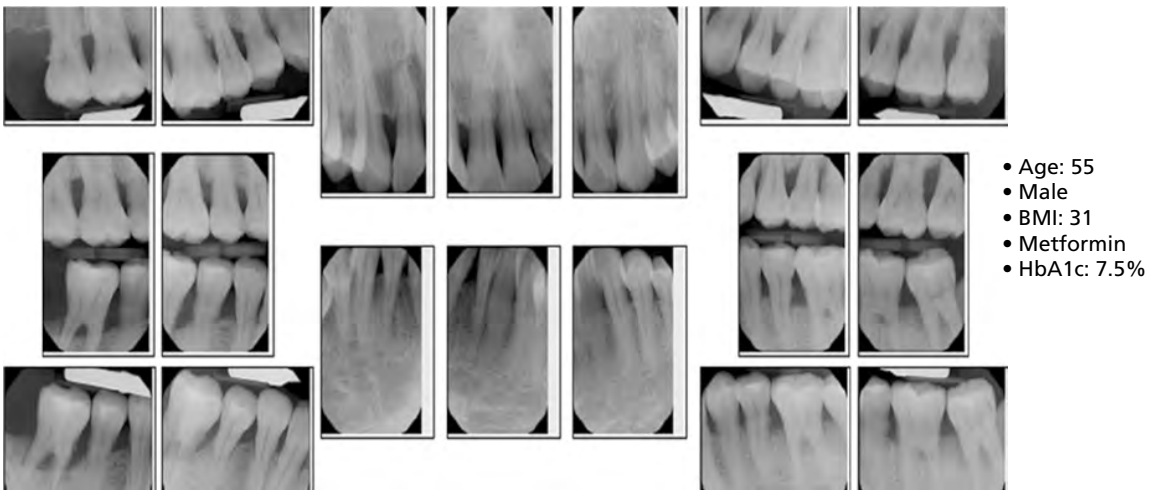
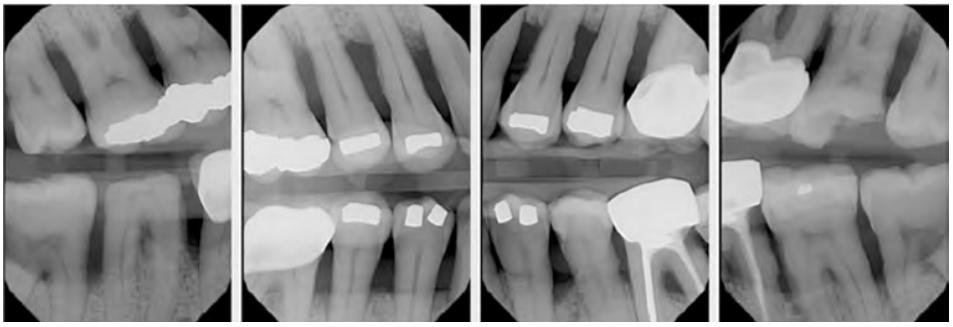
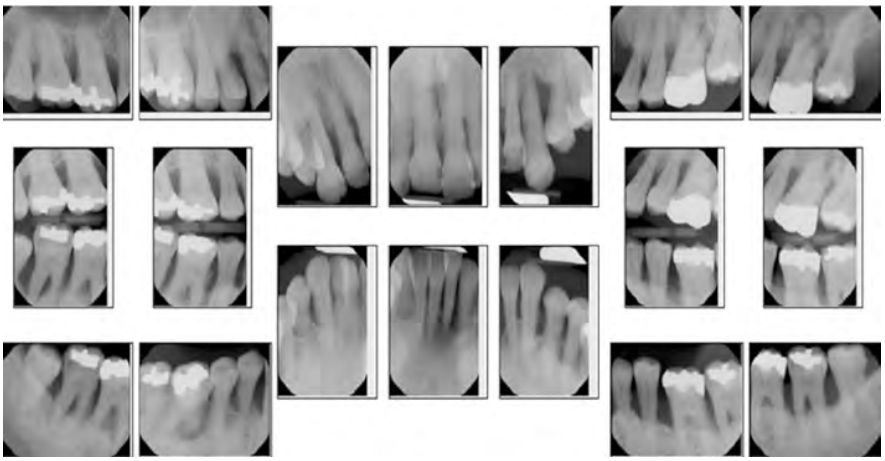


Fig. 18-7 Stage III generalized periodontitis in a patient with type 2 diabetes. BMI, body mass index. HbA1c, glycated hemaglobin.



- Age: 55 years
- Male
- BMI: 33
- Metformin
- HbA1c: 8.2%

Fig. 18-8 Stage IV generalized periodontitis in a patient with type 2 diabetes. BMI, body mass index. HbA1c, glycated hemaglobin.



- Age: 56 years
- Female
- BMI: 37
- Metformin + Insulin
- HbA1c: 12.7%

Fig. 18-9 Stage IV generalized periodontitis in a patient with type 2 diabetes. BMI, body mass index. HbA1c, glycated hemaglobin.

diabetes. Restoration of diabetic control may reduce or eliminate periodontal pathologies. Likewise, periodontal treatment facilitates diabetic control supporting the bidirectionality of the link between diabetes and periodontal diseases (D'Aiuto *et al*. 2018). Thus, it is plausible that periodontitis in people with diabetes presents with a different biological mechanism (Taylor *et al*. 2001). This view is also supported by epidemiologic evidence (Borgnakke *et al*. 2013).

Conclusion

Lifestyle, genetic and familial predisposition, smoking, gender, and age are the systemic and environmental modifying factors of the biological link between periodontal diseases and systemic diseases. Inflammatory diseases share a common diagnostic and prognostic definition if they remain active: aberrant and uncontrolled inflammation of the target tissues and incurable, progressive outcomes. The severity of the inflammatory pathological condition for human life depends on the affected tissues or organ systems. In vital tissues such as the heart, lung, kidney, or liver, the progression of inflammation can be devastating. In peripheral tissues, however, the inflammatory process can follow a slowly progressive path. Thus, while the mediators may be similar, there exists a tissue specificity for the inflammatory events. Another major issue in understanding inflammation as an entity is the communication between distant organs. Although it is plausible that inflammatory processes in one organ could directly lead to pathologies in another organ or tissue, comorbidity of inflammatory pathways and common signaling mechanisms via cells or soluble mediators are critical for the oral–systemic link (Hasturk *et al*. 2012a).

Figure 18-10 summarizes the plausibility of the link between periodontal and systemic diseases. The transition of health to disease is the result of several factors that affect the body's homeostatic balance. Aging, epigenetics, and infections favor the disease-associated pathological shifts. Activation of inflammation is mediated by molecular pathways and cellular functions that can be measured as markers of pathological transition. A reciprocal transition restores health and requires the resolution of the inflammatory process, which is characterized by health-associated markers. Non-transmittable inflammatory diseases (e.g. obesity, diabetes, cardiovascular diseases, Alzheimer's disease, rheumatoid arthritis, osteoporosis, periodontal disease, and adverse pregnancy outcomes) share similar pathways that affect the body at the local tissue and systemic levels and are therefore connected. Whereas various markers are associated with health, others are linked to disease initiation and severity. These distinctions, however, become blurred as inflammation is an active process that involves both initiation and resolution.

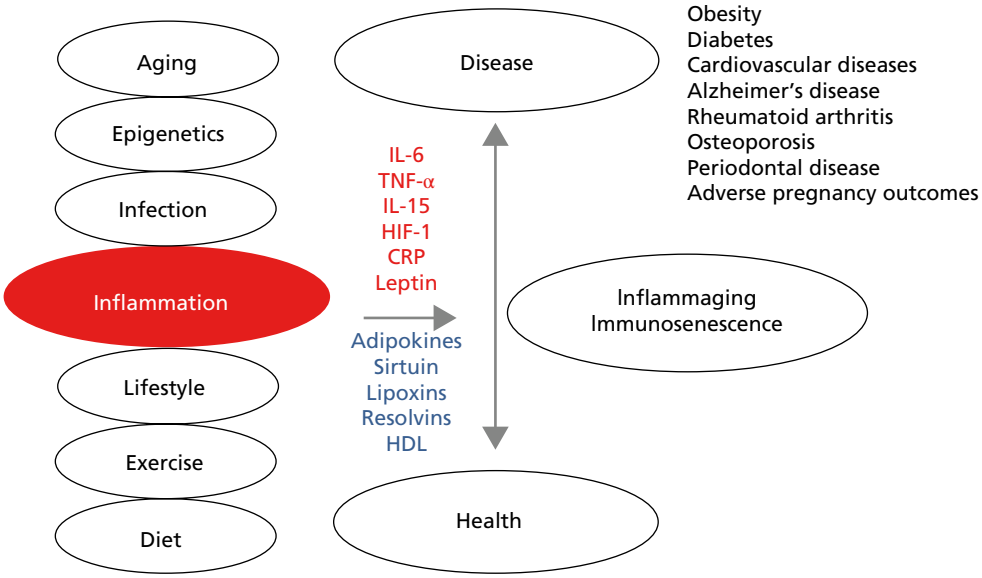


Fig. 18-10 Plausibility of the link between periodontal and systemic diseases. CRP, C-reactive protein; HDL, high-density lipoprotein; HIF-1, hypoxia inducible factor-1; IL-6, interleukin-6; IL-15, interleukin-15; TNF-α, tumor necrosis factor-α.

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Chapter 19

Abscesses, Necrotizing Lesions of the Periodontium, and Endo-Periodontal Lesions

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Introduction

Acute periodontal diseases have been defined as "clinical conditions of rapid onset that involve the periodontium, or associated structures, and may be characterized by pain or discomfort, tissue destruction and infection" (American Academy of Periodontology, 2000). Different diseases and/or conditions have been considered within this category, including gingival abscesses, periodontal abscesses, necrotizing periodontal diseases, herpetic gingivostomatitis, pericoronal abscesses, pericoronitis, and endo-periodontal lesions.

Acute lesions affecting the periodontal tissues often require immediate action, with the patient seeking emergency care because of acute pain, which is not a common situation in the periodontal practice. Moreover, and in contrast with most chronic periodontal diseases and conditions, the onset is rapid and subsequent destruction of periodontal tissues may occur. Diagnosis should be prompt and swift treatment provision is essential (Papapanou *et al*. 2018). Two of these conditions can be considered as solely periodontal diseases: periodontal abscesses and necrotizing periodontal diseases. Abscesses in the periodontium are relevant since they are common dental emergencies, requiring immediate management. They present with rapid destruction of the periodontal tissues, which negatively affects the prognosis of the affected tooth and they may have severe systemic consequences (Herrera *et al*. 2000b, 2014). On the other hand, necrotizing periodontal diseases represent the most severe conditions associated with

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

dental biofilms, with very rapid tissue destruction (Herrera *et al*. 2014).

Endo-periodontal lesions are pathological conditions that affect both the pulp and the periodontal tissues in the same tooth. These lesions may have an acute progression and develop as an abscess, but most of the time they have a chronic course. They may occur as a result of a microbial challenge in the periodontal and/or endodontic tissues, or because of trauma, iatrogenic events, and root resorption. Endo-periodontal lesions are not very common clinical conditions (Rhee *et al*. 2014), but are considered one of the most challenging problems for clinicians as they are relatively difficult to treat and may severely compromise the tooth prognosis (Herrera *et al*. 2018).

Abscesses in the periodontium

Abscesses in the periodontium are a major reason for patients seeking emergency care in the dental clinic. They represent a heterogeneous group of lesions, characterized by the presence of a localized purulent infection in the periodontal tissues. Different etiological factors may explain the occurrence of these lesions: pulp necrosis, periodontal infections, pericoronitis, trauma, or surgery (Gill & Scully 1990). Specific terminology is used to refer to the abscesses associated with pulp necrosis (endodontal, periapical, or dentoalveolar abscess), with periodontal infections (Papapanou *et al*. 2018), or with pericoronitis (pericoronal abscess), which are referred to together as odontogenic or dental abscesses (van Winkelhoff *et al*. 1985).

Periodontal abscess

A periodontal abscess has been defined as a lesion with an expressed periodontal breakdown occurring during a limited period of time, and with easily detectable clinical symptoms, including a localized accumulation of pus located within the gingival wall of the periodontal pocket (Herrera *et al*. 2000b). More recently, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, defined periodontal abscesses as "acute lesions characterized by localized accumulation of pus within the gingival wall of the periodontal pocket/sulcus, rapid tissue destruction, and are associated with risk for systemic dissemination".

Classification

Although defined by the general term "periodontal abscesses", this group of acute periodontal conditions has been classified according to the course (chronic or acute), to the number of lesions (single or multiple), or to the location (gingival, restricted to the marginal gingiva, or periodontal, extended to the supporting periodontal tissues). A classification system for these lesions was proposed by Meng (1999a), and included the following categories: *gingival abscesses* (in previously healthy sites, caused by impaction of foreign bodies), *periodontal abscesses* (either acute or chronic, in relation with a periodontal pocket), and *pericoronal abscesses* (in relation with a partially erupted tooth). This classification was included in the revised classification system developed by the American Academy of Periodontology (AAP) International Workshop for a Classification of Periodontal Diseases in 1999, which for the first time included periodontal abscesses as an independent entity. In the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, a new classification of periodontal abscesses, based on etiological factors, was adopted (Herrera *et al*. 2018; Papapanou *et al*. 2018). The development of a periodontal abscess may occur in an existing periodontal pocket, but it can also initiate in a site without a periodontal pocket. Therefore, two main types of periodontal abscesses can be distinguished: (1) those which require the previous presence of a periodontal pocket and thus, they are only found in patients with periodontitis; and (2) those which can develop without a pre-existing pocket, so they can be found both in periodontitis and in non-periodontitis patients (Herrera *et al*. 2018) (Table 19-1).

Periodontal abscess in periodontitis patients

A periodontal abscess in a patient with periodontitis may be associated with two distinct clinical scenarios, either with a period of disease exacerbation (acute exacerbation) or associated with a therapeutic procedure (after treatment).

Acute exacerbation

Abscesses because of acute exacerbation of periodontitis are favoured by the existence of tortuous pockets, the presence of furcation involvement (Darbar *et al*. 1993), or of a vertical defect (Fasciano & Fazio 1981; Kareha *et al*. 1981; Darbar *et al*. 1993). Acute exacerbation may occur in untreated periodontitis (Dello Russo 1985), in "refractory" periodontitis patients (Fine 1994), or in patients in periodontal maintenance (Kaldahl *et al*. 1996; McLeod *et al*. 1997; Silva *et al*. 2008).

After treatment

Post-treatment periodontal abscesses may occur after the following interventions:

- Scaling and root planing or professional mechanical plaque removal, either because a dislodged fragment of calculus is lodged into the tissues (Dello Russo 1985), or because incomplete scaling allows the presence of calculus in the pocket, while the healing in the coronal area occludes the normal drainage (Kaldahl *et al*. 1996).

Table 19-1 Classification of periodontal abscesses, based on the etiological factors involved, according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Sources: Herrera *et al*. 2018; Papapanou *et al*. 2018).

Periodontal abscess in a periodontitis patient (abscess in a pre-existing periodontal pocket)						**Periodontal abscess in a non-periodontitis patient** (not mandatory to have a pre-existing periodontal pocket)				
Acute exacerbation			**After treatment**			Impaction (2)	Harmful habits (3)	Orthodontic factors (4)	Gingival overgrowth	Alteration of root surface (5)
Untreated periodontitis	Refractory periodontitis	Supportive periodontal therapy	Post-scaling	Post-surgery	Post-medication (1)					

(1) Systemic antimicrobials, other drugs (nifedipine);
(2) Dental floss, orthodontic elastic, toothpick, rubber dam, or popcorn hulls;
(3) Biting wire, nail biting and clenching;
(4) Orthodontic forces or a cross-bite;
(5a) Severe anatomic alterations: invaginated teeth, dens evaginatus, or odontodysplasia;
(5b) Minor anatomic alterations: cemental tears, enamel pearls, or developmental grooves;
(5c) Perforations: iatrogenic conditions;
(5d) Severe root damage: fissure or fracture, cracked tooth syndrome;
(5e) External root resorption.

- Surgical periodontal therapy, normally associated with the presence of foreign bodies such as membranes for regeneration, sutures, or periodontal dressing (Garrett *et al*. 1997).
- Systemic antimicrobial intake, without concomitant subgingival instrumentation, has been associated with periodontal abscesses in patients with advanced periodontitis (Helovuo & Paunio 1989; Topoll *et al*. 1990; Helovuo *et al*. 1993). Helovuo *et al*. (1993) followed patients with untreated periodontitis who were given broad-spectrum antibiotics (e.g. penicillin, erythromycin) for non-oral reasons and reported that 42% of them developed "marginal" abscesses within 4 weeks of the antibiotic therapy, and they suggest that a plausible explanation was an overgrowth of opportunistic bacteria (Helovuo *et al*. 1993).
- Use of other systemically delivered drugs, such as nifedipine (Koller-Benz *et al*. 1992).

Periodontal abscess in non-periodontitis patients

They may occur both in periodontally healthy sites or in periodontal pockets. Therefore, the pre-existence of a periodontal pocket is not mandatory for abscess development, in contrast with the abscesses described in the previous section. Five different groups of etiological factors are listed in this category:

- Impaction of foreign bodies, including dental floss, orthodontic elastics, toothpicks, rubber dam fragments, pieces of nails, or popcorn hulls.
- Harmful habits, such as biting wire, nail biting, or clenching, that could favour abscess development, either because of subgingival impaction or coronal closure of the pocket/sulcus.
- Orthodontic factors, including inadequate orthodontic forces or a cross-bite.
- Gingival enlargement (Holtzclaw & Toscano 2008).
- Alterations of the root surface, including severe anatomic alterations (invaginated tooth, *dens evaginatus* or grooves, or odontodysplasia), minor anatomic alterations (cemental tears, enamel pearls or developmental grooves), iatrogenic conditions (perforations), severe root damage (vertical root fracture or cracked tooth syndrome extending through the root), or external root resorption.

Etiology, pathogenesis, and histopathology

The development of a periodontal abscess is associated with the inability to maintain the normal drainage of the periodontal pocket/sulcus. This may be caused by a partial or total closure of the coronal portion or by an increase in the material to be drained, because of changes in the composition of the subgingival microbiota, an increase in bacterial virulence, or a decrease in the host defenses. The inability of the appropriate drainage of the pocket/sulcus could lead to an extension of the infection into the surrounding periodontal tissues (Newman & Sims 1979; Kareha *et al*. 1981; DeWitt *et al*. 1985), bacterial invasion of those tissues surrounding the periodontal pocket, and development of an inflammatory process through the chemotactic factors released by bacteria, which attract polymorphonuclear (PMN) leukocytes and other cells. This will trigger intensive release of cytokines, destruction of the connective tissues, encapsulation of the bacterial infection, and the production of pus. Once the abscess is formed, the rate of destruction within the abscess will depend on the growth of bacteria inside the foci and their virulent

capacity, and the local pH (an acidic environment will favor the activity of lysosomal enzymes) (DeWitt *et al*. 1985).

The periodontal abscess contains bacteria, bacterial products, inflammatory cells, tissue breakdown products, and serum. The histopathology of the abscess shows a central area filled with neutrophils, bacteria, and debris of soft tissue destruction. At a later stage, a pyogenic membrane, composed of macrophages and neutrophils, is organized to enucleate this central core. DeWitt *et al*. (1985) studied biopsies sampled from 12 abscesses. These biopsies extended apically to the centre of the abscess and were processed histologically. This revealed a normal oral epithelium and lamina propria, but the presence of an inflammatory cell infiltrate located laterally to the pocket epithelium. Within this infiltrate, there were accumulations of neutrophils and lymphocytes together with tissue destruction and a mass of granular, acidophilic, debris (Fig. 19-1). Some of these biopsies were evaluated by electron microscopy, which demonstrated the presence of Gram-negative bacteria invading the pocket epithelium and the infiltrated connective tissue. From outside to the inside, the following could be observed: a normal oral epithelium and lamina propria; an acute inflammatory infiltrate; intense focus of inflammation with presence of neutrophils and lymphocytes in an area of destroyed and necrotic connective tissue; and a destroyed and ulcerated pocket epithelium (DeWitt *et al*. 1985).

Microbiology

Based on reviews of the literature, it is usually mentioned that purulent oral infections are polymicrobial and mainly caused by endogenous bacteria (Tabaqchali 1988). There are very few studies, however, that have investigated the specific microbiota of periodontal abscesses. Newman and Sims (1979) studied nine abscesses and found that 63.1% of the microbiota was comprised of strict anaerobes. Topoll *et al*. (1990) analysed 20 abscesses in 10 patients who had taken antibiotics prior to the study, and reported that 59.5% of the microbiota was made up of strict anaerobes. Herrera *et al*. (2000a) reported that 45.1% of the bacteria in the abscess material were anaerobes.

These studies have shown that the microbiota of periodontal abscesses (Table 19-2) does not differ from the microbiota of chronic periodontitis lesions. This microbiota is polymicrobial and dominated by non-motile, Gram-negative, strict anaerobic, rod-shaped species. Among these bacteria, *Porphyromonas gingivalis* is probably the most virulent and relevant microorganism. The reported occurrence of *P. gingivalis* in periodontal abscesses ranged from 50% to 100% in studies using bacterial culture (Newman & Sims 1979; van Winkelhoff *et al*. 1985; Topoll *et al*. 1990; Hafstrom *et al*. 1994; Herrera *et al*. 2000a; Jaramillo *et al*. 2005). Eguchi *et al*. (2008), using a commercial molecular test (IAI-PadoTest 4.5; IAI Inc., IAI Institute, Zuchwil, Switzerland), also reported high prevalence of *P. gingivalis, Tannerella forsythia*, and *Treponema denticola*. Other anaerobic species that are usually found include *Prevotella intermedia*, *Prevotella melaninogenica,* and *Fusobacterium nucleatum*. Spirochetes (*Treponema* spp.) were found in most cases. The majority of the Gram-negative anaerobic species are non-fermentative and display moderate to strong proteolytic activity. Strict anaerobic, Gram-positive species frequently present in periodontal abscesses include *Parvimonas micra*, *Actinomyces* spp., and *Bifidobacterium* spp. Facultative anaerobic Gram-negative bacteria that can be isolated from periodontal abscesses include *Campylobacter* spp., *Capnocytophaga* spp., and *Aggregatibacter actinomycetemcomitans* (Hafstrom *et al*. 1994). The presence of Gram-negative enteric rods has also been reported (Jaramillo *et al*. 2005).

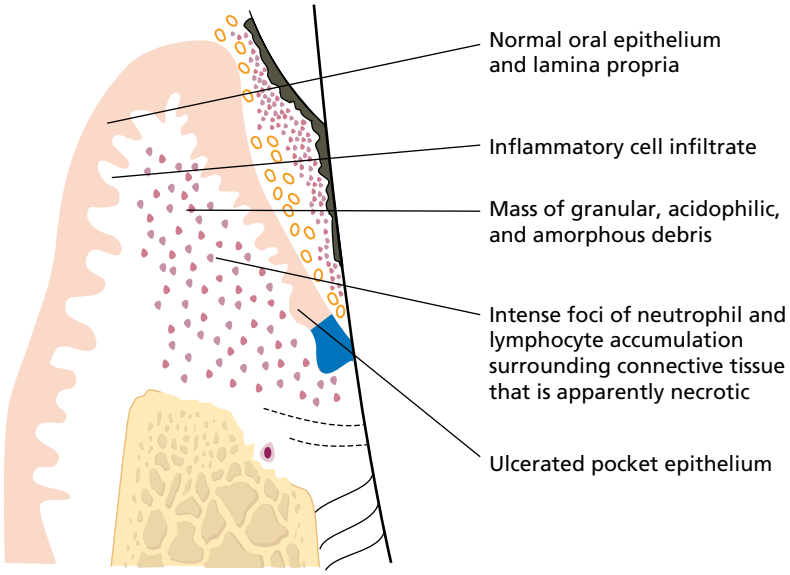

Fig. 19-1 Histopathology of a periodontal abscess.

Table 19-2 Microbiological features of periodontal abscesses: frequency of detection of target bacterial species.

References	Group	*n*	*Aa*	*Pg*	*Pi*	*Tf*	*Pm*	*Cr*	*Fn*	*Pmel*	*Ec*	*Td*	*Pen*	*Cap*	*Sel*	*Vibrio*	*Eu*	*Dn*	Enteric
Newman & Sims (1979)	Control	4		25%	0%				0%	25%				75%	0%	50%			
Newman & Sims (1979)	Exudate	7		71%	14%				71%	14%				100%	14%	29%			
Newman & Sims (1979)	Apical	9		78%	56%				44%	22%				78%	0%	67%			
van Winkelhoff *et al*. (1985)	Pus	3		100%	100%														
Topoll *et al*. (1990)	Previous antibiotic intake	20		95%	25%				65%										
Hafstrom *et al*. (1994)	Baseline	20	25%	55%	65%			80%	55%					30%					
Herrera *et al*. (2000a)	Baseline	24	0%	50%	63%	47%	71%	4%	71%	17%									
Jaramillo *et al*. (2005)	Baseline	60	30%	52%	60%	15%	3%	12%	75%		23%						8%	7%	22%
Eguchi *et al*. (2008)	Test	46	11%	72%		70%						70%							
Eguchi *et al*. (2008)	Control	45	2%	58%		60%						60%							

Aa, A. actinomycetemcomitans; Pg, P. gingivalis; Pi, P. intermedia; Tf, T. forsythia; Pm, P. micra; Cr, C. rectus; Fn, F. nucleatum; Pmel, P. melaninogenica; Ec, E. corrodens; Td, T. denticola; Pen, P. endodontalis; Cap, Capnocytophaga sp.; Sel, Selenomonas sp.; Eu, Eubacterium sp.; Dn, Dialister pneumosintes.

Diagnosis

The diagnosis of a periodontal abscess should be based on the overall evaluation and interpretation of the patient´s symptomatology, together with the clinical and radiographic signs found during the oral examination (Corbet 2004).

The case definition of a periodontal abscess, according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou *et al*. 2018) was established based on two primary criteria as detectable signs/symptoms: ovoid elevation in the gingiva along the lateral part of the root and bleeding on probing. Other secondary signs/symptoms also listed were pain, suppuration on probing, deep periodontal pocket, and increased tooth mobility. This case definition was proposed based on the findings of the review paper presented at the Workshop (Herrera *et al*. 2018), which pooled together studies with a relevant number of cases and their comprehensive descriptions (Smith & Davies 1986; Hafstrom *et al*. 1994; Herrera *et al*. 2000a; Jaramillo *et al*. 2005; Chan & Tien 2010).

The most frequent sign of a periodontal abscess is the presence of an ovoid elevation in the periodontal tissues along the lateral side of the root (Fig. 19-2). Abscesses located deep in the periodontium may be more difficult to identify as they may manifest as a diffuse swelling or simply a red area (Fig. 19-3), rather than a prominent swelling of the soft tissues. Another common finding is suppuration either through a fistula or, most commonly, through the pocket opening (Fig. 19-4). This suppuration may be spontaneous or occur when pressure is applied to the outer surface of the lesion. Some studies found molars more frequently affected (Smith & Davies 1986; Herrera *et al*. 2000a), while others found equal distribution (Chan & Tien 2010) or predominance in anterior teeth (Jaramillo *et al*. 2005). One study reported a higher number of abscesses at the interdental area (Smith & Davies 1986), while others observed more frequent abscess formation at buccal sites (Herrera *et al*. 2000a; Chan & Tien 2010). The clinical symptomatology usually includes pain (from light discomfort to severe pain), tenderness of the gingiva, swelling, and sensitivity to percussion of the affected tooth. Other related symptoms are tooth elevation and increased tooth mobility (Fig. 19-5).

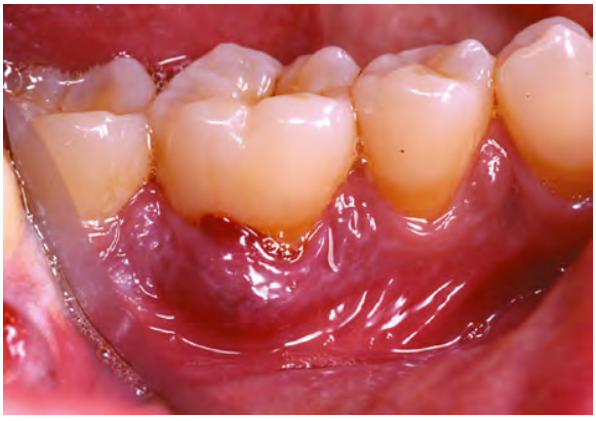

Fig. 19-2 Periodontal abscess associated with a lower right first molar. Note the association between the abscess formation and the furcation lesion in this molar.

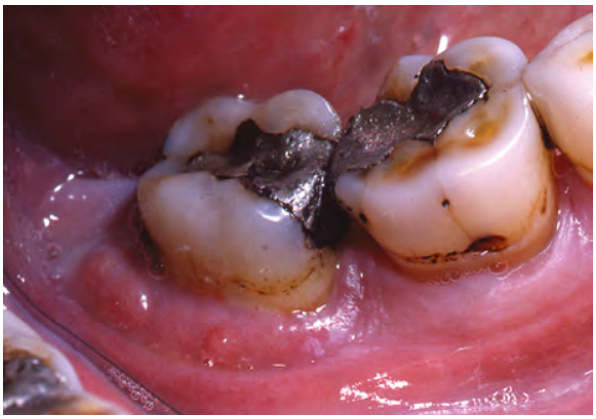

Fig. 19-3 Periodontal abscess associated with a mandibular second molar. Note the diffuse swelling affecting the entire buccal surface of the molar.

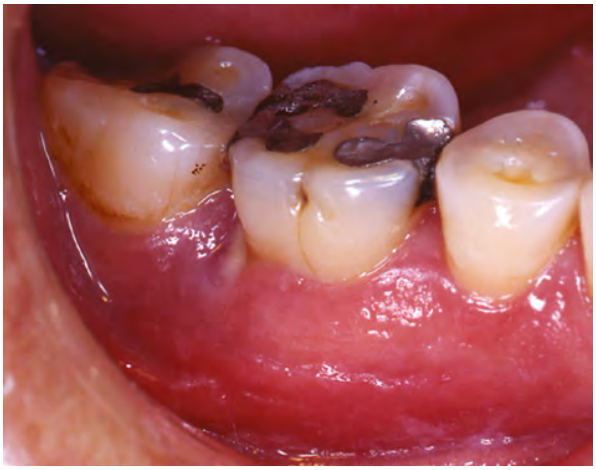

Fig. 19-4 Periodontal abscess associated with a lower right first molar. Note the spontaneous suppuration expressed through the gingival margin.

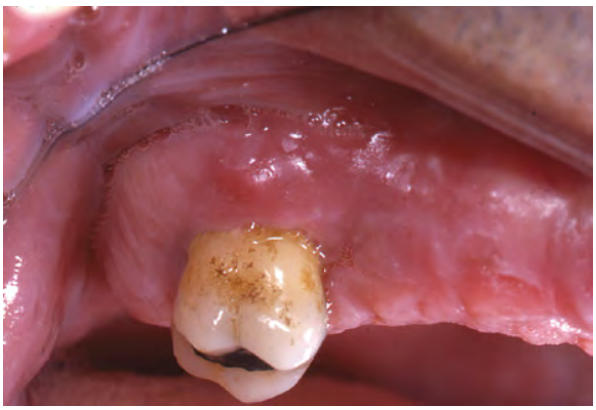

Fig. 19-5 Periodontal abscess associated with an upper right third molar. Note how this lesion is associated with tooth extrusion and mobility.

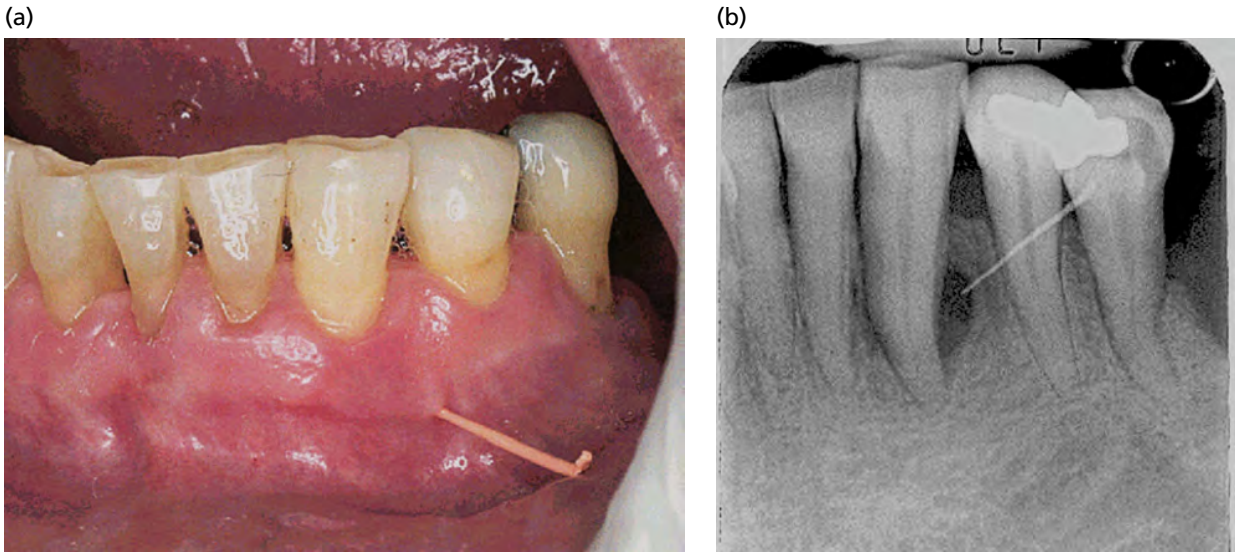

Fig. 19-6 (a) Periodontal abscess associated with a lower left canine. Note the fistulous tract opening demonstrated with a gutta-percha point. (b) Radiographic image of the lower canine shown in (a). Diagnosis of a periapical abscess was made from the positive tooth vitality and absence of caries or restoration in the canine, and the presence of a deep periodontal pocket in the lingual aspect of this tooth.

During periodontal examination, the abscess is usually found at a site with a deep periodontal pocket. Signs associated with periodontitis such as bleeding on probing, suppuration, and sometimes increased tooth mobility are also frequently present. The radiographic examination may either reveal a normal appearance of the interdental bone or evident bone loss, ranging from just a widening of the periodontal ligament space to pronounced bone loss involving most of the affected root (Fig. 19-6).

In some patients, the occurrence of a periodontal abscess may be associated with elevated body temperature, malaise, and regional lymphadenopathy (Smith & Davies 1986; Herrera *et al*. 2000a). Herrera *et al*. (2000a) studied samples from the blood and urine of patients, taken immediately after the diagnosis of a periodontal abscess, and reported that in 30% of the patients the number of blood leukocytes was elevated. The absolute number of blood neutrophils and monocytes was also elevated in 20–40% of the patients.

The patient history may also provide relevant information for the diagnosis of abscesses, especially in cases associated with previous treatments (scaling and root planing, periodontal surgery, intake of systemic antimicrobials or other drugs [e.g. nifedipine], and endodontic treatment), or in abscesses related to foreign body impaction. Most abscesses affect periodontitis patients, either untreated, in periodontal maintenance or undergoing active therapy.

Differential diagnosis

The differential diagnosis of periodontal abscesses should always consider other abscesses that may occur in the oral cavity (Ahl *et al*. 1986). Acute infections, such as periapical abscesses, lateral periapical cysts, vertical root fractures, and endo-periodontal lesions may have a similar appearance and symptomatology, although their etiology is different, and therefore, their appropriate treatment will depend on an accurate differential diagnosis. Signs and symptoms indicating a periodontal origin include: history of periodontitis or previous periodontal therapy, presence of deep periodontal pockets with suppuration when probed and, usually, tooth vitality. Radiographically, these affected teeth show crestal bone loss and frequently angular bony defects and furcation lesions. A likely periapical (endodontic) origin will include the following signs and symptoms: history of caries or presence of advanced caries lesions, presence of restorations or root canal treatment, questionable response or non-responsive to pulpal vitality tests, and presence of a sinus fistulous tract. Radiologically, there is usually evidence of a periapical radiolucency associated with a carious, restored, or endodontically treated tooth. From the radiograph, the quality of the root canal therapy and the existence of endodontic files or post perforations can be recognized.

The differential diagnosis should also consider other lesions that, although rare, may appear in the oral cavity and have a similar appearance to a periodontal abscess (Table 19-3). In cases where the abscess does not respond to conventional therapy, a biopsy and histopathologic diagnosis is always recommended:

- Tumor lesions, including metastatic lesions, odontogenic myxoma, non-Hodgkin´s lymphoma, squamous cell carcinoma, metastatic carcinoma.
- Other oral lesions: pyogenic granuloma, osteomyelitis, odontogenic keratocyst, eosinophilic granuloma.
- Self-inflicted gingival injuries.
- Sickle cell anemia.
- Abscesses after surgical procedures.

Table 19-3 Differential diagnosis of periodontal abscesses, as shown in different case reports.

Reference	Country	Follow up	Patients (*n*)	Age	Lesions (*n*)	Initial diagnosis	Final diagnosis
Torabinejad & Rick (1980)	USA	16 months	1	49	1	Periodontal abscess	Squamous cell carcinoma
Goose (1981)	UK	5 years	1	56	1	Periodontal abscess	Cracked tooth syndrome
Kirkham *et al*. (1985)	USA	1 year	1	37	1	Odontogenic abscess	Squamous cell carcinoma
Parrish *et al*. (1989)	USA	Variable	3	25–45	3	Periodontal abscess	Osteomyelitis
Girdler (1991)	UK	None	1	27	1	Chronic lateral periodontal abscess	Eosinophilic granuloma
Gunhan *et al*. (1991)	Turkey	4 years	1	27	1	Periodontal abscess	Odontogenic myxoma
Rodd (1995)	UK	5 years	1	7	Multiple	Periodontal condition	Self-inflicted gingival injury
Park (1998)	USA	Unclear	1	52	1	Dental abscess	Non-Hodgkin´s lymphoma
Selden *et al*. (1998)	USA	4 weeks	1	49	1	Acute/dental abscess	Metastatic carcinoma
Hokett *et al*. (2000)	USA	5 years	1	64	1	Abscess	Non-Hodgkin´s lymphoma
Elkhoury *et al*. (2004)	USA	2–3 months	1	44	Multiple	Multiple periodontal abscesses	Metastatic tumoral lesions
Preston & Narayana (2005)	USA	None	1	83	1	Periodontal abscess	Odontogenic keratocyst
Mozaffari *et al*. (2007)	USA	None	1	82	1	Periodontal abscess	Keratocysts
Martinelli-Klay *et al*. (2009)	Brazil	3 years	1	46	1	Dental abscess	Non-Hodgkin´s lymphoma
Kim *et al*. (2012)	Korea	2 years	1	61	1	Periodontal abscess	Squamous cell carcinoma
Panseriya & Hungund (2011)	India	3 months	1	30	1	Periodontal abscess	Pyogenic granuloma
Poulias *et al*. (2011)	USA	2 years	1	55	1	Periodontal abscess	Metastatic breast carcinoma
Farag & Treister (2013)	USA	None	1	33	1	Acute periodontal abscess	Sickle cell anemia

Why periodontal abscesses are relevant

Prevalence

Periodontal abscesses represented approximately 7.7–14.0% of all dental emergencies, being ranked the third most prevalent infection demanding emergency treatment, after dentoalveolar abscesses and pericoronitis (Ahl *et al*. 1986). In an army dental clinic, 27.5% of periodontitis patients presented with periodontal abscesses, with clear differences between patients undergoing active periodontal treatment (13.5%) and untreated patients (59.7%) (Gray *et al*. 1994). Among 114 patients undergoing periodontal maintenance, periodontal abscesses were detected in 42 patients (37%) followed up for 5–29 years (McLeod *et al*. 1997). In the Nebraska prospective longitudinal study, 27 periodontal abscesses were observed for 7 years, and 23 of them occurred in sites that received coronal scaling (Kaldahl *et al*. 1996). Out of the 27 abscesses, 16 had an initial probing pocket depth >6 mm, while at eight sites, it was 5–6 mm.

Tooth loss

The rapid destruction of periodontal tissues, caused by a periodontal abscess, may negatively affect the prognosis of the affected tooth, and it has been considered the main cause of tooth extraction during periodontal maintenance (Smith & Davies 1986; Chace & Low 1993; McLeod *et al*. 1997; Silva *et al*. 2008). Similarly, teeth with repeated abscess formation were considered to have a "hopeless prognosis" (Becker *et al*. 1984), and 45% of teeth with a periodontal abscess found during periodontal maintenance were extracted (McLeod *et al*. 1997). The main reason for tooth extraction of teeth with a questionable prognosis, which had been followed up for 8.8 years, was the presence of periodontal abscess (Chace & Low 1993). Smith and Davies (1986) evaluated 62 teeth with

abscesses: 14 (22.6%) teeth were extracted as initial therapy, and nine (14.5%) after the acute phase and, out of the 22 teeth treated and subsequently monitored, 14 had to be extracted during the following 3 years. It has been suggested that early diagnosis and adequate therapy might be important in the management of a periodontal abscess in patients in supportive periodontal care, since under these conditions the prognosis of the affected tooth may not be affected (Silva *et al*. 2008).

Systemic dissemination of the infection

Periodontal abscesses may be associated with a systemic dissemination of the, initially, localized infection. Numerous case reports/series (Table 19-4) have described the occurrence of systemic infections resulting from a suspected source in a periodontal abscess, either through dissemination (via bacteremia or directly to adjacent tissues), occurring during the treatment of the abscess or related to an untreated abscess.

Necrotizing periodontal diseases

What are necrotizing periodontal diseases

Necrotizing periodontal diseases (NPDs) are a group of periodontal diseases with a characteristic clinical phenotype (papilla necrosis, bleeding, and pain) and associated with different degrees of host immune response impairment (Papapanou *et al*. 2018).

Classification

In the AAP International Workshop for a Classification of Periodontal Diseases in 1999, necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP) were included in NPDs (Lang *et al*. 1999). Some studies suggested that they may represent different stages of the same disease, since they have similar etiology, clinical characteristics and treatment, and may even progress to more severe forms such as necrotizing stomatitis (NS) and noma (Novak 1999; Rowland 1999). The terminology "ulcerative" was

Table 19-4 Systemic complications of periodontal abscesses.

Reference	Country	Study design	Follow up	Patients (*n*)	Age	Name of the condition	Main results
Gallagher *et al*. (1981)	USA	Case report	2 months	1	54	Periodontal abscess	Brain abscess
Suzuki & Delisle (1984)	USA	Case report	18 months	1	62	Multiple periodontal abscess	Pulmonary actinomycosis
Rada *et al*. (1987)	USA	Case series	Variable	2	17, 25	Periodontal abscess	Sickle cell crisis
Pearle & Wendel (1993)	USA	Case report	>9 days	1	42	Periodontal abscess	Acute necrotizing cavernositis
Chan & McGurk (1997)	UK	Case report	1 year	1	40	Periodontal abscess	Cervical necrotizing fascitis
Haraden & Zwemer (1997)	USA	Case report	20 day	1	23	Dental abscess	Descending necrotizing mediastinitis
Manian (1997)	USA	Case series	7–8 months	2	65, 51	Dental abscess	Arm and chest cellulitis, after breast cancer therapy
Waldman *et al*. (1997)	USA	Retrospective	>6 months	3490/74	Not reported	Periodontal abscess	Total knee arthroplasty infection
Sancho *et al*. (1999)	Brazil	Case series	Variable	7	9–71	Odontogenic/dental abscess	Descending necrotizing mediastinitis
Corson *et al*. (2001)	UK	Case report	5 months	1	56	Abscess	Brain abscess
Sawalha & Ahmad (2001)	Jordan	Case report	6 weeks	1	14	Periodontal abscess	Descending necrotizing mediastinitis and pleural empyema
Roy & Ellenbogen (2005)	USA	Case report	Not defined	1	56	Periodontal abscess	Brain abscess
Ren & Malmstrom (2007)	USA	Prospective	1 week	40	Not reported	Acute periodontal abscess	Elevated C-reactive protein levels
Schulze *et al*. (2007)	Germany	Case report	40 days	1	70	Periodontal abscess	Glucose intolerance
Weaver *et al*. (2010)	USA	Case report	Variable	2	37, 60	Odontogenic abscess	Descending necrotizing mediastinitis
Duke *et al*. (2014)	USA	Case report	3 minutes	1	17	Periodontal abscess	Lemierre syndrome with respiratory distress

eliminated, since ulceration was considered to be secondary to necrosis (Feller & Lemmer 2005). NPD patients are frequently susceptible to future recurrence of disease (Johnson & Engel 1986; MacCarthy & Claffey 1991) and NPD could also become a "chronic condition", with a slower rate of destruction (Pindborg 1951). In cases of severe systemic involvement, progression of NPD into other oral lesions could occur (Williams *et al*. 1990; Felix *et al*. 1991).

NUG has been diagnosed for centuries with different names, including Vincent's disease, trench-mouth disease, necrotizing gingivo-stomatitis, fuso-spirochaetal stomatitis, ulcerative membranous gingivitis, acute ulcerative gingivitis, necrotizing ulcerative gingivitis, or acute necrotizing ulcerative gingivitis (Johnson & Engel 1986; Rowland 1999; Holmstrup & Westergaard 2008). NUP was defined both in the 1989 World Workshop (Caton 1989) and in the 1993 European Workshop (Attström & van der Velden 1993).

In the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Herrera *et al*. 2018; Papapanou *et al*. 2018), a new approach for classifying NPDs was suggested and accepted, since the previous concept did not take into account the huge differences in prevalence, risk of progression, and extent/severity of NPD among patients with different predisposing conditions. NPD in HIV/AIDS patients or in malnourished children in developing countries may represent a severe and even life-threating condition (in the latter case). Conversely, NPD in smokers/stressed adult patients in developed countries represented a relevant but normally non-threatening condition. Therefore, patients with a continuously and severely compromised systemic immune system (see previous examples) have a higher risk of suffering from NPD, and of presenting with a faster and more severe progression of the disease (from necrotizing gingivitis [NG] to necrotizing periodontitis [NP], and even to NS and noma). Conversely, in patients with a compromised systemic immune system for a limited duration (e.g. stressful situation in students or militaries), NG may not progress, although the lesions would be different if affecting a gingivitis or a periodontitis patient (Table 19-5).

Etiology, pathogenesis, and histopathology

NPDs are infectious conditions; however, predisposing factors, including a compromised host immune response, are critical in the pathogenesis.

The bacterial etiology of NPD, with the presence of spirochetes and fusiform bacteria, was previously demonstrated by Plaut in 1894, and Vincent in 1896 (reviewed in Rowland 1999). Moreover, clinical improvements observed after mechanical debridement and antimicrobial treatment further supported the bacterial etiology of these conditions (Socransky & Haffajee 1994). Earlier studies, using electron microscopy, suggested tissue invasion by spirochetes (Listgarten 1965; Courtois *et al*. 1983). Studies using bacterial culture identified *P. intermedia,* as well as *Treponema*, *Selenomonas*, and *Fusobacterium* species, which were considered "constant flora" in NPD lesions (Loesche *et al*. 1982). The role of spirochetes was confirmed by immunoassays (Riviere *et al*. 1991a,b) and polymerase chain reaction (PCR) targeting 16s rRNA (Dewhirst *et al*. 2000). Recent studies by phylogenetic analysis also suggested a role of *P. intermedia* and *Peptostreptococcus* genus in the etiology of NPD. The microbiota associated with NPD in HIV is similar to that of periodontitis in non-HIV patients, with some specific features, such as presence/invasion of *Candida albicans,* herpes viruses, or superinfecting bacterial species.

Necrotizing gingivitis lesions, observed with light microscopy (Listgarten 1965), showed the presence of an ulcer within the stratified squamous epithelium and the superficial layer of the gingival connective tissue, surrounded by a non-specific acute inflammatory reaction. Four regions have been described: (1) superficial bacterial area; (2) neutrophil-rich zone; (3) necrotic zone; (4) spirochaetal infiltration zone. Additional findings included plasma cells in the deeper parts and IgG and C3 between epithelial cells (Hooper & Seymour 1979). These observations have been confirmed by electron microscopy, adding areas of transition to a chronic stage of inflammation (Courtois *et al*. 1983).

Predisposing factors

The most relevant predisposing factors for NPD were shown to be those altering the host immune response and usually more than one factor was necessary to cause onset of the disease (Dufty 2014).

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS)

NPD in HIV patients may be more frequent and show faster progression, with an increased risk of evolving into more severe lesions (NP and NS), and an increased tendency for disease recurrence and poor response to therapy.

Other systemic conditions

Different reports have found NPD lesions associated with, or as a consequence of, different systemic conditions, or mimicking NPD, in which the lesions were part of the systemic pathology (Table 19-6 later in the chapter).

Malnutrition

Malnutrition could also be an important predisposing factor for NPD (Buchanan *et al*. 2006), especially in developing countries (Jimenez & Baer 1975;

Table 19-5 Classification of necrotizing periodontal diseases, based on the predisposing factors (2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions). (Sources: Herrera *et al*. 2018; Papapanou *et al*. 2018).

	Necrotizing periodontal diseases									
Category	Continuously and severely immunocompromised patients					Moderately and/or short-term immunocompromised patients				
Patients	In adults		In children			In gingivitis patients				In periodontitis patients
Predisposing factors	HIV+/AIDS with CD4 counts <200 and viral load	Other severe systemic conditions (immuno-suppression)	Severe mal-nourishment[1]	Extreme living conditions[2]	Severe (viral) infections[3]	Uncontrolled factors: psychological stress, nutrition, smoking, habits	Previous NPD: residual craters	Local factors: root proximity, tooth malposition	Common predisposing factors for NPD (see text)	
Clinical condition	NG, NP, NS, noma. Possible progression					Generalized NG. Possible progression to NP		Localized NG. Possible progression to NP	NG. Infrequent progression	NP. Infrequent progression

[1] Mean plasma/serum concentrations of retinol, total ascorbic acid, zinc, and albumin markedly reduced (very marked depletion of plasma retinol, zinc, and ascorbate) and saliva levels of albumin and cortisol, as well as plasma cortisol concentrations, significantly increased.
[2] Living in substandard accommodations, exposure to debilitating childhood diseases, living in close proximity to livestock, poor oral hygiene, limited access to potable water, and poor sanitary disposal of human and animal faecal waste.
[3] Measles, herpes viruses (cytomegalovirus, Epstein–Barr virus-1, herpes simplex virus), chicken pox, febrile illness.
NG, necrotizing gingivitis; NP, necrotizing periodontitis; NPD, necrotizing periodontal diseases; NS, necrotizing stomatitis.

Osuji 1990; Enwonwu *et al*. 2006). A marked reduction in key antioxidant nutrients and an altered acute phase response against infection ("protein energy malnutrition") (Enwonwu 1972; Melnick *et al*. 1988a) have been reported. Other consequences were an inverse proportion in the ratio of helper/suppressor T-lymphocytes, histaminaemia, increased free cortisol in blood and saliva, and defects in mucosal integrity (Enwonwu 1972; Enwonwu *et al*. 1999).

Psychological stress and insufficient sleep

Certain situations of acute psychological stress or stressful situations, some personality traits, or the ability to cope with a stressful situation, may predispose individuals to NPD. During stress periods, the immune response is altered, and the subject's behavior is changed. The biological plausibility of this assumption is based on the reduction of gingival microcirculation and salivary flow; increase in serum and urine levels of 17-hydroxycorticosteroid (17-OHCS) (Maupin & Bell 1975); change in the function of PMN and lymphocytes, and increase in periodontal pathogen levels (*P. intermedia)* (Loesche *et al*. 1982).

Inadequate oral hygiene, pre-existing gingivitis, and previous history of NPD

Plaque accumulation has been considered a predisposing factor for NPD, which may also be aggravated by limited tooth brushing because of pain (Johnson & Engel 1986; Taiwo 1993; Horning & Cohen 1995). NPD usually occurred secondarily to a previously existing periodontal disease: chronic gingivitis (Pindborg 1951; Wilton *et al*. 1971), previous NPD (Horning & Cohen 1995).

Tobacco and alcohol consumption

Most adult patients with NPD are smokers (Pindborg 1951; Giddon *et al*. 1964; Shields 1977; Stevens *et al*. 1984; Robinson *et al*. 1998; Lopez & Baelum 2009). Alcohol consumption has also been associated with the physiological and psychological factors favoring NPD (Horning & Cohen 1995; Magan-Fernandez *et al*. 2015).

Young age and ethnicity

Young people (15–34 years old) in the developed world are at a higher risk of suffering from NPD, frequently in combination with other predisposing factors (Skach *et al*. 1970; Stevens *et al*. 1984; Falkler *et al*. 1987; Horning & Cohen 1995). Children are at a higher risk in developing countries, and this is normally associated with malnutrition and other infections (Malberger 1967; Jimenez & Baer 1975). Some studies suggested that Caucasians suffered from NPD more frequently (Barnes *et al*. 1973; Stevens *et al*. 1984; Horning & Cohen 1995) than other ethnic groups. However, this finding needs to be confirmed.

Seasonal variations

Different studies have evaluated the hypothesis of the effect of seasonal variations on the prevalence of NPD: in central Africa, NPD peaked in the rainy season; less clear patterns were observed in military personnel, students or general populations, although winter months were normally peak periods, except in South Africa.

Other factors

Local factors, including decorative restorations (Flaitz & Agostini 2002) or orthodontic therapy (Sangani *et al*. 2013) may favor the onset of NG. Body geometry (Clark & Giddon 1971), thermoregulatory abnormalities (Giddon *et al*. 1969), allelic variants for complement factors and properdin factor B (Melnick *et al*. 1988b), or erythrocyte catalase activity (Nicol *et al*. 1971) have also been studied with inconclusive results.

Diagnosis

Diagnosis of NPD should be primarily based on clinical findings (Rowland 1999; Corbet 2004). Microbiological or biopsy assessments may be recommended in cases of atypical presentations or non-responding cases.

Necrotizing gingivitis

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou *et al*. 2018), a case of NG is primarily defined by the presence of necrosis/ulcer of the interdental papillae, gingival bleeding, and pain. Secondary signs/symptoms include halitosis, pseudomembrane formation, regional lymphadenopathy, fever, and sialorrhea (in children). This case definition was proposed based on the findings of the review paper presented at the Workshop (Herrera *et al*. 2018), which pooled together studies with a relevant number of cases (35 or more) (Barnes *et al*. 1973; Stevens *et al*. 1984; Falkler *et al*. 1987; Horning & Cohen 1995). In these studies, the most relevant clinical findings were: necrosis/ulcer in the interdental papilla (94–100%), gingival bleeding (95–100%), pain (86–100%), pseudomembrane formation (73–88%), and halitosis (84–97%) (Fig. 19-7). Extraoral signs included adenopathy (44–61%) or fever (20–39%). In children (Jimenez & Baer 1975), pain and halitosis were less frequent, while fever, adenopathy, and sialorrhea were more frequent.

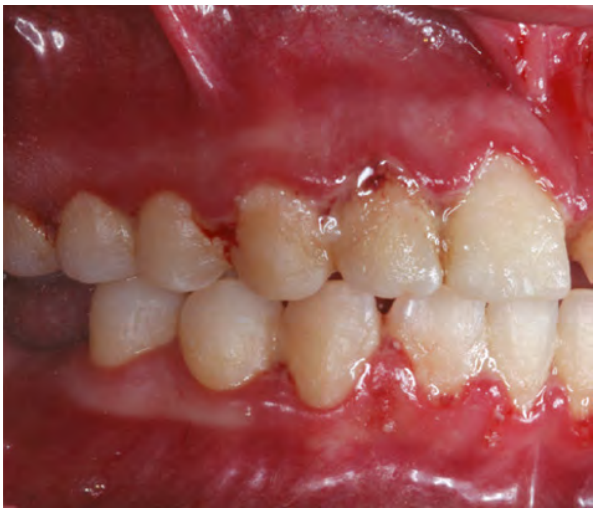

Fig. 19-7 Necrotizing gingivitis in a 22-year-old woman: bleeding, necrosis, and pseudomembrane can be observed. (Source: Courtesy of Dr. Belén Retamal-Valdes.)

Necrotizing periodontitis

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou *et al*. 2018), a case of NP should primarily include necrosis/ulcer of the interdental papillae, gingival bleeding, halitosis, pain, and rapid bone loss (Fig. 19-8). Secondary signs/symptoms are pseudomembrane formation, lymphadenopathy, and fever. This case definition was proposed based on the findings of the review paper presented at the Workshop (Herrera *et al*. 2018), in which, in addition to the signs/symptoms observed in NG, periodontal attachment and bone destruction were considered as relevant, together with more frequent extraoral signs (Cobb *et al*. 2003). In severely immune-compromised patients, bony sequestra can occur (Umeizudike *et al*. 2011). NP could be the result of one or various episodes of NG (not always associated with pocket formation), or of NG occurring at a site previously affected by periodontitis (periodontal pocketing would be found) (Barr & Robbins 1996; Novak 1999).

Necrotizing stomatitis

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Papapanou *et al*. 2018), NS is primarily defined by the presence of soft tissue necrosis that extends beyond the gingiva, with bone denudation that may occur through the alveolar mucosa, with larger areas of osteitis and formation of bone sequestrum. It typically occurs in severely systemically compromised patients (HIV/AIDS patients, severe malnutrition). Atypical cases have also been reported, in which NS may develop without prior appearance of NG/NP lesions (Jones *et al*. 2000; Barasch *et al*. 2003; Salama *et al*. 2004; Feller *et al*. 2005).

It is mandatory to establish a differential diagnosis with vesicular–bullous diseases, primary or recurrent herpetic gingivostomatitis (Guggenheimer & Fletcher 1974; Lerman & Grodin 1977), oral manifestation mimicking NPD lesions, and toothbrush abrasion (Page *et al*. 1980) (Table 19-6).

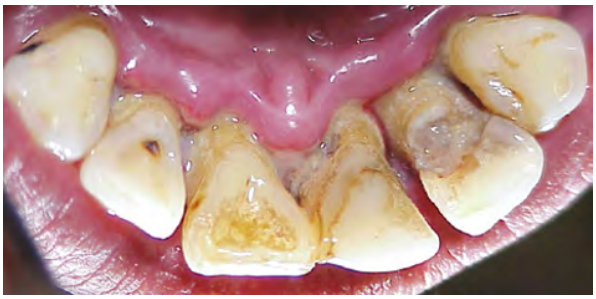

Fig. 19-8 Necrotizing periodontitis: presence of necrosis/ulcer of the interdental papillae. (Source: Courtesy of Dr. Mauro Santamaria.)

Why necrotizing periodontal diseases are relevant

Epidemiology

Prevalence/incidence of NPDs has been reported for the overall population or for specific groups of individuals:

- In general populations attending dental clinics, the prevalence of NG ranged from 0.51 to 3.30% (Skach *et al*. 1970; Stevens *et al*. 1984; Falkler *et al*. 1987; Arendorf *et al*. 2001).
- In military personnel (Schluger 1949; Pindborg 1951; Grupe 1956; Shannon *et al*. 1969; Barnes *et al*. 1973; Horning *et al*. 1990; Minneman *et al*. 1995), the prevalence/incidence reported was higher close to the end of the Second World War (3.96–20.6%) than it was in more recent studies (0.19–6.19%).
- In African populations (Sheiham 1966; Malberger 1967; Enwonwu 1972; Osuji,1990; Taiwo 1993; Enwonwu *et al*. 1999; Kaimenyi 1999), highly variable results have been reported.
- In students (Giddon *et al*. 1963, 1964; Lopez *et al*. 2002; Lopez & Baelum 2004; Lopez & Baelum 2009), prevalence ranged from 0.9 to 6.7%.
- In HIV/AIDS patients data showed wide variations: children (2.2–5%), HIV adult patients (0.0–27.7% for NG and 0.3-9% for NP), and HIV/AIDS patients (10.1–11.1% for NG and 0.3–9% for NP) (Laskaris *et al*. 1992; Riley *et al*. 1992; Glick *et al*. 1994a,b; Robinson *et al*. 1998; Flaitz *et al*. 2001; Tappuni & Fleming 2001; Reichart *et al*. 2003; Sharma *et al*. 2006; Tirwomwe *et al*. 2007; Sontakke *et al*. 2011).

Severe destruction, sequalae, and risk of recurrence

NPD are considered among the most severe inflammatory conditions associated with oral biofilm bacteria (Holmstrup & Westergaard 2008), as they can progress rapidly and cause severe tissue destruction.

Table 19-6 Differential diagnosis of necrotizing periodontal diseases in case reports.

Reference	Country	Study	Patients (*n*)	Age	Gender	Periodontal condition	Other condition	Main results
Aker *et al*. (1978)	USA	Case report	1	17	Male	Initially "trench mouth" NUG	Acute lymphocytic leukemia	Disorders (leukemia) may share some of the clinical features of NUG
Page *et al*. (1980)	USA	Case report	1	35	Male	ARG	Unknown etiology, toothbrush abrasion	ARG is self-limiting and recurrent
Groot *et al*. (1990)	Netherlands	Cases series	3	44, 35, 42	Males	Initially generalized periodontitis with ANUG in AIDS patient	Primary oral malignant NHL	Striking resemblance to ANUG
Musa *et al*. (2002)	USA	Case report	1	9	Female	NUG	Oral cicatricial pemphigoid	Child with cicatricial pemphigoid, clinically manifested as NUG
Mucke *et al*. (2010)	Germany	Case report	1	76	Male	NG	Gingival angiosarcoma	Gingival angiosarcoma mimicking NG
Genuis & Pewarchuk (2014)	Canada	Case report	1	32	Female	Severe NG	Granulomatosis with polyangiitis (Wegener´s)	Granulomatosis with polyangiitis poses a significant diagnostic dilemma due its diverse presentations

ACPD, advanced chronic periodontal disease; AIDS, acquired immune deficiency syndrome; ARG, acute recurrent gingivitis; ANUG, acute necrotizing ulcerative gingivitis; ChP, chronic periodontitis; EBV-1 and EBV-2, Epstein-Barr viruses type 1 and type 2; GenP, generalized periodontitis; HCMV, human cytomegalovirus; HHV-6, human herpes virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HSV, herpes simplex virus; LPJ, localized juvenile periodontitis; NG, necrotizing gingivitis; NHL, non-Hodgkin's lymphoma; NUG, necrotizing ulcerative gingivitis; P, periodontitis.

It is, therefore, important to control predisposing factors, and once disease develops, to act quickly in order to limit its progression and exacerbation. Thus, these conditions should be managed promptly, and there is evidence that NPD can be controlled by means of an adequate periodontal treatment (Fig. 19-9), combined with effective oral hygiene measures and control of predisposing factors (Johnson & Engel 1986) (see Chapter 31).

NG patients, however, are frequently susceptible to future disease recurrence, mostly because of the difficulties in controlling predisposing factors as well as the challenge in achieving proper supragingival biofilm control. This is in part because of the sequelae of these diseases, mainly the presence of gingival craters (MacCarthy & Claffey 1991). NG can heal without clinical sequelae (Bermejo-Fenoll & Sanchez-Perez 2004), but often the necrotizing lesion extends laterally from the papilla to the gingival margin, affecting both the buccal and lingual sites and progresses to other sites in the mouth, progressing also from a localized into a generalized disease. It may also extend apically, leading to NP. As explained before, NP can be the result of one or more episodes of NG, or the result of an NPD affecting a site with periodontitis (Novak 1999). NPD can also become chronic, with a slow reduction in its symptomatology and progression, with ensuing destruction, although at a slower rate (Pindborg 1951; Holmstrup & Westergaard 2008).

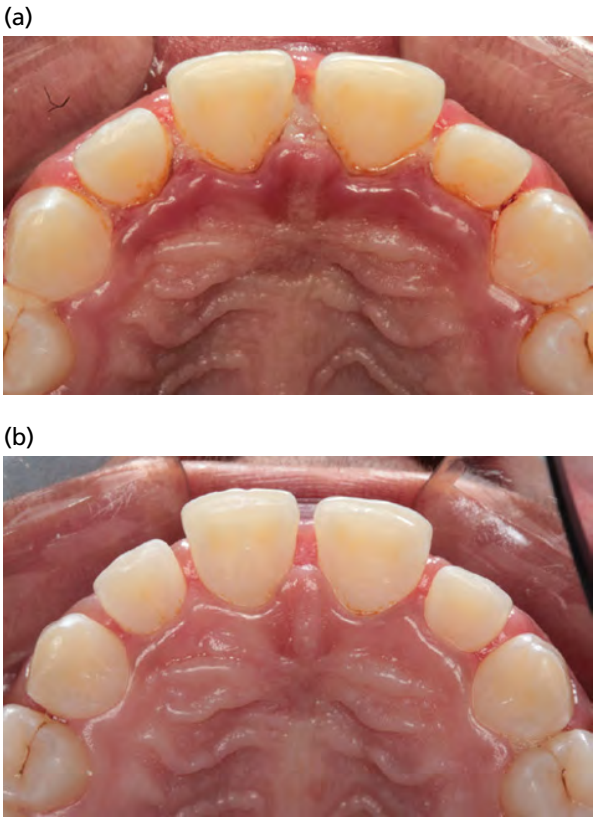

Fig. 19-9 Healing of necrotizing gingivitis lesions in the upper anterior sextant. (a) Active lesions with necrosis the interdental papillae. (b) Complete resolution after 60 days. (Source: Courtesy of Dr. Nidia Castro dos Santos and Dr. Mauro Santamaria.)

Life-threatening conditions

In cases of severe systemic involvement, such as in AIDS or severe malnutrition, NG and NP can progress further, with rapid involvement of the oral mucosae. The severity of these lesions is normally related to the severity of the systemic condition and the compromised immune host-response, leading to extensive bone destruction and presence of large osteitis lesions and oral-antral fistulae (Williams *et al*. 1990), with common features with *Cancrum oris* or noma. Some investigators suggested that noma is a progression of NP affecting the skin, whereas others believe that NS and noma are two distinct clinical entities. Noma is a destructive gangrenous disease affecting the facial tissues. It is associated with high mortality and morbidity rates (Enwonwu 1985; Baratti-Mayer *et al*. 2003; Enwonwu *et al*. 2006), and it is almost exclusively observed in developing countries, especially in children suffering from systemic diseases, including severe malnutrition. Noma is normally preceded by measles, malaria, severe diarrhea, and NG, which highlights the importance of prevention, early detection, and treatment during the first stages of the disease (Rowland 1999).

Endo-periodontal lesions

Under physiological conditions, the periodontal supporting tissues and the pulp/root canal complex exist in equilibrium. If the pulp or the periodontium suffer an injury, microorganisms and inflammatory products affecting one structure may also affect the other. Most of the time, these pathological communications are contained after effective periodontal or root canal treatment. For example, if the root canal is infected, even if a certain degree of cross-contamination with the periodontium occurs, in most cases this contamination would vanish after the proper root canal treatment. However, serious damage to the pulp/root canal complex and the periodontium in the same tooth, accompanied by a deep periodontal pocket and altered sensitivity test, is called an endo-periodontal lesion (EPL).

Classification

EPLs have been termed retrograde periodontitis, endodontic–periodontal lesions, or periodontal–endodontic lesions (Simring & Goldberg 1964; Simon *et al*. 1972; Al-Fouzan 2014). In 1972, Simon *et al*. published the first classification system for EPLs, which was widely used for decades and included five main categories: (1) primary endodontic lesions; (2) primary endodontic lesions with secondary periodontal involvement; (3) primary periodontal lesions; (4) primary periodontal lesions with secondary endodontic involvement; and (5) "true" combined lesions. The rationale behind this classification system, and a recent proposed amendment (Al-Fouzan 2014), is the assumption that lesions of periodontal origin have a worse prognosis than those of endodontic origin. However, it became clear that using "history of the disease" as the main criterion for diagnosis was not practical, because once the lesion is established, it is difficult to be sure whether the lesion was primarily endodontic, periodontal, or a combination of both (Herrera *et al*. 2018). In addition, determining the primary source of infection may not be so relevant for the treatment of EPLs, as both the root canal and the periodontal tissues would require treatment (Chapple & Lumley 1999; Meng 1999b). In 1999, the AAP included EPLs for the first time in its classification system, under the name "combined periodontal–endodontic lesions" (Armitage 1999; Meng 1999b). However, no categories were proposed, reducing the usefulness of this system. Ideally, classification systems should be based on signs and symptoms that can be assessed when the lesion is detected, and should provide categories able to guide the prognosis and treatment of the condition. In 2017, the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Caton *et al*. 2018; Herrera *et al*. 2018; Papapanou *et al*. 2018) proposed a new classification for EPLs, based on the prognosis of the tooth involved and on the following signs and symptoms: (1) presence or absence of root damage; (2) presence or absence of periodontitis; and (3) the extent of the periodontal destruction around the affected tooth. This classification scheme is presented in Table 19-7. Three main prognostic categories for a tooth affected by an

Table 19-7 Endo-periodontal lesions classification. (Source: Herrera *et al*. 2018.)

Endo-periodontal lesion with root damage	Root fracture or cracking	
	Root canal or pulp chamber perforation	
	External root resorption	
Endo-periodontal lesion without root damage	Endo-periodontal lesion in periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in more than 1 tooth surfaces
	Endo-periodontal lesion in non-periodontitis patients	*Grade 1* – narrow deep periodontal pocket in 1 tooth surface
		Grade 2 – wide deep periodontal pocket in 1 tooth surface
		Grade 3 – deep periodontal pockets in more than 1 tooth surfaces

EPL were suggested: hopeless, poor, and favorable. The hopeless prognosis is normally associated with EPL accompanied by root damage (e.g. fracture or perforation), whereas the prognosis of a tooth with an EPL associated with endodontic and periodontal infections may range from favorable to hopeless, depending on the extent of the periodontal destruction around the affected tooth, and the presence and severity of periodontitis in the mouth (Herrera *et al*. 2018).

Etiology

EPLs are always associated with variable degrees of microbial contamination of the dental pulp and the periodontal tissues. However, the primary etiology of these lesions may be: a trauma and/or iatrogenic factor (non-infectious origin), or an endodontic and/or periodontal infection (infectious origin) (Herrera *et al*. 2018).

Endo-periodontal lesions associated with trauma and iatrogenic factors

These are EPLs of non-infectious origin. They normally have a hopeless or poor prognosis and are caused by trauma or iatrogenic events affecting the pulp and the periodontium. The most common lesions in this category are: (1) root/pulp chamber/furcation perforation (e.g. because of root canal treatment or tooth preparation for post-retained restorations) (Karabucak & Setzer 2009; Asgary & Fazlyab 2014; Tobón-Arroyave *et al*. 2004); (2) root fracture or cracking (e.g. because of trauma or tooth preparation for post-retained restorations) (Nicopoulou-Karayianni *et al*. 1997; Karabucak & Setzer 2009; Floratos & Kratchman 2012); (3) external root resorption (because of trauma) (White & Bryant 2002); and (4) pulp necrosis (because of trauma) draining through the periodontium (Tobón-Arroyave *et al*. 2004). The latter type of lesion has the best prognosis among all lesions in this category, because it is not associated with root damage.

Endo-periodontal lesions associated with endodontic and periodontal infections

These are lesions of infectious origin that may be initiated: (1) by a carious lesion that affects the pulp and, secondarily, affects the periodontium; (2) by periodontal destruction that secondarily affects the root canal; or (3) by both events concomitantly. The latter type occurs less frequently and it is usually referred to as a "true-combined" or "combined" lesion (Simon *et al*. 1972; Solomon *et al*. 1995; Singh 2011; Didilescu *et al*. 2012). Their prognosis varies, from favorable to very poor, depending on the extension of the lesion and the presence of periodontitis in the mouth.

EPLs may occur in subjects with periodontal health or disease, and the periodontal status was one of the main features in the new classification scheme of EPLs (Tables 19-7, 19-8, and 19-9). The periodontal condition has an important impact on the prognosis of these lesions because of the striking changes in the oral ecology of subjects with periodontitis (Socransky *et al*. 1998; Ximenez-Fyvie *et al*. 2000a,b; Mager *et al*. 2003; Socransky & Haffajee 2005; Faveri *et al*. 2006; Haffajee *et al*. 2008). Converting this ecology back into a healthy state is quite a difficult task (Teles *et al*. 2006; Soares *et al*. 2014; Feres *et al*. 2015; Tamashiro *et al*. 2016), especially in patients with advanced periodontitis and in teeth with deep pockets, as is the case in EPLs. Therefore, a detailed periodontal examination is a very important step for an accurate diagnosis, prognosis, and treatment plan of EPLs.

Microbiology

The microbiota of EPLs has been assessed by several investigators using different diagnostic tests (Table 19-10), such as microbial culture (Kipioti *et al*. 1984; Kobayashi *et al*. 1990; Pereira *et al*. 2011), PCR (Rupf *et al*. 2000; Pereira *et al*. 2011; Didilescu *et al*. 2012; Xia & Qi 2013; Li *et al*. 2014), checkerboard DNA–DNA hybridization (Didilescu *et al*. 2012), next generation sequencing (NGS) (Gomes *et al*. 2015), and denaturing gradient gel electrophoresis (DGGE)/cloning and sequencing (Xia & Qi 2013; Li *et al*. 2014). Taken together, the results of these studies suggested a marked similarity between the microbiota of root canals and periodontal pockets. Most of the species found in both niches are well recognized periodontal pathogens from the so-called red and orange complexes (Socransky *et al*. 1998), such as *P. gingivalis*, *T. forsythia*, *P. micra*, and species from the genera *Fusobacterium*, *Prevotella,* and *Treponema* (Rupf *et al*. 2000; Pereira *et al*. 2011; Didilescu *et al*. 2012). The studies using molecular techniques (Xia & Qi 2013; Aksel &Serper 2014; Gomes *et al*. 2015) observed high microbial diversity in both periodontal and endodontic samples and identified less common taxa, such as *Filicator alocis*, *Enterococcus faecalis*, and species from the genera *Desulfobulbus, Dialister*, and *Fretibacterium*. Incidentally, most of these species/genera have also been associated, recently, with the etiology of periodontitis (Griffen *et al*. 2012; Abusleme *et al*. 2013; Galimanas *et al*. 2014; Perez-Chaparro *et al*. 2014; Camelo-Castillo *et al*. 2015; Chen *et al*. 2015a; Kirst *et al*. 2015; Park *et al*. 2015; Dabdoub *et al*. 2016; Oliveira *et al*. 2016; Perez-Chaparro *et al*. 2018; Shi *et al*. 2018; Schulz *et al*. 2019; Feres *et al*. 2020; Ikeda *et al*. 2020).

It should be emphasized that with the exception of one study (Xia & Qi 2013), all the other studies evaluated the microbiota of EPLs in subjects with periodontitis, in teeth with advanced periodontal destruction, and without extensive restorations or cavities, suggesting that the primary source of infection was the periodontal microbiota. Therefore, one could argue that cases of EPLs of primary endodontic origin could harbor a different microbiota. Nonetheless, the studies that evaluated the microbiota associated

Table 19-8 Main characteristics of the endo-periodontal lesions, stratified by periodontal condition and study design. (Source: Herrera *et al*. 2018.)

Periodontal condition	Study design	References	Number of teeth included	Percentage (%) of studies reporting different signs and symptoms according to study design								
				Deep periodontal pocket (≥5 mm)	Altered pulp response	Purulent exudate	Apical bone resorption	Sinus tract	Tooth mobility	Gingival color alteration	Crow color alteration	Pain
Periodontitis patients	CR	Blanchard *et al*. (2010); Aksel & Serper (2014)	5	100	100	50	100	50	50	0	0	100
	CS	Kipioti *et al*. (1984); Kobayashi *et al*. (1990); Rupf *et al*. (2000); Pereira *et al*. (2011); Didilescu *et al*. (2012); Fatemi *et al*. (2012); Li *et al*. (2014); Gomes *et al*. (2015)	190	100	100	0	75	0	12.5	0	0	25
	RCT	Cortellini *et al*. (2011); Gupta *et al*. (2015)	62	100	100	0	0	0	0	0	0	0
	Total		**257**	**100**	**100**	**8.3**	**83.3**	**8.3**	**16.6**	**0**	**0**	**33.3**
Non-periodontitis patients	CR	Haueisen & Heidemann (2002); White & Bryant (2002); Kerezoudis *et al*. (2003); Koyess &Fares (2006); Ballal *et al*. (2007); Karabucak & Setzer (2009); Oh *et al*. (2009); Singh (2009); Attam *et al*. (2010); Gandhi *et al*. (2011); Mali *et al*. (2011); Pickel (2011); Floratos & Kratchman (2012); Oh (2012); Coraini *et al*. (2013); Asgary & Fazlya (2014); Fujii *et al*. (2014); Goyal (2014); Jivoinovici *et al*. (2014); Kambale *et al*. (2014); Keceli *et al*. (2014); Kishan *et al*. (2014); Castelo-Baz *et al*. (2015); Miao *et al*. (2015); Nagaveni *et al*. (2015); Sharma *et al*. (2015); Sooratgar *et al*. (2016)	39	100	100	33.3	70.3	33.3	29.6	3.7	7.4	55.5
	CS	Xia & Qi (2013)	13	100	100	0	100	0	0	0	0	0
	Total		**52**	**100**	**100**	**32.1**	**71.4**	**32.1**	**28.5**	**3.5**	**7.1**	**53.5**
Unclear	CR	Solomon *et al*. (1995); Tseng *et al*. (1996); Tobón-Arroyave *et al*. (2004); Narang *et al*. (2011); Karunakar *et al*. (2014); Varughese *et al*. (2015)	8	100	100	83.3	100	33.3	66.6	0	0	50
	CrS	Rhee *et al*. (2014)	168	100	100	0	100	0	0	0	0	0
	CS	Li *et al*. (2014); Nicopoulou-Karayianni *et al*. (1997); (Pereira *et al*. (2011)	69	100	100	0	100	0	0	0	0	0
	Total		**245**	**100**	**100**	**50**	**100**	**20**	**40**	**0**	**0**	**30**
Final total		**Number of studies: 50**	**554**	**100**	**100**	**30**	**80**	**24**	**28**	**5**	**4**	**44**

CR, Case report; CrS, Cross-sectional; CS, Clinical study; RCT, Randomized clinical trial.

Table 19-9 Risk factors reported in clinical studies that evaluated endo-periodontal lesions stratified by study design. (Source: Herrera *et al*. 2018.)

Study design	Number of studies	Reference	Number of teeth included	Percentage (%) of studies reporting different risk factors according to study design						
				Grooves	Trauma	Furcation involvement	Porcelain-fused-to-metal crowns	Post-preparation	Carious lesions	Periodontitis
Clinical study	7	Kipioti *et al*. (1984); Kobayashi *et al*. (1990); Rupf *et al*. (2000); Pereira *et al*. (2011); Didilescu *et al*. (2012); Li *et al*. (2014); Gomes *et al*. (2015)	170	0.0	0.0	0.0	0.0	0.0	0.0	100
Case report	20	White & Bryant (2002); Kerezoudis *et al*. (2003); Tobón-Arroyave *et al*. (2004); Ballal *et al*. (2007); Karabucak & Setzer (2009); Oh *et al*. (2009); Attam *et al*. (2010); Blanchard *et al*. (2010); Gandhi *et al*. (2011); Mali *et al*. (2011); Pickel (2011); Floratos & Kratchman (2012); Coraini *et al*. (2013); Asgary & Fazlyab (2014); Goyal (2014); Kambale *et al*. (2014); Kishan *et al*. (2014); Castelo-Baz *et al*. (2015); Miao *et al*. (2015); Sharma *et al*. (2015)	30	50.0	20.0	20.0	20.0	10.0	10.0	0.0
Final total		**Number of studies: 27**	**200**	**37.0**	**14.8**	**14.8**	**14.8**	**7.4**	**7.4**	**25.9**

with different types of endodontic lesions (e.g. necrotic pulp, endodontic infection associated with pulp space exposed or unexposed to the oral cavity, acute or chronic apical endodontic lesions, and symptomatic irreversible pulpitis) also mainly identified those microorganisms normally found in the periodontal microbiota (Sassone *et al*. 2007; Siqueira & Rocas 2009; Siqueira *et al*. 2011; Santos *et al*. 2011; Sassone *et al*. 2012; Rocas *et al*. 2016).

Taken together, the abovementioned data suggest that there are no major differences between the microorganisms found in endodontic and periodontal lesions, or a specific microbial profile associated with the EPLs. This was somehow expected, as both sites of infection (root canal and periodontal pockets) are anaerobic environments exposed to similar nutrients.

Pathogenesis and histopathology

The dental pulp and the periodontium have different communication pathways, such as the apical radicular foramina, accessory (or lateral) canals, and dentinal tubules (Seltzer *et al*. 1963). The prevalence and location of accessory canals have been studied as they may influence the development of EPLs. Studies evaluating extracted teeth described a high prevalence of accessory canals, predominantly at the apical third of the roots. Nonetheless, they were also observed in high numbers in other portions of the roots, such as in the furcation regions of multirooted teeth (Seltzer *et al*. 1963; Rubach & Mitchell 1965). Under normal conditions, these paths between the pulp/canal complex and the periodontal tissues are aseptic and filled with capillaries, cells, fluids, and fibers (Seltzer *et al*. 1963; Rubach & Mitchell 1965). The pathological communication between these structures was first described in 1964 by Simring and Goldberg, and this may allow the migration of microorganisms or their by-products and/or inflammatory mediators from the root canal to the periodontium, or vice-versa, leading to an EPL (Lang & McConnell 1920;

Seltzer *et al*. 1963; Mazur & Massler 1964; Rubach & Mitchell 1965; Simon *et al*. 1972; Langeland *et al*. 1974; Zuza *et al*. 2012).

The influence of pulp disease in the periodontium is overall, well established, but the opposite route of contamination has been a topic of controversy. Granulomatous lesions or abscesses caused by infected/necrotic pulp can be formed around the root apex or in other parts of the root. It was demonstrated that the progression of this periradicular lesion may generate localized periodontal attachment loss, bone destruction, and may drain through the gingival sulcus/periodontal pocket (Seltzer *et al*. 1963; Rubach & Mitchell 1965; Hirsch & Clarke 1993). The influence of periodontal diseases in the pulp was reported by several histological studies that analyzed extracted teeth with periodontal destruction but free of carious lesions and/or extensive restorations. These studies consistently showed varying degrees of pulp alterations, such as altered nutritional supply, necrosis, atrophic, and degenerative changes (e.g. reduction/increase in number of pulp cells), and presence of calcifications, fibrosis, and reparative dentine (Lang 1920; Seltzer *et al*. 1963; Rubach & Mitchell 1965: Langeland *et al*. 1974: Zuza *et al*. 2012). Although most of these studies have suggested a positive association between the severity of periodontal destruction and the pulp alterations, a few histological (Mazur & Massler 1964; Bergenholtz & Lindhe 1978; Czarnecki & Schilder 1979) and animal studies (Hattler *et al*. 1977; Bergenholtz & Lindhe 1978) failed to show any correlation.

Risk factors

The main risk factors for the occurrence of EPL are advanced periodontitis, trauma, and iatrogenic events. Other reported risk factors were the presence of grooves, furcation involvement, porcelain-fused-to-metal crowns, and active carious lesions (Herrera *et al*. 2018) (Table 19-9). Several of these studies clearly specified that the teeth affected by EPLs had porcelain-fused-to-metal crowns, and thus, this type of crown was listed above as a risk factor for this condition. Nonetheless, in theory, any type of prosthesis could be considered as a risk factor for EPLs through different mechanisms: they may invade the biological width or favor the accumulation of biofilm, with consequent coronal leakage and recontamination of the endodontic filling.

Furcation involvement, severe bone destruction around the affected tooth, and anatomic problems (e.g. the presence of grooves) could worsen the prognosis of EPLs. Indeed, most of the single EPLs in non-periodontitis patients reported in the literature were associated with palatal grooves (Kerezoudis *et al*. 2003; Ballal *et al*. 2007; Attam *et al*. 2010; Gandhi *et al*. 2011; Coraini *et al*. 2013; Kishan *et al*. 2014; Castelo-Baz *et al*. 2015; Chen *et al*. 2015b; Sharma *et al*. 2015; Sooratgar *et al*. 2016).

Clinical presentation and diagnosis

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Caton *et al*. 2018; Herrera *et al*. 2018; Papapanou *et al*. 2018), an EPL is a pathologic communication between the pulpal and periodontal tissues at a given tooth that may occur in an acute (symptomatic) or a chronic (asymptomatic) form. The review paper presented at the Workshop to support the new classification of EPLs revealed that the most relevant clinical findings associated with EPLs are the presence of deep periodontal pockets reaching or close to the apex and negative or altered response to pulp sensitivity tests (Herrera *et al*. 2018). Normally, EPLs do not present evident symptoms, but if they are associated with a recent traumatic or iatrogenic event (e.g. root fracture or perforation), the most common manifestation is an abscess accompanied by spontaneous pain or pain on palpation and/or percussion. The other described signs and symptoms were: bone resorption in the apical or furcation region, purulent exudate, tooth mobility, sinus tract, presence of crown, and gingival color alterations (Table 19-8) (Herrera *et al*. 2018).

The diagnosis of EPLs should primarily comprise anamneses and clinical findings, including radiography (Meng 1999b; Herrera *et al*. 2018). Patient history is important for identifying the occurrence of trauma, and previous endodontic treatment/instrumentation or post preparation. If one or more of these events are identified, detailed clinical and radiographic examinations should be conducted to evaluate the presence of perforation, fracture, cracking, or external root resorption. Careful radiographic evaluation and clinical examination of the root anatomy is of great importance at this stage, to assess the integrity of the root and to help with diagnosis. A radicular groove, for example, might mimic a vertical root fracture in the radiograph (Attam *et al*. 2010).

If perforations and fractures are not identified, the diagnosis should proceed to a second stage, consisting of full-mouth periodontal assessment, including probing depth, presence of cavities, attachment level, bleeding on probing, suppuration and mobility, as well as tooth vitality and percussion tests. The sensitivity test is an essential step of the diagnosis, since an altered or negative test is required to define the presence of an EPL (Gupta *et al*. 2011). Even if a radiographic communication between the root canal and the periodontium through the apical foramen is detected, a vital pulp suggests that the host's defense system is being effective to protect the pulp tissue against the invasion of microorganisms (Yu & Abbott 2007; Zuza *et al*. 2012). Figure 19-10 presents

Table 19-10 Studies that evaluated the microbiota of endo-periodontal lesions. (Source: Herrera *et al*. 2018.)

Reference	Study design	Number of teeth studied	Technique	Periodontitis patient	Main finding
Kipioti *et al*. (1984)	Clinical study	16	Culture	Yes	The majority of isolates in periodontal pockets and root canals were *Bacteroides gingivalis* (currently *Porphyromonas gingivalis*) and *Bacteroides melaninogenicus ss intermedius* (currently *Prevotella intermedia*)
Kobayashi *et al*. (1990)	Clinical study	15	Culture	Yes	The predominant bacterial species in periodontal pockets and root canals were from the genera *Streptococcus*, *Peptostreptococcus*, *Eubacterium*, *Bacteroides*, *Fusobacterium*, *Actinomyces*, and *Streptococcus*
Pereira *et al*. (2011)	Clinical study	27	Culture/PCR	Yes	The most prevalent species in periodontal pockets and root canals were *Porphyromonas gingivalis*, *Prevotella intermedia,* and *Prevotella nigrescens*
Didilescu *et al*. (2012)	Clinical study	46	PCR/ checkerboard DNA–DNA hybridization	Yes	The predominant bacterial species in periodontal pockets and root canals were *Fusobacterium nucleatum*, *Campylobacter rectus, Eubacterium nodatum, Eikenella corrodens, Parvimonas micra*, and *Capnocytophaga sputigena*
Xia & Qi (2013)	Clinical study	13	PCR/DGGE, cloning, and sequencing	No	The similarity of bacteria in dental plaque and necrotic pulp ranged from 13.1% to 62.5%. The main genera identified in dental plaque were *Campylobacter*, *Fusobacterium*, *Neisseria*, *Peptostreptococcus, Veillonella, Aggregatibacter, Enterobacter*, and *Haemophilus,* and in necrotic pulps were *Mogibacterium*, *Corynebacterium, Neisseria and Actinomyces*
Li *et al*. (2014)	Clinical study	20	PCR/DGGE, cloning, and sequencing	Yes	The predominant bacterial species in periodontal pockets and root canals were *Filifactor alocis*, *Parvimonas micra*, *Porphyromonas gingivalis*, and *Tannerella forsythia*
Rupf *et al*. (2000)	Clinical study	31	Real-time PCR	Yes	The most prevalent bacterial species in periodontal pockets and root canals were *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Eikenella corrodens, Fusobacterium nucleatum, Prevotella intermedia, Porphyromonas gingivalis*, and *Treponema denticola*
Gomes *et al*. (2015)	Clinical study	15	Next generation sequencing	Yes	*Enterococcus faecalis, Parvimonas micra* **and** *Filifactor alocis* were among the most prevalent species in both root canals and periodontal pockets. Other species were also predominant in root canals (*Mogibacterium timidum*, *Fretibacterium fastidiosum*) or in periodontal pockets (*Streptococcus constellatus*, *Eubacterium brachy*, *Tannerella forsythia*).

DGGE, denaturing gradient gel electrophoresis; PCR, polymerase chain reaction.

the main steps for a proper diagnosis of an EPL in clinical practice.

Some EPLs are associated with a sinus tract, which are not always located in the exact direction of the affected root/tooth. In these cases, the clinician may use the gutta-percha tracing approach to help locate the tooth/root affected by the lesion. It consists of introducing a gutta-percha cone in the sinus tract in order to trace its path using x-rays. By inserting the gutta-percha cone in the periodontal pocket, the same strategy may be used to track the path of the pocket to the apex of the affected root/tooth.

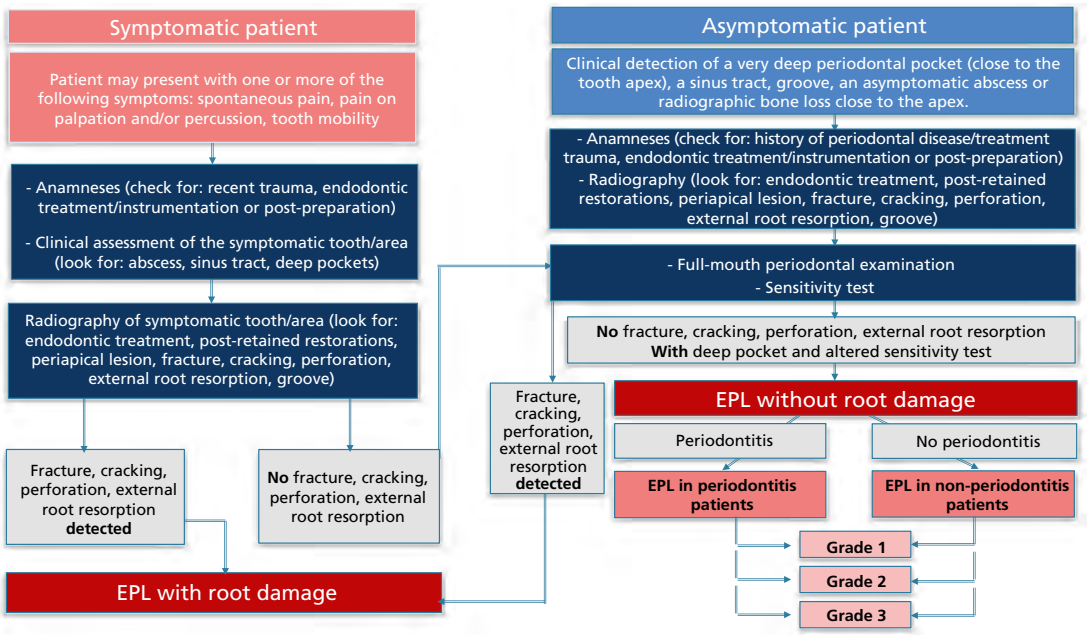

Fig. 19-10 Diagnostic tree for endo-periodontal lesions (EPL).

Summary

Periodontal abscesses should be classified according to the etiological factors involved in their development, since they can present distinct etiologies, commonly associated with reduced drainage of a deep periodontal pocket. Their relevance is based on rapid tissue destruction, which may compromise tooth prognosis, becoming one of the main reasons for tooth extraction in supportive periodontal care. In addition, relevant, but not frequent, systemic risks have been associated with periodontal abscesses.

NPDs typically show three main clinical findings, namely papillary necrosis, bleeding, and pain, and they are considered as the most severe biofilm-related periodontal conditions. A compromised host immune response is crucial to the onset, severity, extent, and progression of NPDs. As such, these diseases need to be classified according to the level of impairment of the immune system.

For EPLs, a pathological communication between the endodontic and periodontal tissues is established, and the lesion can show an acute or a chronic course. It is recommended that they should be classified according to the signs and symptoms that may have a direct impact on their prognosis and treatment, including the presence or absence of fractures and perforations, the presence or absence of periodontitis, and the extent of periodontal destruction around the affected teeth.

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Part 7: Peri-Implant Pathology

Chapter 20

Peri-Implant Mucositis and Peri-Implantitis

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Introduction

Peri-implant disease is a collective term used to describe inflammatory processes in tissues that surround dental implants and includes two entities: peri-implant mucositis and peri-implantitis. A new classification of peri-implant diseases was proposed at the 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions (Berglundh *et al*. 2018) and case definitions for peri-implant health, peri-implant mucositis, and peri-implantitis were presented. It is important in this context to distinguish between the terms *case definition* and *disease definition*. A disease definition is descriptive and provides information on the characteristics of the disease, whereas a case definition serves as a directive for the clinical assessment of the disease, that is, the diagnosis. While peri-implant mucositis and peri-implantitis will be described in detail in this chapter, the main characteristics of healthy peri-implant mucosa will also be reviewed to highlight important differences between peri-implant tissues and periodontal tissues (Fig. 20-1). The etiology and pathogenesis of peri-implant diseases including the transition from healthy peri-implant mucosa to peri-implant mucositis and from peri-implant mucositis to peri-implantitis are similar to that of periodontal diseases at teeth. Case definitions are fundamental for diagnosis of peri-implant diseases and the clinical assessment of bleeding on probing (BoP) is the key method to differentiate between healthy and inflamed tissue. Peri-implant mucositis and peri-implantitis, however, are distinguished by the assessment of peri-implant bone loss in radiographs. Bone loss represents an apical shift of the crestal bone level between two examinations and should, in addition, exceed bone level changes that may occur during a phase of initial bone remodeling after implant installation (see also Chapter 5). Case definitions and their role in the appraisal of the prevalence and risk factors for peri-implant disease are discussed in Chapter 7.

Healthy peri-implant mucosa

A healthy peri-implant mucosa is characterized by the absence of visible signs of inflammation, such as redness and swelling. While BoP should not occur during clinical examination, there is no defined range of probing depth compatible with healthy peri-implant mucosa.

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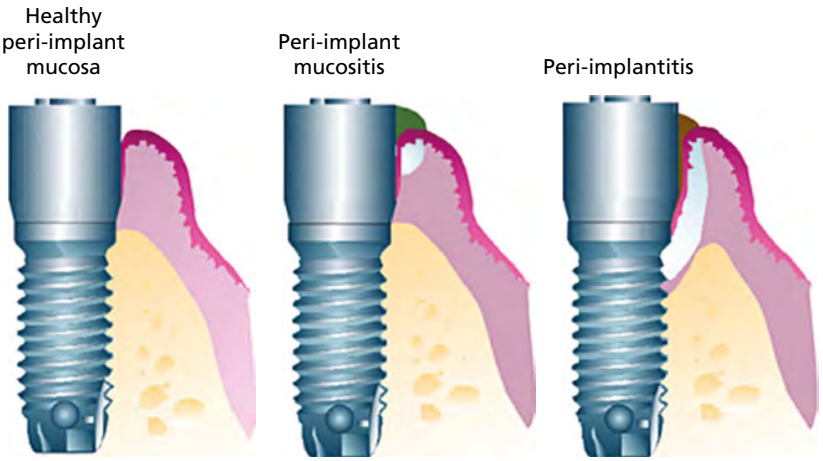

Fig. 20-1 Healthy peri-implant mucosa, peri-implant mucositis, and peri-implantitis.

Most information on histological characteristics of the healthy peri-implant mucosa are derived from pre-clinical *in vivo* studies (Araújo & Lindhe, 2018; Berglundh *et al*. 2018). Thus, following implant installation, a transmucosal passage is formed around the abutment portion of the device. The ridge mucosa at such sites adapts to the new functional demands and a peri-implant mucosa becomes established. The mucosa surrounding implants and the gingiva at teeth have many features in common (Berglundh *et al*. 1991). Both types of tissues are often lined with a keratinized oral epithelium; at clinically healthy sites, this is continuous with a thin non-keratinized barrier or junctional epithelium that faces the implant or the tooth surface. In the connective tissue immediately lateral to these thin epithelial linings, small infiltrates of inflammatory cells (neutrophils, macrophages, T cells, B cells) are frequently seen (Liljenberg *et al*. 1997; Tomasi *et al*. 2014, 2016). The inflammatory cells represent the host's defense against bacterial products and hence they may be considered as an integral component of the biologic seal that separates the peri-implant and periodontal attachment tissues from the oral cavity (see also Chapters 4 and 10).

In contrast to periodontal tissues, peri-implant tissues do not present with a root cementum and a periodontal ligament. In the connective tissue zone between the bone crest and the junctional epithelium of the peri-implant mucosa there are no inserting collagen fibers into the implant and the vascular density is lower than that in corresponding compartments of periodontal tissues (Araújo & Lindhe 2018; Berglundh *et al*. 2018). It is anticipated that this lack of a root cementum and a periodontal ligament entails an impaired capacity to encapsulate the progressing lesion of the developing peri-implant disease process.

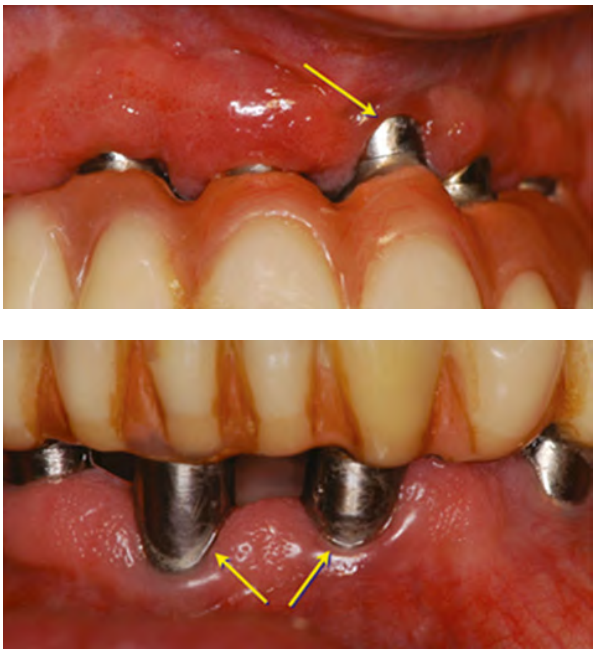

Fig. 20-2 Clinical symptoms of peri-implant mucositis, including varying signs of redness and swelling. Probing resulted in bleeding from the margin of the mucosa (arrows).

Peri-implant mucositis

Clinical features and diagnosis

Peri-implant mucositis is an inflammatory lesion of the soft tissues surrounding an endosseous implant in the absence of loss of supporting bone (Berglundh *et al*. 2018; Heitz-Mayfield & Salvi, 2018). Its clinical features are in many respects similar to those of gingivitis at teeth and include classical symptoms of inflammation, such as swelling and redness. It should be noted, however, that visible signs of inflammation may vary and be masked by the metal of the device or the crown restoration. The clinical assessment of peri-implant mucositis must therefore always include assessment of bleeding following probing (Fig. 20-2). While BoP is the main clinical characteristic in sites with peri-implant mucositis, an increase of probing depth may also occur due to swelling or decrease in probing resistance. Thus, the diagnosis of peri-implant mucositis is based on the observations of BoP and absence of bone loss (Fig. 20-3). Case definitions for peri-implant mucositis are discussed in Chapter 7.

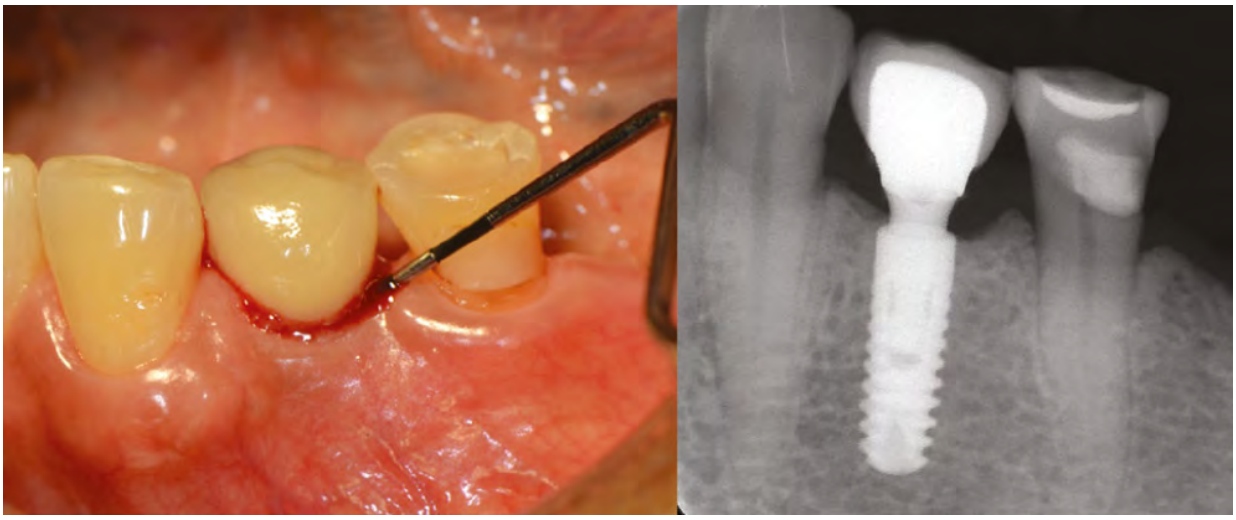

Fig. 20-3 Diagnosis of peri-implant mucositis indicated by the clinical finding of bleeding on probing and absence of radiographic bone loss.

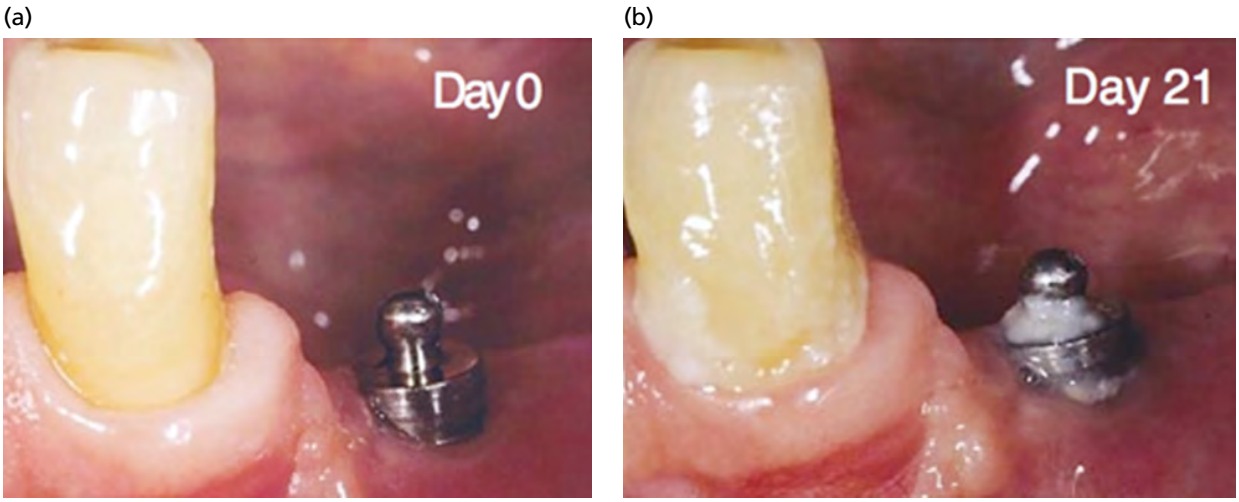

Fig. 20-4 (a) Healthy gingiva and peri-implant mucosa. (b) Same site following 3 weeks of plaque formation.

Clinical models

The response of the gingiva and the peri-implant mucosa to early and more longstanding periods of plaque formation was analyzed both in studies in humans and in preclinical models. Pontoriero *et al*. (1994) engaged 20 partially edentulous human subjects in a clinical "experimental gingivitis in man" (Löe *et al*. 1965) study. All subjects had been treated for advanced periodontal disease and thereafter had been restored with implants in one or several segments of the dentition. During a 6-month period following the prosthetic rehabilitation, the subjects were enrolled in a meticulous maintenance program that included regularly repeated supportive measures. A baseline examination was subsequently performed including assessment of plaque, soft tissue inflammation, probing pocket depth (PPD), soft tissue recession, and composition of oral biofilms. The participants refrained from all oral hygiene measures for 3 weeks. It was observed that during this interval, plaque build-up (amount and composition) and the soft tissue response to the microbial challenge, for example inflammation and PPD change, developed in a similar manner in the tooth and implant segments of the dentition.

Zitzmann *et al*. (2001) studied the response to plaque formation in the soft tissues at implant and tooth sites in humans. Twelve subjects with healthy periodontal and peri-implant conditions were asked to refrain from all oral hygiene measures for a period of 3 weeks (Fig. 20-4). Clinical examinations were performed and soft tissue biopsies were harvested prior to and at the end of the plaque accumulation period. It was demonstrated that plaque build-up was associated with clinical signs of soft tissue inflammation and also an increase in the scale of soft tissue infiltrate by inflammatory cells in tissues around teeth and implants.

Salvi *et al*. (2012) reported on the reversibility of experimentally induced gingivitis/peri-implant

mucositis in a study including 15 partially dentate subjects. Following an initial period of plaque formation to induce mucosal inflammation, oral hygiene procedures were re-instituted. The inflammation gradually resolved in the gingiva as well as in the peri-implant mucosa.

Untreated peri-implant mucositis may progress to peri-implantitis. Costa *et al*. (2012) reported that patients with peri-implant mucositis at baseline and not receiving regular supportive peri-implant therapy presented with an incidence of peri-implantitis of 44% during a 5-year period. In a parallel group of patients with peri-implant mucositis who attended a regular supportive therapy program, the incidence of peri-implantitis over 5 years was 18%. This observation underlines the importance of detecting and treating peri-implant mucositis to prevent progression to peri-implantitis.

Preclinical models

In an experiment in the dog, Berglundh *et al*. (1992) compared the reaction of the gingiva and the peri-implant mucosa with 3 weeks of *de novo* plaque formation. The mandibular premolars in one side of the mandible were extracted, leaving the premolars on the contralateral side as controls. After 3 months of socket healing, implants were inserted in the edentulous ridge. The animals were placed in a plaque-control program to allow for ideal healing of the mucosa at the implants and to prevent gingivitis from occurring in the tooth segments of the dentition. After this healing period, the dogs were examined and samples from the minute biofilms that were present on the implant and the tooth surfaces were harvested. The plaque-control program was terminated and the animals given a soft diet that allowed gross plaque formation. Re-examinations, including clinical assessment, sampling of plaque from teeth and implants, as well as biopsy, were performed after 3 weeks. During the course of the study, similar amounts and composition of plaque formed on teeth and implants. It was therefore concluded that early microbial colonization on titanium implants followed the same pattern as that on teeth (Leonhardt *et al*. 1992). Both the gingiva and the peri-implant mucosa responded to this plaque build-up with the establishment of overt

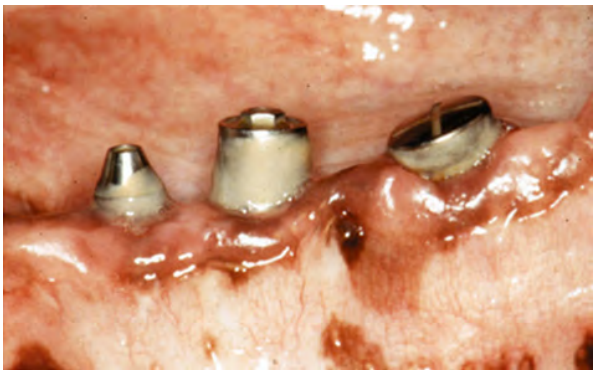

Fig. 20-5 Five months of undisturbed plaque formation on three different types of implants in a dog.

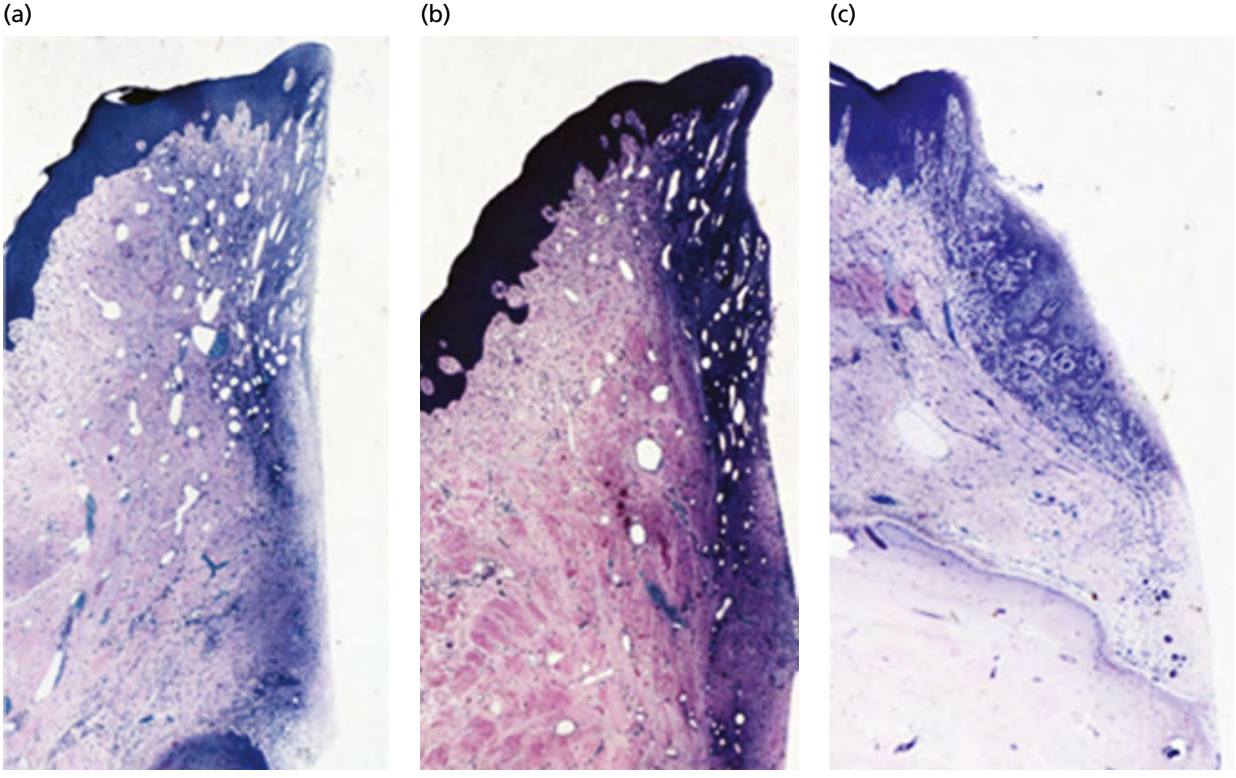

Fig. 20-6 (a–c) Photomicrographs illustrating inflammatory cell infiltrates (ICT) established in the peri-implant mucosa around the three implant types shown in Fig. 20-5. The apical extension of the ICT is consistently within the dimension of the barrier epithelium for all three implant types.

inflammatory lesions, that is infiltrates of leukocytes in the connective tissue. The lesions in the gingiva and in the peri-implant mucosa were similar both with respect to size and location. Hence, both lesions were consistently found in the marginal portion of the soft tissues and between the keratinized oral epithelium and the junctional or barrier epithelium.

With increasing duration of plaque build-up (3 months) in the dog model described above, the lesions in the peri-implant mucosa seemed to expand and progress further "apically", while the gingival lesions remained unchanged (Ericsson *et al*. 1992). Furthermore, the lesions in the peri-implant mucosa contained a much smaller number of fibroblasts than the corresponding infiltrates in the gingiva. In any inflammatory lesion of longstanding, periods of breakdown and periods of repair interchange. It was therefore suggested, that in the gingival lesion, the amount of tissue breakdown that occurred during the 3-month interval was more or less fully compensated for by tissue build-up during a subsequent phase of repair. In the lesions in the peri-implant mucosa, the tissue breakdown was not fully recovered by reparative events. This reduced build-up may have been the reason for the resulting additional propagation and spread of the lesion in the peri-implant mucosa.

In a similar dog experiment, Abrahamsson *et al*. (1998) studied soft tissue lesions after 5 months of plaque formation at three different implant systems (Fig. 20-5). They observed that the response of the peri-implant mucosa to longstanding plaque formation appeared to be independent of the implant system that harbored the biofilm and that the apical extension of the inflammatory lesion was consistently within the dimensions of the barrier epithelium for all three implant systems (Fig. 20-6).

Conclusion: Peri-implant mucositis and gingivitis have many features in common. The host response to bacterial challenge at teeth and implants includes the development of clinical signs of inflammation and the establishment of inflammatory lesions in the mucosal/gingival connective tissues. Since peri-implant mucositis represents the obvious precursor of peri-implantitis, as does gingivitis for periodontitis, prevention and treatment of mucositis appears to be an important prerequisite for the prevention of peri-implantitis (Lang & Berglundh, 2011; Jepsen *et al*. 2015).

Peri-implantitis

Clinical features and diagnosis

Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants. It is characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of peri-implant bone (Berglundh *et al*. 2018; Schwarz *et al*. 2018). Therefore, diagnosis of peri-implantitis requires detection of both BoP and bone loss assessed on radiographs (Fig. 20-7). Peri-implantitis initially affects the marginal part of the peri-implant tissues and the implant may remain stable and in function for varying periods of time. Implant mobility is therefore not an essential symptom for peri-implantitis but may occur in the final stage of disease progression and indicates complete loss of integration.

As pointed out for the clinical characteristics of peri-implant mucositis, various factors such as the morphology of the peri-implant mucosa and position of the implant may also influence the clinical appearance of inflammation in peri-implantitis. Probing is therefore a prerequisite in the examination of peri-implant tissues and should include assessments of both BoP and PPD. Pus is a common finding in peri-implantitis sites (Fransson *et al*. 2008).

Hence, the clinical appearance of peri-implantitis may vary and is not consistently associated with overt signs of pathology. Two different cases are shown in Figs. 20-8 and 20-9. While plaque and calculus together with clinical signs of inflammation are present in the case shown in Fig. 20-8, the case shown in Fig. 20-9 does not disclose such symptoms. Probing the site shown in Fig. 20-9, however, revealed a PPD of about 10 mm, BoP, and suppuration.

Bone loss around implants observed in radiographs obtained from sites with peri-implantitis (Fig. 20-10) appears to be symmetric, that is there is a similar amount of bone loss circumferentially at the implants. The morphology of the osseous defect, however, may vary depending on the buccal–lingual (palatal) dimension of the alveolar ridge. Thus, in sites where the width of the ridge exceeds that of the

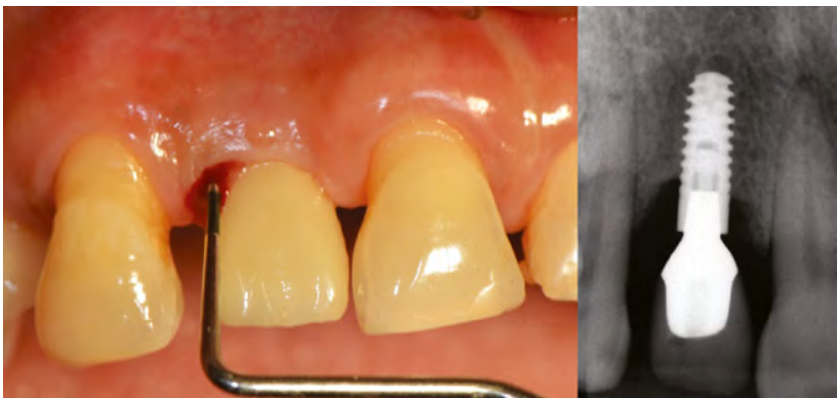

Fig. 20-7 Diagnosis of peri-implantitis indicated by the clinical finding of bleeding on probing and radiographic bone loss.

peri-implantitis lesion, a buccal and lingual bone wall may remain, and a contained, crater-formed defect occurs. Conversely, in sites with a narrow ridge, the buccal and lingual bone will be resorbed and lost during progression of peri-implantitis.

Progression of peri-implantitis occurs in a non-linear and accelerating pattern (Fransson *et al*. 2010; Derks *et al*. 2016) and appears to be faster than that observed in periodontitis (Berglundh *et al*. 2018). As the onset of peri-implantitis may occur early during follow-up, clinical examinations including assessments of PPD and BoP of peri-implant sites should be carried out on a regular basis to indicate the possible need for additional radiographic examinations for bone level assessments. While the diagnosis of peri-implantitis requires the detection of BoP and bone loss, it is assumed that previous examination data are available. In the absence of such data, however, the diagnosis of peri-implantitis is based on the combination of BoP, PPD ≥6 mm and bone levels located ≥3 mm apical of the most coronal portion of the intraosseous part of the implant periodontitis (Berglundh *et al*. 2018). Case definitions for peri-implantitis in day-to-day clinical practice and in epidemiological research are discussed in detail in Chapter 7.

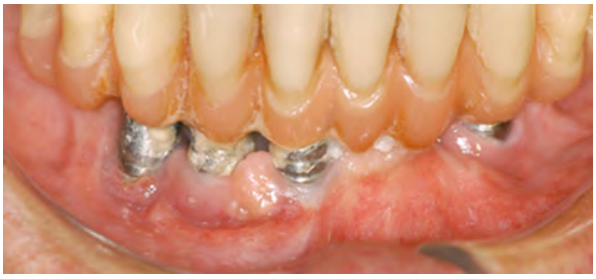

Fig. 20-8 Clinical symptoms of peri-implantitis. Note the large amounts of plaque and calculus, and visible signs of inflammation in the peri-implant mucosa.

Conclusion: Symptoms of peri-implantitis relate to the infectious/inflammatory nature of the lesion. Thus, in addition to radiographic evidence of bone loss, there are clinical signs of mucosal inflammation, including swelling and redness of the mucosa as well as bleeding on gentle probing. Suppuration from the "pocket" may also occur. Progression of peri-implantitis occurs in a non-linear and accelerating pattern and appears to be faster than that observed in periodontitis. The implant may remain stable until only minute amounts of "osseointegration" remain.

Human biopsy material

While precise information exists on the histopathology of human periodontitis, the number of studies on peri-implantitis lesions in humans is increasing but remains small in comparison (Berglundh *et al*. 2011; Schwarz *et al*. 2018). Studies providing information on tissues harvested from peri-implantitis sites disclosed that the mucosa contained large inflammatory cell infiltrates. Sanz *et al*. (1991) analyzed soft tissue

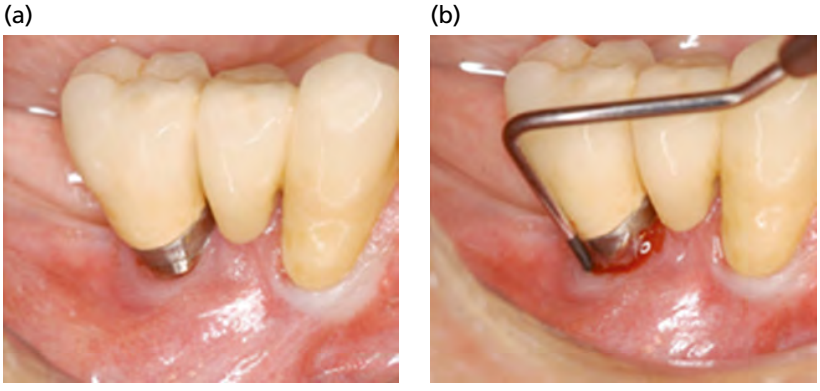

Fig. 20-9 An implant-supported crown in the premolar position in the right side of the mandible. (a) No or minor signs of inflammation in the surrounding mucosa. (b) Probing resulted in bleeding and suppuration from the implant site.

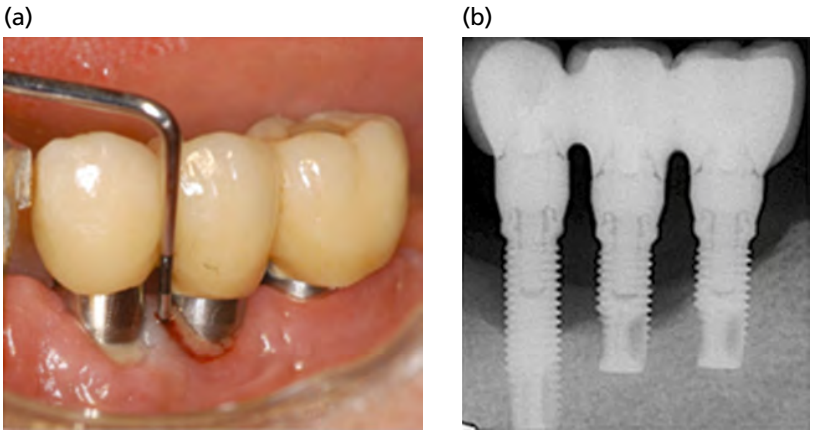

Fig. 20-10 Clinical (a) and radiographic (b) characteristics of three implant sites with peri-implantitis in the left side of the mandible. Note the presence of swelling and suppuration in the peri-implant mucosa (a) and the pronounced bone loss around the implants in the radiograph (b).

biopsies from six patients with peri-implantitis and reported that 65% of the connective tissue portion was occupied by inflammatory cells. Piattelli *et al*. (1998) described some pathologic features of tissues harvested from 230 retrieved implants: at sites where the implants had been removed due to peri-implantitis, "an inflammatory infiltrate, composed of macrophages, lymphocytes and plasma cells, was found in the connective tissue around the implants". In a study including 12 human peri-implantitis lesions, Berglundh *et al*. (2004) found that the mucosa contained very large lesions in which numerous plasma cells, lymphocytes, and macrophages were present (Fig. 20-11). It was furthermore observed that the inflammatory cell infiltrate consistently extended to an area apical to the pocket epithelium and that the apical part of the soft tissue lesion frequently reached the bone tissue. Berglundh *et al*. (2004) also reported that numerous neutrophil granulocytes (polymorphonuclear leukocytes) were present in the lesions. Such cells occurred not only in the pocket epithelium and associated areas of the lesions, but also in perivascular compartments in the center of the infiltrate, that is distant from the implant surface. In the apical part of the lesion, the inflamed connective tissue appeared to be in direct contact with the biofilm on the implant surface. Gualini and Berglundh (2003) used immunohistochemical techniques to analyze the composition of peri-implantitis in a study of six subjects. Neutrophils were found in large numbers in the central portions of the infiltrate. This finding was in agreement with that made by Hultin *et al*. (2002) who analyzed the exudate that could be harvested from implant sites in 17 patients with peri-implantitis and reported the presence of large numbers of neutrophils. Immunohistochemical techniques have also been used to evaluate differences between peri-implantitis and periodontitis lesions. Bullon *et al*. (2004) observed that both types of lesions contained T and B lymphocytes, plasma cells, and macrophages, while Konttinen *et al*. (2006) reported that the number of cells positive for interleukin-1 alpha (IL-1α) and IL-6 was larger and the number of tumor necrosis factor-alpha (TNF-α)–positive cells smaller in peri-implantitis than in periodontitis lesions. A more comprehensive evaluation of human peri-implantitis and periodontitis lesions was presented by Carcuac and Berglundh (2014). Soft tissue biopsies were collected from diseased sites (PPD ≥7 mm, BoP, and marked bone loss) in 40 patients with advanced peri-implantitis and 40 patients with severe periodontitis. The histological examination revealed that peri-implantitis lesions were more than twice as large as the periodontitis lesions (Fig. 20-12). In addition, the inflammatory cell infiltrate in peri-implantitis extended to a position that was apical of the pocket epithelium and was less walled-off in apical and lateral directions than the periodontitis lesions. The immunohistochemical analysis revealed that the density of plasma cells, neutrophil granulocytes, and macrophages was considerably larger in peri-implantitis than in periodontitis lesions.

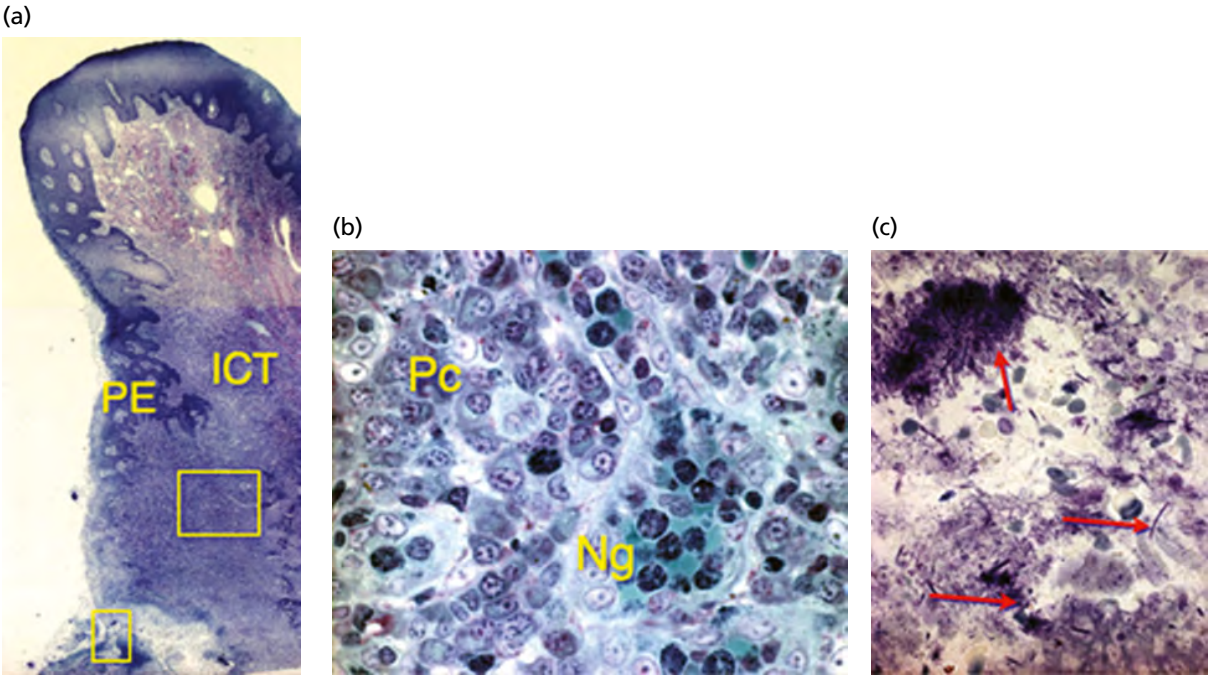

Fig. 20-11 (a) Photomicrograph showing a human peri-implantitis lesion. Note the large inflammatory cell infiltrate (ICT) lateral to the pocket epithelium (PE). The implant was positioned to the left. (b) Outlined area in (a) in the profound portion of the ICT including large numbers of plasma cells (Pc) and neutrophil granulocytes (Ng). (c) Outlined area in (a) in the apical part of the ICT facing the pocket. Arrows indicate clusters of microorganisms.

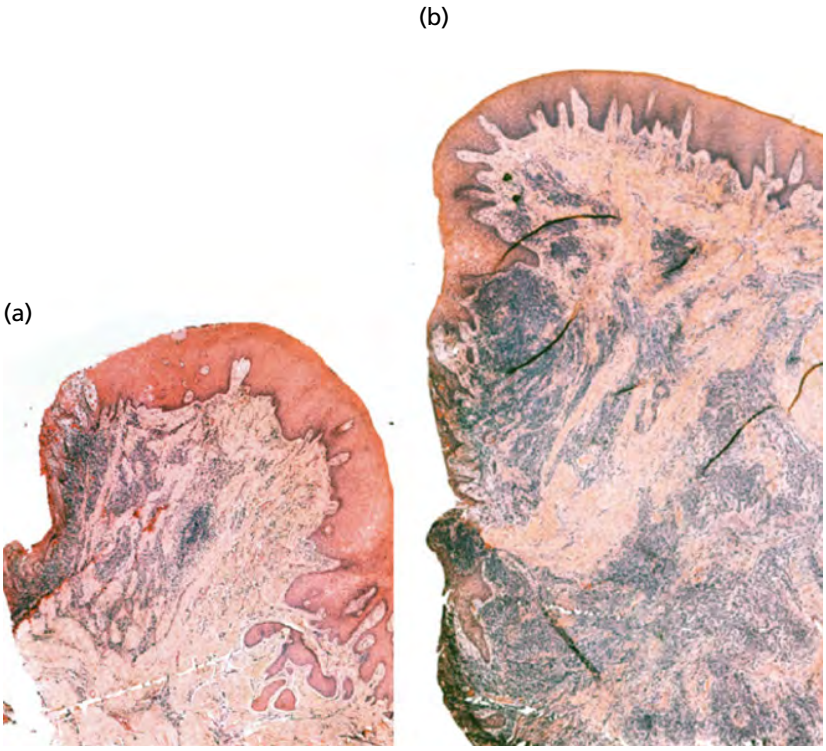

Fig. 20-12 Photomicrographs showing human specimens obtained from sites with severe periodontitis (a) and (b) severe peri-implantitis (Carcuac & Berglundh 2014). Note the difference in size of the inflammatory cell infiltrate lateral to the pocket epithelium (left) between periodontitis (a) and (b) peri-implantitis.

Preclinical models

In order to study the response of the peri-implant mucosa to long-standing plaque exposure, an experimental periodontitis/peri-implantitis model was developed in the dog (Lindhe *et al*. 1992) and in the monkey (Lang *et al*. 1993; Schou *et al*. 1993). Although the experiments had somewhat varying designs, their outcomes were almost identical and, hence, only the result from the dog model will be reported.

In the dog model (Lindhe *et al*. 1992), the premolars were extracted on one side of the mandible, implants were inserted, and abutment connection performed 3 months later. During the healing phase, a strict plaque control regimen was maintained and healthy tissue conditions were thereby established in all tooth and implant sites to be monitored. On a given day, the periodontitis and peri-implantitis lesions were induced. This was accomplished by terminating the plaque control regimen and placing cotton ligatures around the neck of both the premolar teeth and the implants. The ligatures were forced into a position apical to the soft tissue margins. A "pocket" between the tooth/gingiva and implant/mucosa was thereby created, a submarginal biofilm rapidly formed, and inflammatory lesions developed in the neighboring tissues. Radiographs obtained after 6 weeks of the experiment revealed that a substantial amount of bone tissue had been lost at both teeth and implant sites. The ligatures were removed. After a further 4 weeks, the animals were re-examined, radiographs obtained, plaque sampled, and biopsies of tooth and implant sites harvested. It was observed that the plaque that had formed in the deep "pockets" had a similar composition at tooth and implant sites, and was dominated by Gram-negative and anaerobic species (Leonhardt *et al*. 1992). This observation is consistent with findings in humans indicating that the microbiota at teeth and implants shares many features, but also that the microbiota at healthy and diseased sites – tooth sites as well as implant sites – is very different. Thus, implants and teeth that are surrounded by healthy soft tissues are associated with biofilms with small numbers of Gram-positive coccoid cells and rods. Sites with extensive periodontal and peri-implant inflammation harbor biofilms with large numbers of Gram-negative anaerobic microorganisms (see Chapter 9).

Histopathologic examination of the biopsy samples from the dog study (Lindhe *et al*. 1992) revealed that there were marked differences in the size and location of the inflammatory lesions at periodontal and peri-implant sites. Thus, while the lesions in the periodontal sites were consistently separated from the alveolar bone by a 1-mm wide zone of non-inflamed connective tissue, the lesion in the peri-implant tissue in most situations extended to the alveolar bone. It was concluded that the pattern of spread of inflammation was different in periodontal and peri-implant tissues. It was suggested that the peri-implant tissues, in variance with the periodontal tissues, are poorly organized to resolve progressive, plaque-associated lesions. The validity of this

conclusion was substantiated in subsequent studies (Marinello *et al*. 1995; Ericsson *et al*. 1996; Persson *et al*. 1996; Gotfredsen *et al*. 2002), using similar models but allowing for different periods of tissue breakdown.

In the preclinical studies reported above, the experimental models used ligatures to disrupt the soft tissue seal around the implant and thereby allowing a biofilm to form in a submarginal location. The ensuing host response included an inflammatory lesion in the mucosa that over time became progressively larger. Cells in the lesion activated systems of reactions that promoted degradation of connective tissue and bone. The placement of a new ligature in a more "apical" position allowed the destructive process to continue. The size and type of ligature (e.g. cotton, silk), their corono-apical position in the pocket, as well as the number of replacements determined the rate and magnitude of tissue breakdown in this so-called experimental peri-implantitis model (Berglundh *et al*. 2011).

Zitzmann *et al*. (2004) used 21 sites in dogs to study experimental peri-implantitis. After the lesions had become established, the ligatures were removed, and the sites were monitored for an additional 12 months. It was observed that in 16 sites the destructive conditions persisted and caused progressive bone loss. In the remaining five sites, however, the lesions became encapsulated and no further breakdown of peri-implant bone took place.

This so-called "spontaneous progression model" (Zitzmann *et al*. 2004) was subsequently used by Berglundh *et al*. (2007). They examined the tissue reaction around custom-made implants with either a smooth, polished surface or a roughened SLA (sand-blasted, large grit, acid etched) surface. During the pre-experimental period of ligature-induced breakdown, similar amounts of bone loss occurred around the two types of implants. Evaluation 5 months after the removal of ligatures, however, revealed that bone loss had progressed and that the size of the inflammatory lesion in the connective tissue was larger at the implants with the rough than with the smooth surface. The area of plaque was also larger at implants with the rough surface. It was concluded that the progression of peri-implantitis, if left untreated, is more pronounced at implants with a moderately rough surface than at implants with a smooth/polished surface.

While the study by Berglundh *et al*. (2007) used implants with custom-made surfaces, Albouy *et al*. (2008, 2009) analyzed differences in spontaneous progression of experimental peri-implantitis between commercially available implants with SLA, TiOblast, TiUnite, and turned surfaces. Spontaneous progression occurred with all implant types during the 6-month period after ligature removal. The histologic examination revealed that all specimens presented with large inflammatory lesions that extended apical of the pocket epithelium. The pocket compartment was occupied by biofilm, calculus, and pus, and the uncovered apical part of the inflammatory cell infiltrate faced the biofilm. Osteoclasts in large numbers were detected on the surface of the crestal bone and other giant-like cells occurred in the soft tissue lesion, distant from the crestal bone.

Albouy *et al*. (2012) in a subsequent experiment in dogs repeated the spontaneous progression model using implants with a similar geometry and with two different surfaces (turned and modified). During the 6 months after ligature removal, a significantly larger amount of bone loss occurred around the implants with the modified than with the turned surface. In addition, the dimensions of inflammatory lesions, pocket epithelium, and biofilm were larger at the implants with a modified surface.

The spontaneous progression model was also used in an experiment aimed at evaluating differences between peri-implantitis and periodontitis. Thus, Carcuac *et al*. (2013) used the dog model and two kinds of implants. Experimental peri-implantitis and periodontitis were induced by ligature placement and plaque formation. The ligatures were removed after 10 weeks and bone level changes were evaluated in radiographs during the following 6 months. It was reported that the amount of bone loss that occurred following ligature removal was significantly larger at implants with a modified surface than at implants with a turned surface and at teeth (Fig. 20-13). The results from the histologic examination confirmed previous findings (Lindhe *et al*. 1992) and revealed that peri-implantitis sites exhibited inflammatory lesions that were larger and extended closer to the bone crest than those in periodontitis (Figs. 20-14,

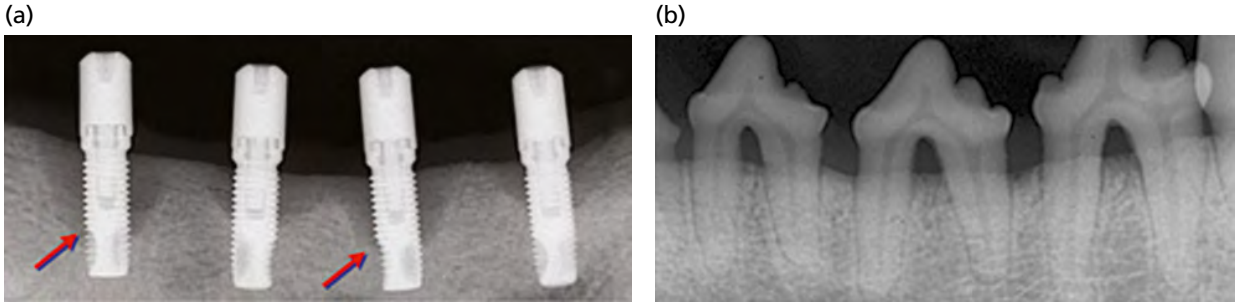

Fig. 20-13 Radiographs showing (a) experimental peri-implantitis and (b) periodontitis in the Labrador dog. Compare the greater bone loss around the implant with a modified and a turned surface (arrows).

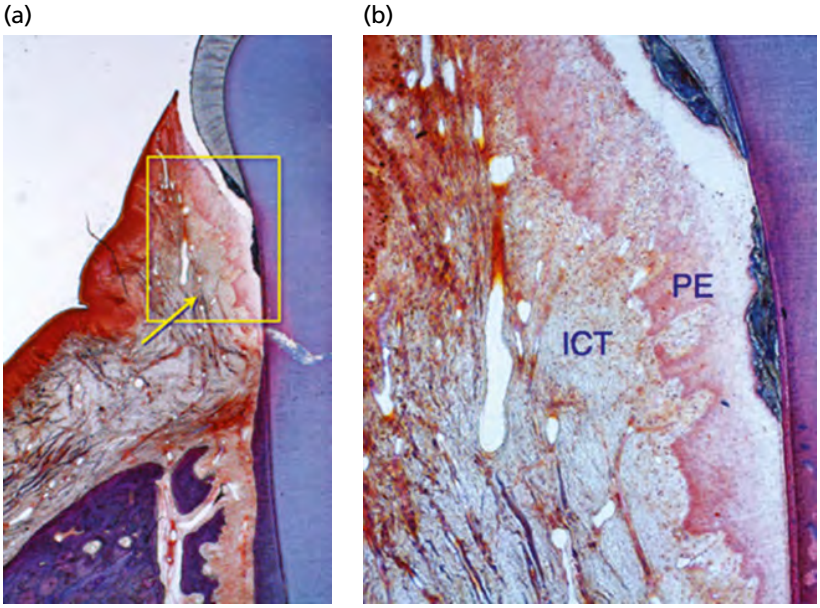

Fig. 20-14 (a) Photomicrograph of a buccolingual ground section showing a periodontitis lesion. Note the apical extension of the infiltrate (arrow), but also the presence of a zone of normal connective tissue between the infiltrate and the bone crest. (b) Larger magnification of outlined area in (a). Note the calculus on the tooth surface, the pocket epithelium (PE), and the infiltrate (ICT).

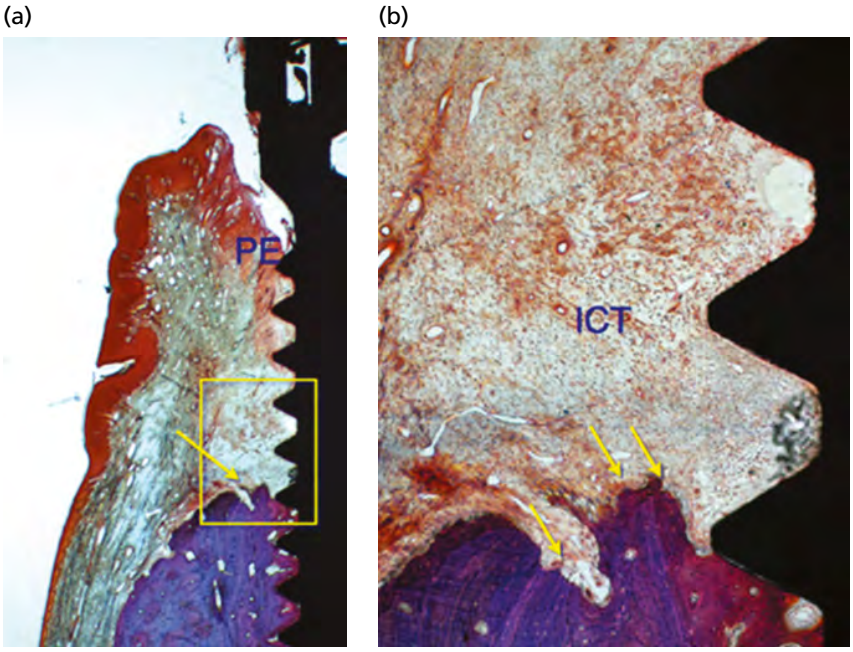

Fig. 20-15 (a) Photomicrograph of a buccolingual ground section showing a peri-implantitis lesion. The apical portions of the infiltrate (arrow) extend into contact with the bone. (b) Close-up of outlined area in (a) showing the large infiltrate (ICT) apical of the pocket epithelium and in direct contact with the biofilm on the implant surface. Osteoclasts (arrows) are present on the bone surface. PE, pocket epithelium.

20-15). Carcuac *et al*. (2013) also reported that the lesions in peri-implantitis contained larger proportions of neutrophil granulocytes and osteoclasts than lesions in periodontitis.

A new approach of the spontaneous progression model was presented by Carcuac *et al*. (2020) in a study on experimental peri-implantitis in augmented and pristine bone. While a standard osteotomy preparation procedure was applied at pristine bone sites at implant placement, a modified osteotomy was used at test sites, resulting in a 1 mm wide and 5 mm deep circumferential gap following implant installation. The gap was filled with a bone substitute and was covered by a resorbable collagen membrane. After several months of healing, experimental peri-implantitis was initiated by placement of ligatures and plaque accumulation. In contrast to previous experiments using the spontaneous progression model, the ligatures were removed already after 4 weeks. Thus, spontaneous progression of experimental peri-implantitis was initiated without a preceding period of significant ligature-induced bone loss. Carcuac

et al. (2020) reported that differences in bone loss during the spontaneous progression period following ligature removal between pristine and augmented sites were small and that implants with turned, non-modified surfaces exhibited smaller amounts of bone loss than implants with modified surfaces. These observations indicate that the short-term disruption of the soft tissue barrier around implants promoted by the ligature together with plaque formation, initiated a host response with the formation of an inflammatory lesion in the mucosa that over time progressed in an apical and lateral direction. Thus, following the initial short period of ligatures, inflammation persisted in the peri-implant connective tissue together with continuous crestal bone loss during the subsequent 6-month period.

Data obtained from pre-clinical studies presented above (Berglundh *et al*. 2007; Albouy *et al*. 2008, 2009, 2012; Carcuac *et al*. 2020) indicate that the implant surface characteristics influenced the degree of spontaneous progression of experimentally induced peri-implantitis. It should be kept in mind, however, that in these studies, a limited number of implant types were evaluated. It is thus not possible to determine if any particular type of implant system or implant surface is associated with a greater risk for peri-implantitis. On the other hand, the experimental studies do demonstrate that continuous plaque formation at sites where a peri-implantitis lesion has become established and ligatures removed, may result in additional destruction of soft and hard tissue components of peri-implant tissues and that this progression of disease is influenced by implant surface characteristics.

Conclusion: Peri-implantitis lesions are poorly encapsulated, extend to the marginal bone tissue, and may, if allowed to progress, lead to the loss of the implant. The large numbers of neutrophils in the peri-implantitis lesion and the absence of an epithelial lining between the lesion and the biofilm, indicate that the peri-implantitis lesions have features that are different from those of periodontitis lesions. Progression of peri-implantitis is more pronounced at implants with modified surfaces than at those with smooth, non-modified surfaces.

Conclusion

Studies in man and experiments in animals have documented that *de novo* formation of a biofilm on the implant surface initiates a host response that involves the establishment of an inflammatory lesion in the peri-implant mucosa (peri-implant mucositis). This lesion is initially located in the connective tissue immediately lateral to the barrier epithelium and is, in many respects, similar to that which develops in the gingiva when plaque forms on adjacent tooth surfaces. In the continued presence of a submarginal biofilm, the lesion in the marginal mucosa around implants may occasionally spread in an "apical" direction to involve the hard tissue, compromise osseointegration, cause varying degrees of marginal bone loss (peri-implantitis), and, in the absence of treatment also cause the loss of the implant.

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Part 8: Tissue Regeneration

Chapter 21

Periodontal Wound Healing and Regeneration

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Introduction

The coordinated sequence of events involved in periodontal wound healing is critical for maintenance of intact, periodontally healthy tissues as well as in situations where the clinician employs therapeutic approaches to regenerate the periodontium when these tissues are lost or compromised. The structure and function of the periodontium is determined by the dynamic interactions and interfaces of four main tissues: periodontal ligament (PDL), tooth root cementum, alveolar bone, and gingiva. Collectively, these tissues provide a biologic and physical barrier to a multitude of external insults sustained by the teeth as a result of normal occlusal function and the complex microbial environment of the oral cavity. The most common reason that the integrity of the periodontium is compromised is due to chronic inflammation triggered by complex bacterial communities, namely periodontal pathogens. Nonetheless, the periodontium represents a resilient organ characterized by a dynamic structure being very responsive to a variety of mechanical and biochemical factors to maintain homeostasis (Burger *et al*. 1995; Duncan & Turner 1995; Marotti 2000; Marotti & Palumbo 2007; Bonewald & Johnson 2008). Its structure and function during remodeling and healing is determined by the orchestration of a sequence of events involving biological growth factors, namely: platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), insulin-like growth factor 1 (IGF-1), transforming growth factor beta 1 (TGF-β1), among others (reviewed in Larsson *et al*. 2016). These factors play an important role in modulating the adaptive potential of the periodontium, which is responsible

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for it protecting and maintaining the integrity of its four fundamental components (Fig. 21-1).

Clinically, following breakdown of the periodontium, detrimental changes undermine and disrupt the functional and structural integrity of the alveolar bone, gingiva, the PDL, and the cementum. The restoration of the original structure, properties, and function of these tissues is a major goal of regenerative periodontal therapies. Unfortunately, altered and delayed healing often disrupts the normal restoration of the periodontium and as a result, instead of full restoration of the tissue to its innate form and function, a varying degree of compromised outcomes commonly occurs.

Wound healing: Outcomes and definitions

Before exploring the mechanisms underlying the cellular and molecular events of wound healing, it is important to understand the cascade of healing patterns that have been recognized in the periodontal complex (Table 21-1).

From a histological standpoint, the following types of healing outcomes are observed in the periodontium: repair, reattachment, new attachment, regeneration, resorption, and ankylosis (Table 21-2).

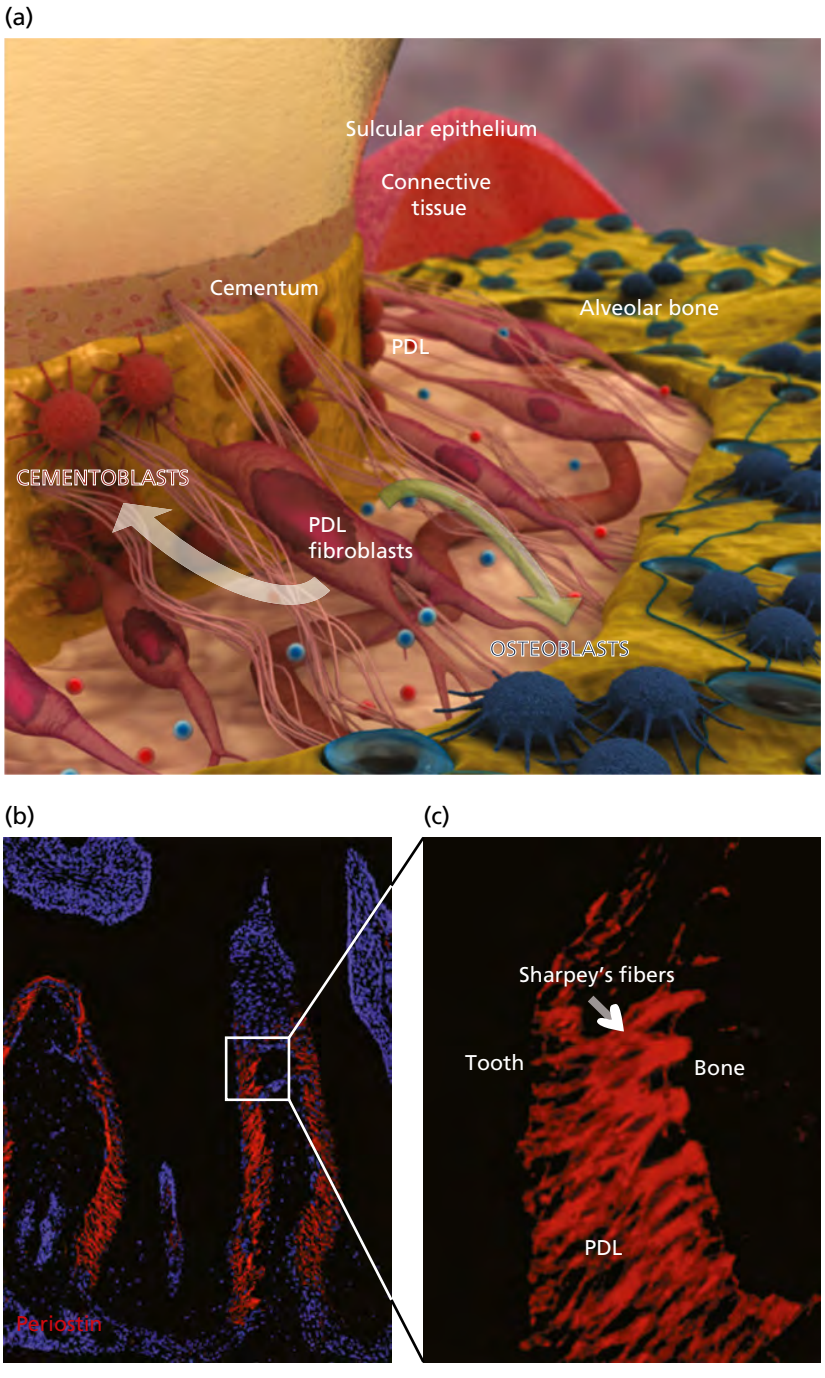

Fig. 21-1 (a) The tooth-supporting apparatus (i.e. periodontium) includes the alveolar bone, the periodontal ligament (PDL), the cementum, and the gingiva. Collectively, they represent a dynamic tissue complex with mechanical and biological functions that synergistically determine the tissue adaptive potential and its ability to sustain microbiological and mechanical challenges. (b) The functional periodontal system is characterized by distinct fibrillar structures known as Sharpey's fibers that connect the alveolar bone to the tooth surface cementum (red fluorescent immunostaining for periostin).

Table 21-1 Healing patterns in the periodontal tissues.

Healing by first intention	Healing through primary intention involves the wound edges being brought together using sutures. Primary intention wounds are associated with minimal tissue loss and regeneration predominates over fibrosis
Healing by second intention	Wound healing by secondary intention occurs in surgical wounds that are left to heal without approximating the edges. The wound then fills with granulation tissue from the bottom up. The epithelium then fills in over the top of the granulation tissue. Scarring is evident as there is significant fibrosis
Healing by third intention	Where there is great loss of tissue, the wound must heal by contraction of the wound edges and the formation of granulation tissue. In some cases, the presence of a foreign body or infection may be suspected, and these wounds are left open deliberately for several days until the potential complication has resolved. When resolution has occurred, the wound edges can be brought together (approximated) and the wound proceeds to heal
Partial-thickness healing	Occurs when a partial-thickness wound is closed primarily by epithelialization. This wound healing involves the superficial portion of the dermis (lamina propria). There is minimal collagen deposition and an absence of wound contraction

Table 21-2 Outcomes of periodontal wound healing.

Repair	Healing of a wound by tissue that does not fully restore the architecture or the function of the part. Within the periodontal wound, it refers to restoration of a normal gingival sulcus at the same level as the base of the previous pathologic periodontal pocket. Often repair is typified by the presence of a long junctional epithelium
Reattachment	Refers to the reattachment of the gingiva to areas from which it was mechanically removed
New attachment	Occurs when newly generated fibers are embedded in new cementum on a portion of the root that was uncovered by disease
Regeneration	Reproduction or reconstruction of a lost or injured part in such a way that the architecture and function of the lost or injured tissues are completely restored. This takes place by growing precursor cells replacing lost tissue
Resorption	Loss or blunting of some portion of a root, sometimes idiopathic, but also associated with orthodontic tooth movement, inflammation, trauma, endocrine disorders, and neoplasia
Ankylosis	Fusion of the tooth and the alveolar bone

Table 21-3 Applications of cell therapies for periodontal tissue engineering.

Cell type	Graft type	Defect type	Studies
Bone marrow stromal cells	Auto	Class III defects	Kawaguchi ***et al***. (2004), Hasegawa ***et al***. (2006)
	Auto	Periodontal fenestration	Li ***et al***. (2009)
	Auto	Osteotomy	Yamada ***et al***. (2004a–c)
	Auto	Papilla	Yamada ***et al***. (2015)
Adipose stromal cells		Periodontal palatal defects	Tobita ***et al***. (2008)
Periodontal ligament cells	Auto	Class II defects	Dogan ***et al***. (2003)
	Auto	Periodontal fenestration	Akizuki ***et al***. (2005)
	Allo/xeno	Periodontal fenestration	Lekic ***et al***. (2001)
Periodontal ligament stem cells	Allo	Ectopic	Seo ***et al***. 2004)
	Allo	Periodontal fenestration	Dogan ***et al***. (2003), Chang ***et al***. (2007)
	Auto	Periodontal defects	Liu ***et al***. (2008)
	Auto	Periodontal defects	Chen ***et al***. (2016)
Cementoblasts	Allo	Ectopic	Jin ***et al***. (2003)
	Allo	Periodontal fenestration	Zhao ***et al***. (2004)
Dental follicle cells	Allo	Ectopic	Jin ***et al***. (2003), Zhao ***et al***. (2004)
	Allo	Periodontal fenestration	Zhao ***et al***. (2004)
Dental pulp stem cells	Allo	Periodontal defect	Hernández-Monjaraz ***et al***. (2018)
Fibroblast	Auto	Recession defects	Milinkovic ***et al***. (2015)

Source: Rios ***et al***. (2011). Reproduced with permission from the American Academy of Periodontology.

Wound healing biology

The process of wound healing is the body's primary mechanism to restore tissue integrity following injury. If wound healing does not occur properly, chronic disruption of the protective barrier may lead to severe physiologic, immunologic, and metabolic abnormalities. Wound healing represents a dynamic process that involves several cell types and biologic mediators. Within the complex microenvironment of the periodontal wound, cell populations migrate, differentiate, and proliferate; epithelial and connective tissues interact; and a vast array of cytokines and extracellular matrix (ECM) molecules orchestrate these processes which take place in overlapping phases (reviewed in Sculean *et al*. 2015).

Phases of wound healing

The general principles of healing, and the cellular and molecular events observed in extraoral sites, also apply to the healing processes that take place following periodontal surgery. Traumatic injury causes capillary damage and hemorrhage, and, as a result, a blood clot is formed. The formation of a clot is the immediate response to any trauma. The clot has two functions: it temporarily protects the denuded tissues and it serves as a provisional matrix for cell migration. The blood clot consists of all cellular components of blood (including red and white blood cells and platelets) in a matrix of fibrin, plasma fibronectin, vitronectin, and thrombosporin. Beyond this, the process has been divided into three stages:

1. Inflammation phase
2. Granulation phase
3. Matrix formation and remodeling (maturation) phase.

Each of the steps of wound healing is essential to restoring tissue structure and function but the initial healing phases often determine the outcome (Susin *et al*. 2015).

Inflammatory phase

The growth factors which are present in the initial blood clot formation are responsible for recruitment of inflammatory cells and serve to regulate the granulation process. Within hours of injury, inflammatory cells (predominantly neutrophils and monocytes) populate the clot. These cells cleanse the wound of bacteria and necrotic tissue through phagocytosis and release of enzymes and toxic oxygen products. Within 3 days, the inflammatory reaction moves into its late phase. Macrophages migrate into the wound area and these macrophages contribute to the cleansing process by phagocytosis of used polymorphonuclear leukocytes and erythrocytes. Additionally, macrophages release a number of biologically active molecules such as inflammatory cytokines and tissue growth factors, which recruit further inflammatory cells as well as fibroblastic and endothelial cells, thus playing an essential role in the transition of the wound from the inflammatory into the granulation tissue formation phase and tissue resolution (Garlet *et al*. 2018).

Granulation phase

The neutrophil population is overtaken by macrophages within a few days. Macrophages also serve the purpose of wound decontamination. They play an important role in the formation of granulation tissue. Granulation tissue formation begins on approximately day 4. Macrophages constitutively release growth factors that promote the healing process. Growth factors and cytokines secreted by macrophages are involved in the proliferation and migration of fibroblasts, endothelial cells, and smooth muscle cells into the wound area. The cells in the wound proliferate around the radius of the wound site developing cell to cell and cell to matrix connections. Macrophages and fibroblasts continue to express growth factors that regulate the healing process, both in an exocrine and autocrine manner. Studies have shown that wound sites supplemented with growth factors have an accelerated rate of granulation tissue formation (Sporn *et al*. 1983). At 7 days after initiation of wound healing, granulation dominates the wound site and the initial collagen fibers are being formed. Eventually, cells and matrix form cell–cell and cell–matrix links that generate a concerted tension resulting in tissue contraction. This phase of granulation tissue formation gradually develops into the final phase of healing in which the reconstituted, more cell-rich tissue undergoes maturation and sequenced remodeling to meet functional needs.

Maturation phase

Fibroblasts responsible for the replacement of the provisional ECM produce a new collagen-rich matrix. Approximately 1 week following wounding, and once the collagen matrix has been synthesized, some fibroblasts undergo transformation into myofibroblasts and express α-smooth muscle actin. This transformation and synthesis is responsible for wound contraction. Endothelial cells, responsible for angiogenesis, migrate into the provisional wound matrix to form vascular tubes and loops, and as the provisional matrix matures, the endothelial cells undergo programmed cell death (apoptosis) and the number of vascular units is reduced. Maturation of the granulation tissue will lead to the regeneration or repair (scar formation) of the injured tissues. Whether the damaged tissues heal by regeneration or repair depends upon two crucial factors: the availability of cell type(s) needed and the presence or absence of cues and signals necessary to recruit and stimulate these cells.

Factors that affect healing

The periodontium is like most other tissues in the body in that its healing capacity is highly influenced by local and systemic factors.

Local factors

Healing after gingival and periodontal surgery can be delayed and altered by various local factors, the most critical of these factors being:

- Plaque microorganisms
- Excessive tissue manipulation during treatment
- Trauma to the tissues
- Presence of foreign bodies
- Repetitive treatment procedures that disrupt the orderly cellular activity during the healing process
- Inappropriate vascular perfusion to the surrounding area.

Healing is therefore improved by debridement (removal of degenerated and necrotic tissue), immobilization of the healing area, and pressure on the wound. The cellular activity in healing entails an increase in oxygen consumption. However, healing of the gingival tissue is not accelerated by artificially increasing the oxygen supply beyond the normal requirements (Glickman *et al*. 1950).

Systemic factors

Age has long been recognized as a variable which negatively impacts the wound healing capacity of most tissues of the body (Holm-Pedersen & Löe 1971). Healing is also impaired by inadequate food intake, systemic disorders that interfere with the uptake of nutrients, and deficiencies in essential vitamins (Barr 1965), proteins (Stahl 1962), and other nutrients.

Hormones also have an impact on healing. Systemically administered glucocorticoids such as cortisone hinder repair by depressing the inflammatory reaction or by inhibiting the growth of fibroblasts, the production of collagen, and the formation of endothelial cells. Systemic stress, thyroidectomy, testosterone, adrenocorticotropic hormone, and large doses of estrogen suppress the formation of granulation tissue and impair healing (Butcher & Klingsberg 1963).

Progesterone increases and accelerates the vascularization of immature granulation tissue (Lindhe & Brånemark 1968) and appears to increase the susceptibility of the gingival tissue to mechanical injury by causing dilation of the marginal vessels (Hugoson 1970).

Periodontal wound healing

For functional periodontal regeneration to occur, a series of temporal and spatial events must occur in a similar sequence to those involved in the natural formation and development of the periodontium (Chen *et al*. 2011). Most of the mechanisms underlying these cellular and molecular events have been identified with the first series of these events including cell migration and attachment to the denuded root surface. In using small animal models, it is clearly observed that a microenvironment is established which favors the proliferation, migration, and maturation of mesenchymal progenitors in the defective area of the PDL or the host bone (Lekic *et al*. 1996a,b). These processes are mediated and coordinated by soluble factors, other cells, and ECM. In the very early healing phases initiated by blood coagulation and migration of neutrophils and monocytes, the primary goals of these cellular events are to achieve wound debridement and bone resorption. Bone formation typically initiates from the bony margins of the lesions (Rajshankar *et al*. 1998). Within days after surgery, a thin cementum layer with a connective tissue attachment can be observed, particularly on the apical side of the teeth where the cementum is thicker compared with the narrow coronal region (King *et al*. 1997). Once mineralized tissues are established, PDL fiber orientation, directionality, and integration into both cementum and alveolar bone are mediated by appropriate mechanical loading (Mine *et al*. 2005; Rios *et al*. 2011). It is therefore highly critical that investigators, according to the timeline these processes follow, select the appropriate time point(s) to determine the therapeutic efficacy "window" of a candidate periodontal-engineered device or bioactive molecule (Fig. 21-2).

Periodontal wound healing is considered a more complex process compared with epidermal wound healing. The native periodontium includes cementum, a functionally oriented PDL, alveolar bone, and gingiva. The interfaces between these tissues as well as the transgingival position of the teeth represent a constant challenge during the restoration of the integrity of the native structures as they seek to create a new connection to the non-vascular and non-vital hard tissue of the root surface within the context of an open system that is permanently contaminated and under a significant "bacterial load". It is therefore not surprising that the healing results following all types of gingival and periodontal therapy can be quite variable.

The most basic requirement for successful periodontal treatment is a clean, biofilm-free, decontaminated root surface. Therapy includes both surgical and non-surgical modalities, which result in instrumentation of the affected tissue. This creates a wound in periodontal tissues that are stressed by inflammation. The results of therapy are dependent on the ability of the body to heal afterwards and the mechanisms that dictate these processes. It is important to understand that the order of events during wound healing after therapy depend on a complex set of biologic communications in the area of interest.

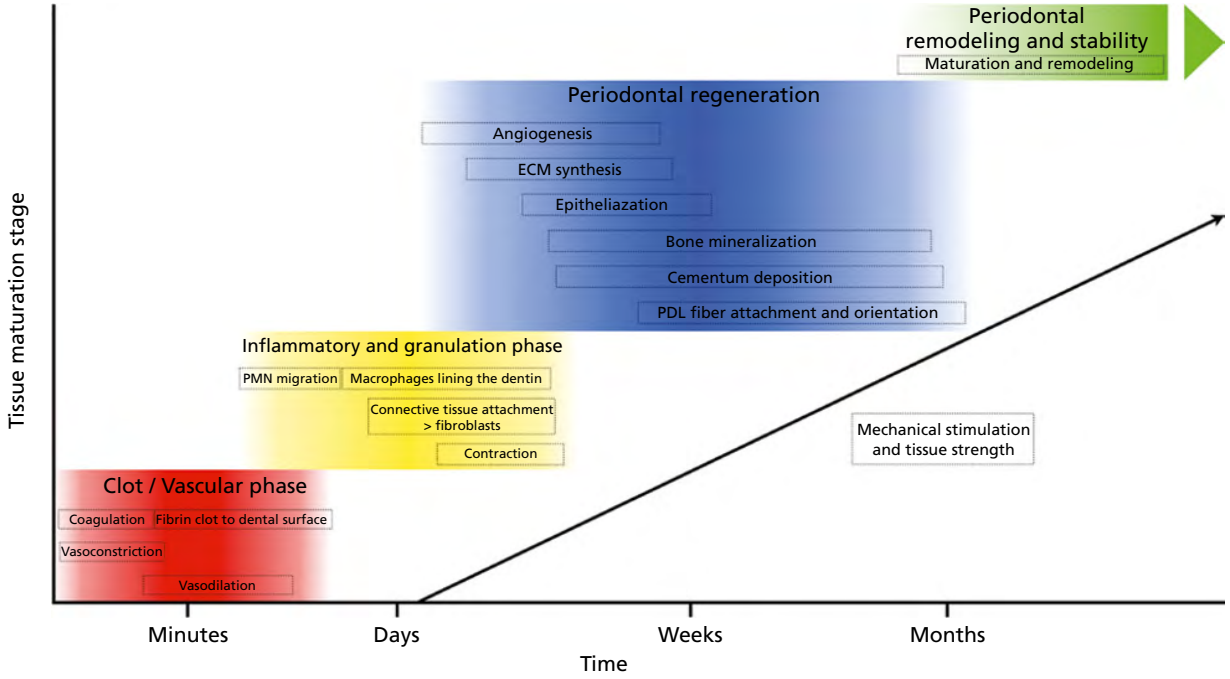

Fig. 21-2 Stages of periodontal wound healing. Optimal periodontal healing requires different processes in a sequential manner. After the initial coagulation phase, inflammatory reaction, and granulation tissue formation events, progenitor cells involved in multitissue regeneration are locally recruited and mediate the bioavailability of important growth factors. As the healing progresses, mechanical stimuli increase and promote an organized ECM synthesis as well as cementum and bone formation and maturation. Once those structures are established, PDL fibers are organized and oriented. Progressively, the tissues mature and ultimately increase its mechanical strength. Remodeling processes continue in the regenerated periodontium as an essential mechanism that monitors the adaptation potential to the challenging local and systemic environment. (Source: Padial-Molina *et al.* 2012.)

Research on periodontal wound healing in the past provided the basic understanding of the mechanisms favoring periodontal tissue regeneration. A number of valuable findings at both the cellular and molecular levels was revealed and subsequently used in the engineering of the regenerative biomaterials that are available in periodontal medicine today.

The morphology of a periodontal wound comprises the gingival epithelium, gingival connective tissue, PDL, and hard tissue components such as alveolar bone and cementum or dentin on the dental root surface. This particular composition affects both the healing events in each tissue component as well as in the entire periodontal site. While the healing of gingival epithelia and their underlying connective tissues concludes in a number of weeks, the regeneration of PDL, root cementum, and alveolar bone generally occurs over a number of weeks or months. With the aim of wound closure, the final outcome of wound healing in the epithelium is the formation of the junctional epithelium surrounding the dentition (Caton *et al*. 1980). The healing of gingival connective tissue, on the other hand, results in a significant reduction of its volume, thus clinically causing both gingival recession and reduction of the periodontal pocket depth. PDL is shown to regenerate on newly formed cementum created by cementoblasts originating from the PDL granulation tissue (Karring *et al*. 1985). Furthermore, alveolar bone modeling occurs following the stimulation of mesenchymal cells from the gingival connective tissue, which are transformed into osteoprogenitor cells by locally expressed BMP (Krebsbach *et al*. 2000; Sykaras & Opperman 2003).

A series of classical animal studies demonstrated that the tissue derived from alveolar bone or gingival connective tissue lacks cells with the potential to produce a new attachment between the PDL and newly formed cementum (Karring *et al*. 1980; Nyman *et al*. 1980). Moreover, granulation tissue derived from the gingival connective tissue or alveolar bone results in root resorption or ankylosis when placed in contact with the dental root surface. It should be expected, therefore, that these complications would occur more frequently following regenerative periodontal surgery, particularly following those procedures which include the placement of grafting materials to stimulate bone formation. The reason for root resorption is rarely identified; however, it may be that following the surgical intervention, the dentogingival epithelium migrates apically along the root surface, forming a protective barrier against the root surface (Bjorn *et al*. 1965; Karring *et al*. 1984). The findings from these animal experiments revealed that ultimately the PDL tissue contains cells with the potential to form a new connective tissue attachment (Karring *et al*. 1985).

Typically, the down-growth of the epithelium along the tooth root surface reaches the level of the PDL before the latter has regenerated with new layers of cementum and newly inserted connective tissue fibers. Therefore, in order to enable and promote the healing towards the rebuilding of cementum and PDL, the gingival epithelium must be hindered in

its creation of a long junctional epithelium along the root surface down to the former level of the PDL.

The principles of periodontal wound healing provide the basic understanding of the events that underlie the events responsible for wound healing following surgical interventions for periodontal therapy. In order to achieve new connective tissue attachment, the granulation tissue derived from PDL cells has to be given both space and time to organize and mature to new cementum and PDL.

Healing after periodontal surgery

Healing after gingival and periodontal surgery represents a more complex situation, particularly in cases where the periodontal tissue is juxtaposed to an instrumented root surface deprived of its periodontal attachment. In this situation, the wound margins are not two opposing vascular gingival margins but comprise the rigid non-vascular mineralized tooth surface on one side, and the connective tissue and epithelium of the gingival flap on the other (Fig. 21-3). Early healing events at the dentogingival interface have been examined using dentin blocks implanted in edentulous alveolar ridges, submerged under gingival flaps, in dogs (Wikesjo *et al*. 1991).

Clot formation at the interface between the tooth and a gingival flap is initiated as blood elements initiate the formation of a clot onto the root surface during surgery and at wound closure. This represents the very first healing event at the tooth–gingival flap interface (i.e. the absorption and adhesion of plasma proteins onto the root surface) (Wikesjo *et al*. 1991). Within minutes, a fibrin clot attached to the root surface is developed. Within hours, the early phase of inflammation may be observed as inflammatory cells, predominantly neutrophils and monocytes, accumulate on the root surface. After a few days, the late phase of inflammation dominates the healing picture as macrophages migrate into the wound followed by the formation of granulation tissue. After a week, a connective tissue attachment may be forming at the root surface as collagenous elements appear to be orientated in close proximity to the dentin surface. Resorptive remodeling of the dentin surface may be evident at this observation interval.

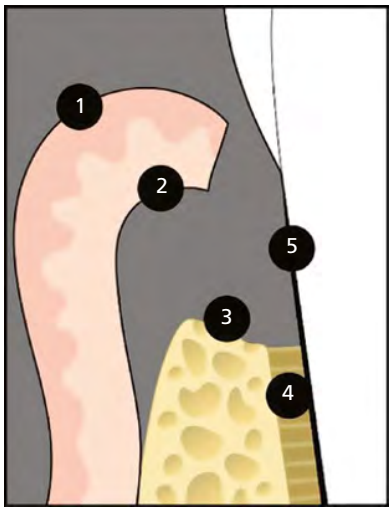

Fig. 21-3 Periodontal wound following flap surgery: (1) gingival epithelium; (2) gingival connective tissue; (3) alveolar bone; (4) periodontal ligament; and (5) cementum or dentin on the dental root surface

Within 14 days, the newly formed collagen fibers may show an arrangement indicative of physical attachment to the dentin (Selvig *et al*. 1988). Ramfjord *et al*. (1966) reported that collagen maturation of collagenous tissues and functional orientation of the connective tissue takes 3–5 weeks. In addition, new bone deposition starts to occur from days 10–21 (Wilderman 1964). Eventually, cementum formation may be initiated, but not until at least 3 weeks after wound closure (Hiatt *et al*. 1968).

Only a few experimental studies have evaluated the functional integrity of a maturing periodontal wound. Hiatt *et al*. (1968) examined the tensile strength of the tooth–gingival flap interface following reconstructive surgery of relatively small surgical dehiscence defects over the maxillary canine teeth in the dog. They found that the tensile strength increased from approximately 200 *g* at 3 days postsurgery to 340 *g* at 5–7 days postsurgery, and to >1700 *g* at 2 weeks postsurgery. In other words, they found that a relatively limited periodontal wound might not reach functional integrity until 2 weeks postsurgery. These data suggest that wound integrity during the early healing phase depends primarily on the stabilization of the gingival flaps achieved by suturing.

Histologic studies have shown that various surgical periodontal procedures can lead to different patterns of healing. Empirically, periodontal healing has generally been characterized by maturation of the gingival connective tissue, some regeneration of alveolar bone and cementum, and, most importantly, epithelialization of the root surface (Listgarten & Rosenberg 1979). Long junctional epithelium is commonly found on the root surface after traditional periodontal surgery and provides protection against bacterial invasion and ankylosis. However, downgrowth of epithelium from the gingival margin prevents the coronal migration of PDL cells, which are responsible for the formation of connective tissue attachment (Fig. 21-4).

Soft tissue management in early regenerative attempts adhering to the principle of epithelial exclusion has included repeated subgingival curettage during healing to control epithelialization of the root surface. More recent approaches have included the prevention of the gingival epithelium from contacting the root surface during the early healing phase by utilization of a cell-occluding membrane. Human as well as animal studies have reported the success with a membrane in facilitating the migration and proliferation of cells from the PDL and alveolar bone in the wound space (Nyman *et al*. 1982; Gottlow *et al*. 1984).

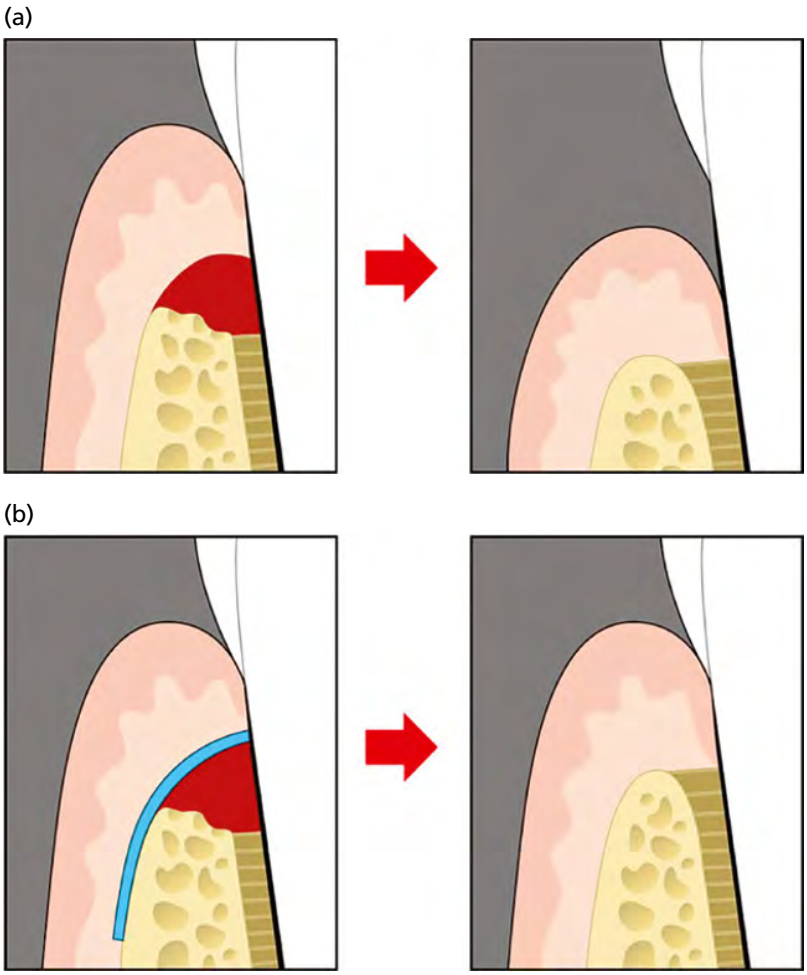

Fig. 21-4 (a) Regular healing process following the periodontal flap adaptation with significant reduction of the attachment apparatus. (b) In order to enable and promote the healing towards the rebuilding of cementum and periodontal ligament, the gingival epithelium must be prevented from creating a long junctional epithelium along the root surface down to the former level of the periodontal ligament (e.g. by placement of a bioresorbable membrane).

The general concepts of healing have been applied in the environment of periodontal tissues. Several investigations have been conducted in attempts to elucidate the exact mechanisms that guide the process and determine the final healing pattern.

Advanced regenerative approaches to periodontal tissue reconstruction

Periodontal regeneration is assessed by probing measures, radiographic analysis, direct measurements of new bone, and histology (Reddy & Jeffcoat 1999). Many cases that are considered clinically successful, including cases with significant regrowth of alveolar bone, may histologically still show an epithelial lining along the treated root surface instead of newly formed PDL and cementum (Listgarten & Rosenberg 1979). In general, however, the clinical outcome of periodontal regenerative techniques has been shown to depend on: (1) patient associated factors such as plaque control, smoking habits, residual periodontal infection, or membrane exposure in guided tissue regeneration (GTR) procedures; (2) effects of occlusal forces that deliver intermittent loads in axial and transverse dimensions; as well as (3) factors associated with the clinical skills of the operator, such as the failure of primary closure of the surgical wound (McCulloch 1993). Even though modified flap designs and microsurgical approaches have been shown to positively affect the outcome of both soft and hard tissue regeneration, the clinical success for periodontal regeneration remains limited in many cases. Moreover, the surgical protocols for regenerative procedures are demanding and may therefore may not be achievable for a number of clinicians. Consequently, both clinical and preclinical research continues to evaluate advanced regenerative approaches (Ramseier *et al*. 2012) using new barrier membrane techniques (Tsai *et al*. 2020), cell-growth stimulating proteins (reviewed in Larsson *et al*. 2016), or gene delivery applications (reviewed in Goker *et al*. 2019), respectively, in order to simplify and enhance the rebuilding of missing periodontal support (Fig. 21-5).

Regenerative surgery

Regenerative periodontal therapy comprises techniques that are particularly designed to restore lost parts of the tooth-supporting structures, including cementum, PDL, and bone. Classically, the most common periodontal indications for these procedures include deep infrabony defects, furcation defects of upper premolar and molar teeth, and localized gingival recession defects. The new classification of periodontal diseases recognizes the key role of

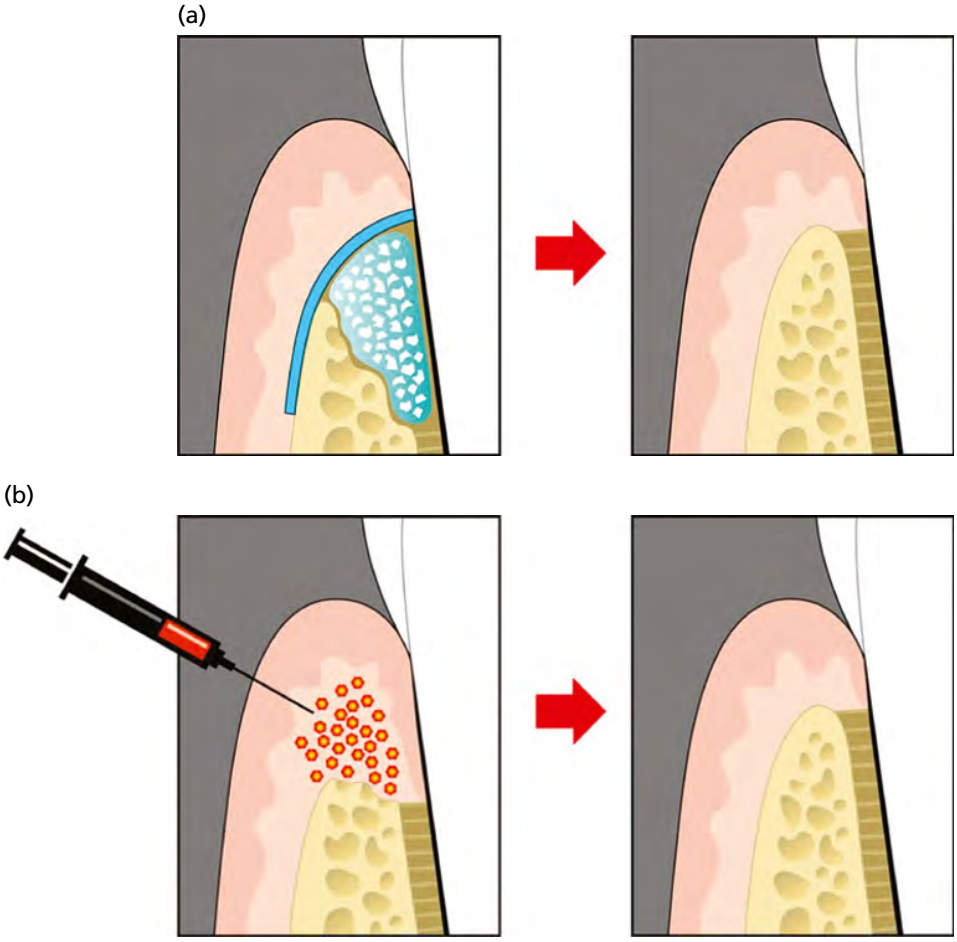

Fig. 21-5 Advanced approaches for regenerating tooth-supporting structures. (a) Application of a graft material (e.g. bone ceramic) and growth factor into an infrabony defect covered by a bioresorbable membrane. (b) Application of gene vectors for the transduction of growth factors producing target cells.

interdental clinical attachment level (CAL) for defining the periodontal status of and the severity (stage) of the periodontal disease (Tonetti *et al*. 2018). Thus, the prognosis (and the stage) of periodontal disease can be improved by regenerating the interdental clinical attachment. Interdental attachment is composed by the supracrestal attachment, which is measured from the cemento-enamel junction (CEJ) to the base of the pocket in the interproximal area. Interproximal bone loss can occur horizontally and/or vertically. This pattern of interdental bone and attachment loss has a major impact not only on patients' esthetic but also on the tooth prognosis. Several attempts have been made for predictably treating these conditions, and to develop new techniques and materials that should be recommended for regenerating the lost interproximal attachment (McGuire & Scheyer 2007; Zucchelli & De Sanctis 2008; Rasperini *et al*. 2013, 2020; Carnio 2014; Aslan *et al*. 2017; Trombelli *et al*. 2017; Zucchelli *et al*. 2017; Ausenda *et al*. 2019). The clinical success for periodontal regeneration may change the long-term prognosis of the tooth (Sculean *et al*. 2008; Nickles *et al*. 2009; Silvestri *et al*. 2011; Cortellini *et al*. 2017). Clinical and preclinical research continues to advance the field of periodontal regenerative therapy by evaluating innovative tissue engineering approaches that include optimized scaffold fabrication technology (Pilipchuk *et al*. 2015), new barrier membrane techniques (Tsai *et al*. 2020), cell-growth stimulating proteins (Dereka *et al*. 2006; Kaigler *et al*. 2006), as well as cell and gene delivery applications (Ramseier *et al*. 2006) (Fig. 21-6).

Guided tissue regeneration

Histologic findings from periodontal regeneration studies and Melcher's concepts of "compartmentalization" revealed that a new connective tissue attachment could be predicted if the cells from the PDL settle on the root surface during healing (Melcher 1976). Hence, the clinical applications of GTR in periodontics involve the placement of a physical barrier membrane to enable the previously periodontitis-affected tooth root surface to be repopulated with cells from the PDL, cells from the lamina propria of the gingival corium, cementum cells, and alveolar bone. GTR techniques utilize barrier membranes to facilitate the migration of bone cells and PDL cells to the defects by preventing soft tissue cells from infiltrating into the defect. This knowledge has been the key to developing standard clinical procedures for the placement of a fabricated membrane in GTR. GTR has recently

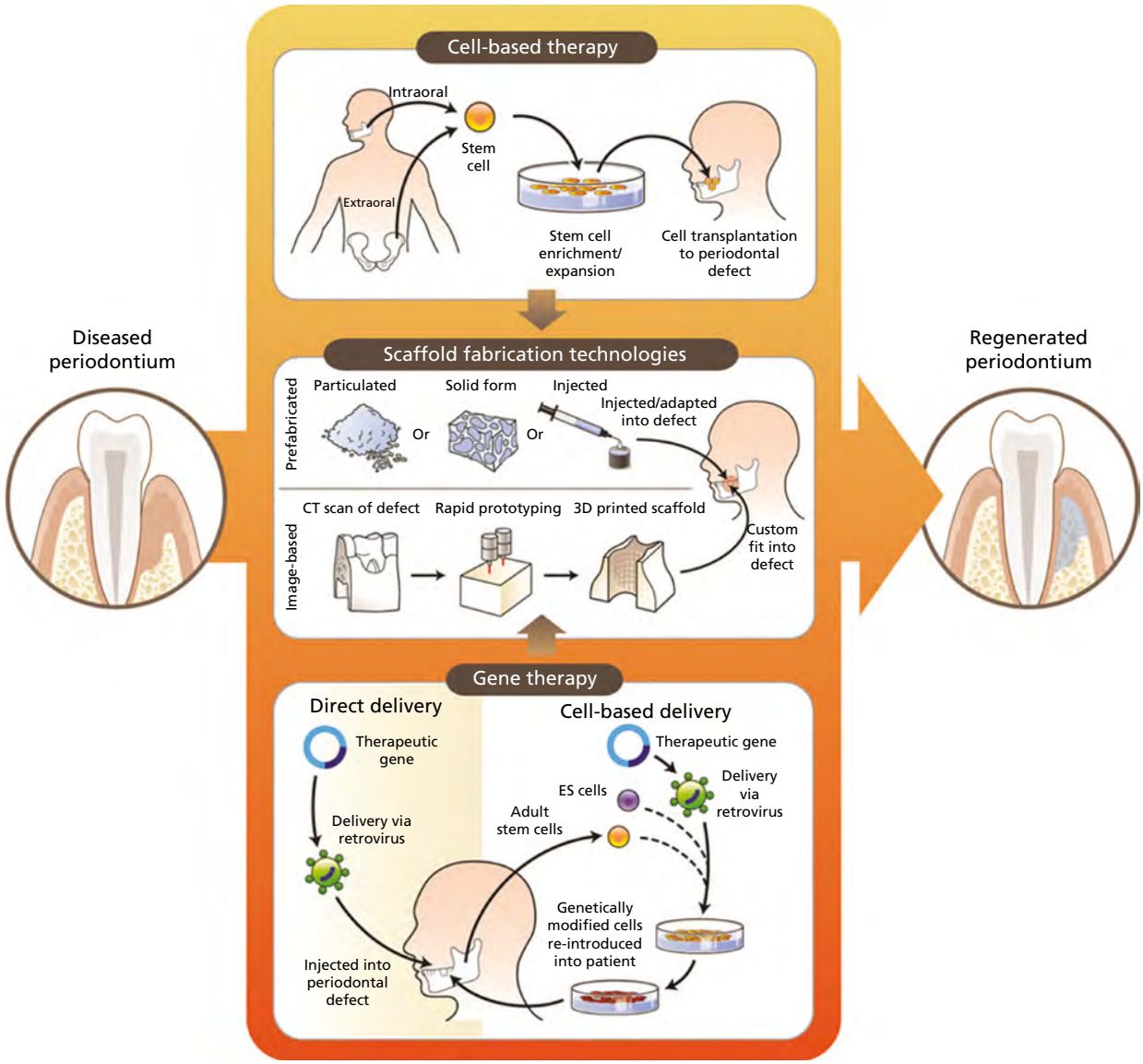

Fig. 21-6 Cell- and gene-based technologies using scaffolding matrices for periodontal tissue engineering. Extraoral and intraoral stem cells represent a viable and accessible alternative source to harvest and expand multipotent colonies. Adequate cell density could be reached *in vitro* in a controlled environment and made readily available for reimplantation into a periodontal defect site. The available direct and cell-based delivery of a therapeutic gene has been shown to increase the regenerative potential and enhance the availability of important factors. The gene of interest is either injected directly into the periodontal defect via a retrovirus or alternatively could be incorporated into a stem cell that is subsequently expanded and delivered into the area of interest. Prefabricated and image-based scaffolds are becoming an essential component in regenerative medicine. A defined supporting structure allows the localization and guidance of the appropriate cells, proteins and the establishment of a mechanically competent environment. Currently, scaffolds for periodontal regeneration are available in particulated, solid, and injectable forms. New developing technology has allowed the customization of scaffolds that would fit into the periodontal defect and include an external and internal architecture that enhances tissue orientation and regeneration. This figure highlights the potential of integrating the available tissue engineering strategies to enhance the outcome of periodontal regenerative therapy. ES cells, embryonic stem cells. (Source: Rios *et al*. 2011).

been combined with the delivery of different factors that are incorporated to augment the regenerative response.

Clinical applications of growth factors for use in periodontal regeneration

A number of studies have focused on the modification of the periodontitis-involved root surface in order to advance the formation of a new connective tissue attachment. However, despite histologic evidence of regeneration following root surface biomodification with citric acid, the outcome of controlled clinical trials have failed to show any improvements in clinical conditions compared with non–acid-treated controls (reviewed in Mariotti 2003). In recent years, biomodification of the root surface with enamel matrix proteins during periodontal surgery and following demineralization with ethylene–diamine–tetra-acetic acid (EDTA) has been introduced to promote periodontal regeneration. The application of enamel matrix proteins (amelogenins) has also been

evaluated as a promoter of periodontal regeneration because it initiates events that occur during the growth of periodontal tissues (Gestrelius *et al*. 2000). Enamel matrix derivative, a purified acid extract of porcine origin contains *enamel matrix derivate* (EMD), which has demonstrated the ability to advance periodontal regeneration (reviewed in Nibali *et al*. 2020). Thus far, EMD alone or in combination with grafts has demonstrated consistent potential to effectively treat intraosseous defects and the clinical results are generally stable over the long term (Trombelli & Farina 2008).

PDGF is a member of a multifunctional polypeptide family and exerts its biologic effects on cell proliferation, migration, ECM synthesis, and antiapoptosis (reviewed in Larsson *et al*. 2016 and Giannobile 1996). The clinical application of PDGF has been shown to successfully advance alveolar bone repair and CAL gain. Initial clinical trials reported the successful repair of class II furcations using demineralized freeze-dried bone allograft (DFDBA) saturated with rhPDGF-BB (Nevins *et al*. 2003). Subsequently, rhPDGF-BB mixed with a synthetic beta-tricalcium phosphate (β-TCP) matrix was shown to advance the repair of deep infrabony pockets as measured by radiographic bone fill in a large multicenter randomized controlled trial (Nevins *et al*. 2005, 2013). Both studies also demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal osseous defects. In a recent systematic review on PDGF clinical applications, there is evidence on the use of this growth factor system to promote healing in extraction sockets, for sinus floor augmentation, intraoral soft tissue grafts, and ridge augmentation procedures (Tavelli *et al*. 2020).

BMPs are multifunctional polypeptides that have potent bone regenerative capacity. Fiorellini *et al*. (2005) reported that in a human buccal wall defect model, bone formation following tooth extraction was significant when the defect was treated with recombinant human BMP-2 (rhBMP-2) delivered by a bioabsorbable collagen sponge, compared with treatment with the collagen sponge alone. Furthermore, BMP-7, also known as osteogenic protein 1 (OP-1), stimulates bone regeneration around teeth, endosseous dental implants, and in maxillary sinus floor augmentation procedures (reviewed in Lin *et al*. 2016 and Avila-Ortiz *et al*. 2016).

In general, topical delivery of growth factors to periodontal wounds has shown promise, but as yet the impact is insufficient for the promotion of predictable periodontal tissue engineering (Kaigler *et al*. 2006). Growth factor proteins, once delivered to the target site, tend to suffer from instability and quick dilution, presumably due to proteolytic breakdown, receptor-mediated endocytosis, and solubility of the delivery vehicle. Because their half-lives are significantly reduced, the period of exposure may not be sufficient to act on osteoblasts, cementoblasts, or PDL cells. A clinical trial evaluated the regenerative effects of systemic delivery of teriparatide, a recombinant form of parathyroid hormone (PTH). The study demonstrated a periodontal anabolic effect favoring a regenerative outcome. Following periodontal surgery, teriparatide was systemically delivered for 6 weeks and results compared with a placebo control. Delivery of this recombinant molecule in this fashion was associated with improved clinical outcomes, including greater resolution of alveolar bone defects and accelerated osseous wound healing (Bashutski *et al*. 2010). More recently, a similar bone anabolic molecule used in the treatment of osteoporosis, the sclerostin monoclonal antibody (described in greater detail in Chapter 2) has shown strong potential to repair periodontal defects by increasing bone volume of alveolar bone (Taut *et al*. 2013; Yao *et al*. 2020).

Cell therapy for periodontal regeneration

Another emerging regenerative approach in the management of soft and hard tissue defects involves cell therapy (see Table 21.3). For regeneration of interdental papillae, early investigations of cell therapy using *ex vivo* cultivated autologous fibroblasts have shown success in the treatment of interdental papillary insufficiency (McGuire & Scheyer 2007). For larger soft tissue defects, a human oral mucosa equivalent, made of autogenous keratinocytes (EVPOME) placed on a cadaveric dermal carrier (Alloderm®), has shown efficacy in wound healing when compared with the dermal carrier alone (Izumi *et al*. 2003). EVPOME has also been successfully used to treat patients affected by squamous cell carcinoma of the tongue, leukoplakia of the tongue, gingiva, and buccal mucosa, or hypoplasia of the alveolar ridge (Hotta *et al*. 2007). In other soft tissue applications, allogenic foreskin fibroblasts have been utilized to promote keratinized tissue formation at mucogingival defects (McGuire & Nunn 2005). A tissue-engineered living cellular construct comprised of viable neonatal keratinocytes and fibroblasts has been evaluated for its ability to increase keratinized gingiva around teeth, and rendered similar clinical outcomes to conventional free gingival autografts (McGuire *et al*. 2011). Compared with the free gingival graft, this particular cell construct has also demonstrated increased potential to promote the expression of angiogenic factors during the early stages of wound healing and, therefore, constitutes a promising material for soft tissue grafting where free gingival grafts are typically indicated (Morelli *et al*. 2011).

The benefits of using somatic cells for the regeneration of soft and hard tissues in the craniofacial area have been illustrated in several preclinical and clinical studies. However, their lack of self-renewal capability and their commitment toward a single cellular phenotype limit their use in the treatment of more challenging craniofacial defects. Stem cells would provide benefit in these applications in that they can reproduce themselves (*self-renewal*) and

differentiate into a variety of specialized cell types (*multipotent*). *Bone marrow stromal cells* (BMSC) are multipotent because they have the ability to differentiate into osteoblasts, chondroblasts, adipocytes, myocytes, and fibroblasts when transplanted *in vivo* (Prockop 1997). *Mesenchymal stem cells* (MSCs) can be obtained from a variety of sources, but autologous MSC isolated from bone marrow of the iliac crest offer a predictable and a cost-effective therapy for the treatment of severely atrophic maxillary and mandibular ridges when compared with harvested autogenous bone (Soltan *et al*. 2007). Bone repair cells (ixmyelocel-T®; Aastrom Biosciences) consisting of *ex vivo* expanded, autologous bone marrow-derived, CD90+ MSCs have recently demonstrated the ability to accelerate bone regeneration and yield better quality bone in localized and large alveolar defects (Kaigler *et al*. 2013, 2015; Bajestan *et al*. 2017). Because these cells include MSCs, they not only serve to provide a source of stem and progenitor cells to a wound healing site, but also produce many growth factors actively involved in the establishment of a vasculature to support and sustain tissue regeneration.

Gene therapeutics for periodontal tissue repair

Although encouraging results for periodontal regeneration have been reported from various clinical investigations using recombinant tissue growth factors, topical protein delivery from existing vehicles has limitations such as transient biologic activity, protease inactivation, and poor bioavailability. Therefore, newer approaches seek to develop methodologies that optimize growth factor targeting to maximize the therapeutic outcome of periodontal regenerative procedures. Genetic approaches in periodontal tissue engineering show early progress in achieving delivery of growth factor genes such as *PDGF* or *BMP* to periodontal lesions (Taba *et al* 2005; Kaigler *et al*. 2006). Gene transfer methods may circumvent many of the limitations with protein delivery to soft tissue wounds (Giannobile 2002; Baum *et al*. 2003). It has been shown that growth factors (Jin *et al*. 2004; Plonka *et al*. 2017) or soluble forms of cytokine receptors (Cirelli *et al*. 2009) applied by gene transfer are more sustainable than proteins applied in a single application. Thus, gene therapy may achieve greater bioavailability of growth factors within periodontal wounds and thus provide greater regenerative potential.

Three-dimensional printed scaffolds for periodontal regeneration

Scaffolds are an integral aspect of tissue engineering approaches to periodontal regeneration, given that space maintenance and wound stability are critical considerations. The scaffold is expected to perform various functions, including the support of cell colonization, migration, growth, and differentiation. The design of the scaffolds also needs to consider biomechanical stability over time, complex 3-dimesional shape, and degradation kinetics (Vaquette *et al*. 2018; Yu *et al*. 2019). Multiphasic three-dimensional scaffolds, incorporating dedicated compartments for PDL, cementum, and bone formation, have the potential to enhance regenerative outcomes by controlling the complex temporal and spatial interactions during periodontal wound healing (Ivanovski *et al*. 2014). Three-dimensional (3D) printing, defined as an additive manufacturing technology for creating 3D objects from a numerical data file in a layer by layer fashion (Fig 21-7a), offers significant promise for the fabrication of multiphasic scaffolds for periodontal regeneration. This is because additive manufacturing is capable of exerting a high level of control over the microstructure and porosity of the multiphasic scaffolds, suitable for regeneration of different components of the periodontium (such as bone and PDL) (Fig 21-7b), and providing guidance for perpendicular periodontal fiber attachment to the root surface (Fig 21-7c, d) (Obregon *et al*. 2015; Staples *et al*. 2020). It also has the advantage of being able to produce custom scaffolds that can be fabricated to intimately fit individual periodontal defects, as recently described in a landmark human case report (Rasperini *et al*. 2015). Data from a computed tomography scan of the patient's defect was used to design and print a customized scaffold made from a biodegradable polymer (polycaprolactone [PCL]) (Fig 21-7e–j). The scaffold was initially well integrated into the host tissue (Fig 21-7k) and demonstrates the 'proof-of-concept' potential of 3D printed scaffolds for the treatment of a periodontal defect.

Conclusion

The periodontal healing process is governed by a complex multifactorial mechanism in which a number of local and systemic, micro- and macro-environmental variables interplay to define the final result. Only a profound understanding of biologic and clinical variables affecting the outcome of gingival and periodontal surgical procedures will allow clinicians to manipulate critical factors effectively in order to optimize the outcome and increase the predictability of periodontal regeneration (Figs. 21-8, 21-9, 21-10). This chapter has given a brief presentation of the healing mechanisms that are initiated in periodontal tissues following basic periodontal surgical procedures. The complexity of the cellular and molecular events that are activated during and after a periodontal intervention lead to some important conclusions:

- As clinicians, we must minimize any deviations from the strict surgical protocols in order to ensure the risk of any unfavorable healing events is minimized. It is important that the PASS principle of promotion of periodontal wound repair: *P*rimary wound stability, *A*ngiogenesis

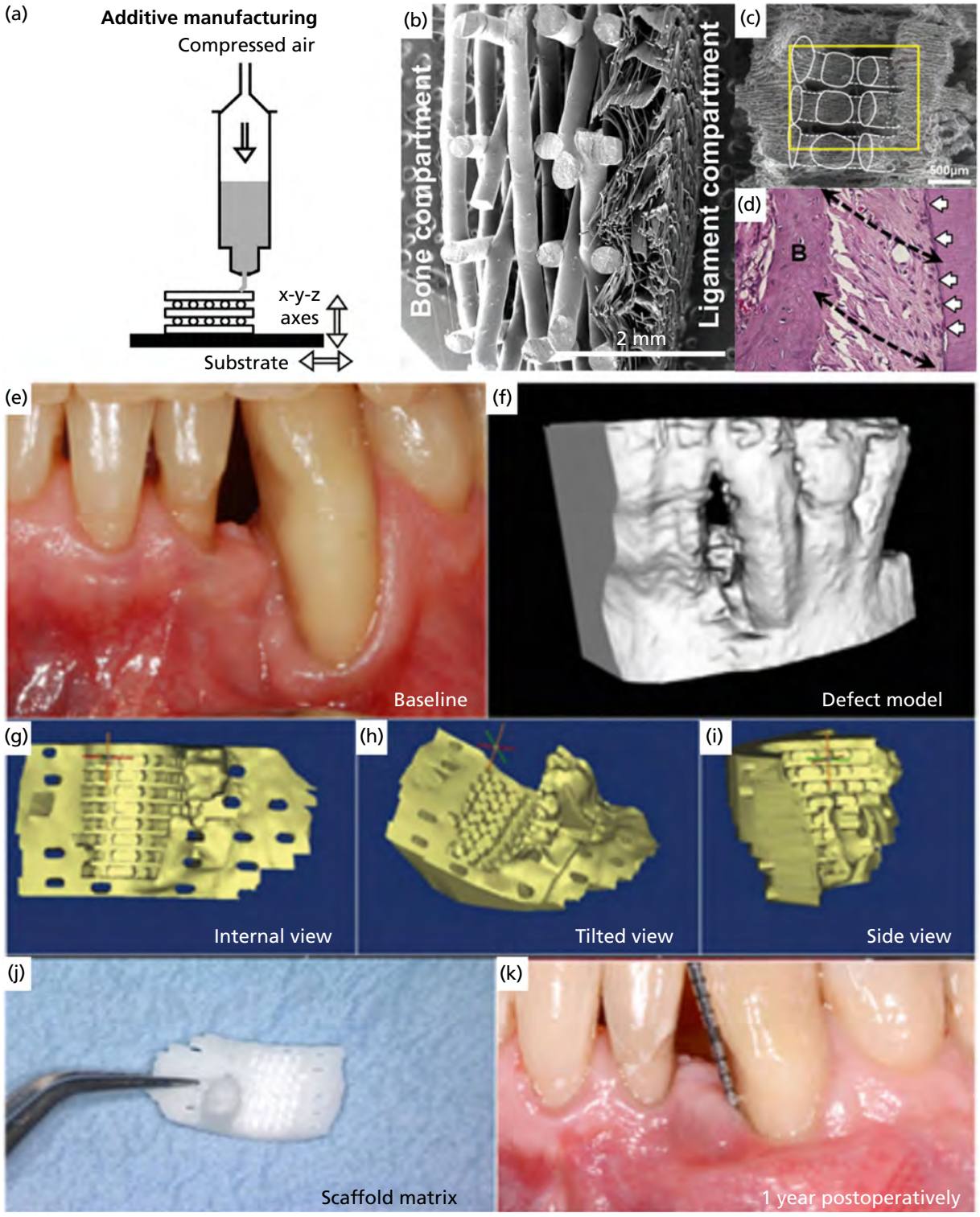

Fig. 21-7 (a) Concept of additive manufacturing (3D printing) of a 3D scaffold in a layer by layer fashion. (b) Multiphasic scaffold with a bone and periodontal ligament compartment. (c) Fiber-guiding microstructure (microchannels) of scaffold. (d) Histological evidence of fiber-guidance *in vivo*. (e–k) Clinical example of 3D-printed scaffold *in vivo*. (Source: Vaquette *et al*. 2018 and Rasperini *et al*. 2015. Reproduced with permission from John Wiley & Sons.)

to promote good wound perfusion, *S*pace creation for repopulation of the wound site by stem cells and those associated with regeneration and wound *S*tability. These principles will owe to a good clinical result (Wang & Boyapati 2006).

- As scientists, we should be able to translate the clinical signs and symptoms into the language of physiology and histology, and understand their nature so that interventions can be modified accordingly

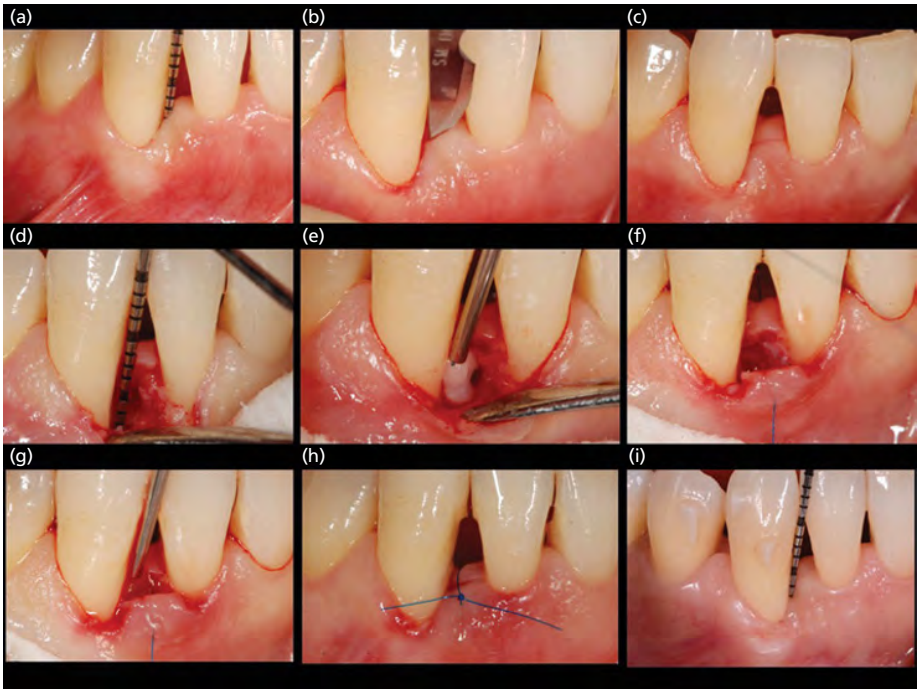

Fig. 21-8 (a) Severe probing pocket depth (PPD) (7 mm), mesial to tooth 43 at the re-evaluation after non-surgical periodontal treatment. (b), (c) A buccal incision of the papilla is performed to allow the elevation of a buccal flap. (d) In this case it was possible to elevate a minimum amount of buccal tissue to visualize the defect, without elevating the interdental papilla, according to the "single flap approach" (Trombelli *et al*. 2009) and modified MIST (Cortellini & Tonetti 2009). (Source: Case presentation courtesy of Giulio Rasperini) (e) After cleaning the root and debriding the defect, EDTA was applied onto the root surface for 2 minutes to remove the smear layer. (f) A simple interrupted monofilament suture is prepared and left loose. (g) After irrigation of the root with saline solution, EMD (Emdogain®, Straumann, Basel, Switzerland) was applied onto the clean root surface. (h) The suture can now be closed with a surgical knot. (i) One year later, the site probes 2 mm with a gain of 5 mm when compared with the baseline.

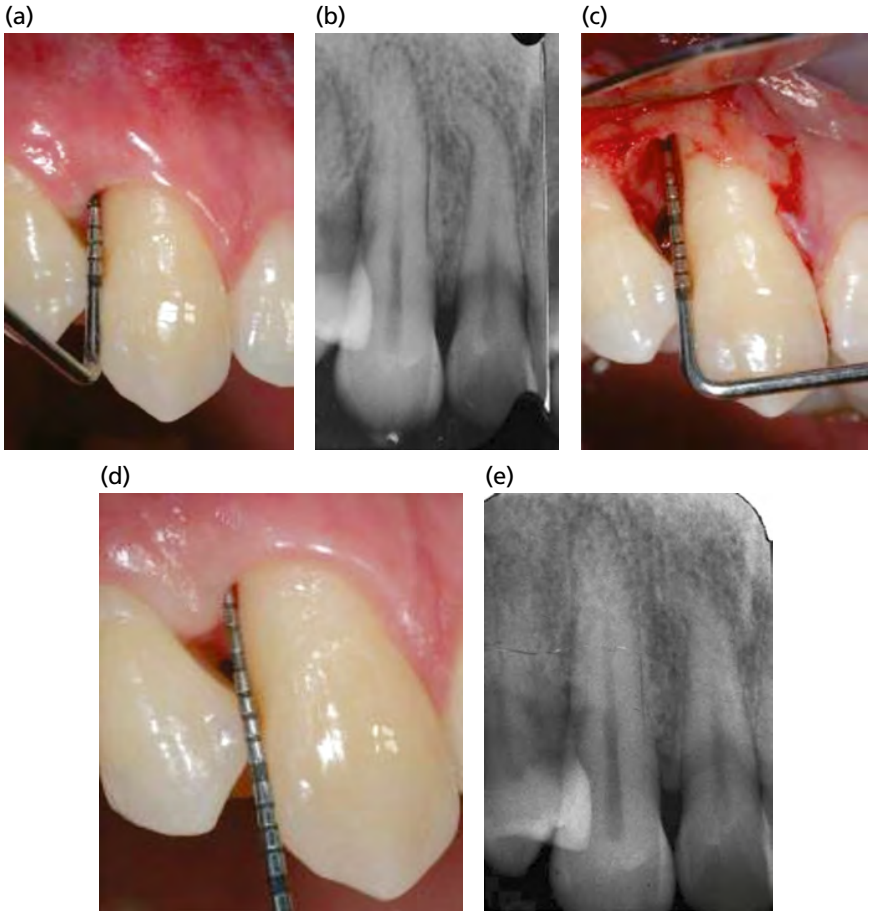

Fig. 21-9 (a) A 32-year-old male patient with severe periodontitis. Tooth 13 shows a probing pocket depth (PPD) of 10 mm distobuccal and a clinical attachment level (CAL) of 14 mm. (b) Periapical radiograph shows the infrabony defect distal to tooth 13. (c) After the buccal incision of the papilla, the interdental tissue is preserved attached to the palatal flap. After debridement of the granulation tissue and root planing, the infrabony defect is classified and measured: the predominant component is a 7-mm deep three-wall defect. One year after surgical intervention, the distal site of tooth 13 shows a PPD of 2 mm (gain of 8 mm from initial measurement) and a CAL of 7 mm (gain of 7 mm) (d) and the radiograph shows defect filling (e).

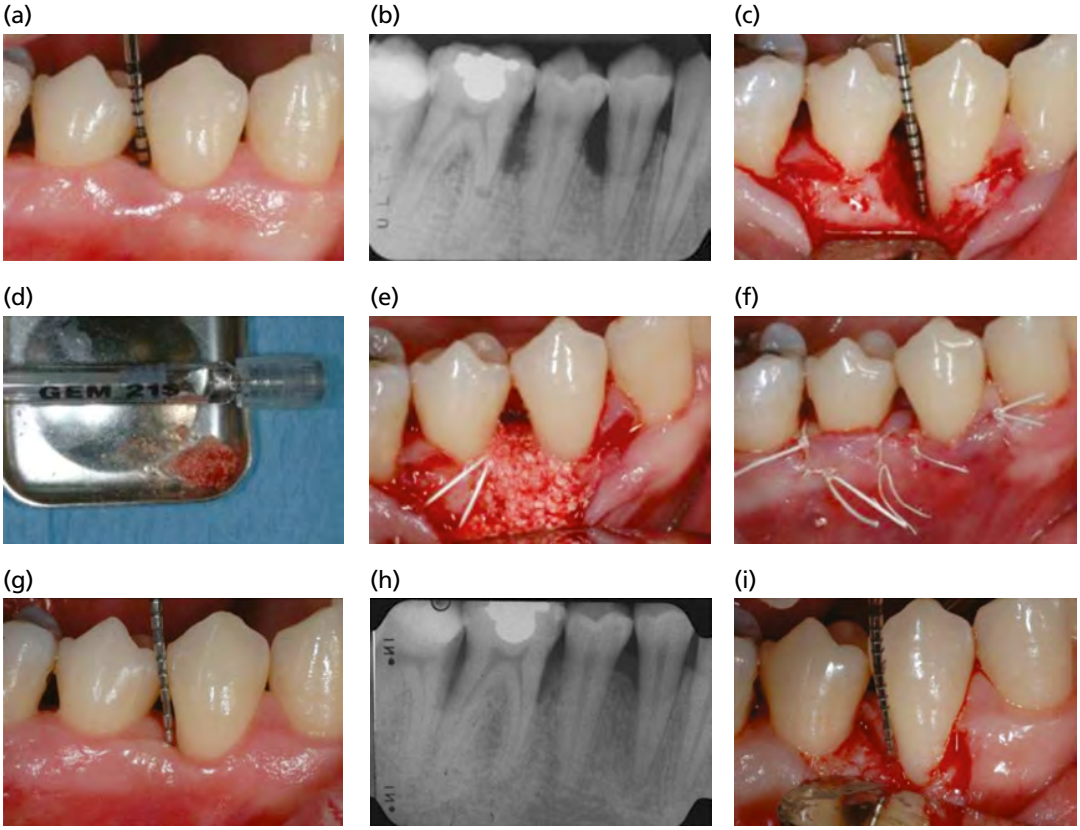

Fig. 21-10 (a) A 27-year-old patient at the re-evaluation visit after the initial phase showed three sites with a pocket probing depth (PPD) of <6 mm; the one distal to tooth 44 had a PPD of 7 mm and no gingival recession. (b) Periapical radiograph shows a one-wall defect distal to tooth 44 and a lesion between teeth 45 and 46. (c) Measurement of the pure one-wall defect shows an infrabony component of 6 mm. (d) Grafting material of the GEM 21S® is mixed with a few particles of autogenous bone chips, collected from the surgical area with a Rhodes instrument, and with the liquid component of the GEM 21S® (platelet-derived growth factor [PDGF]). (e) Liquid PDGF is placed in the defect together with the graft to rebuild the lost bone. (f) An off-set internal mattress suture is performed to keep and stabilize the flap coronal. A second internal mattress suture is performed with 7-0 Gor Tex® to allow optimal adaptation of the flap margins without interference from the epithelium. The two internal mattress sutures are tied but not knotted until there is a perfect tension-free closure of the wound. Two additional interrupted 7-0 sutures are placed to assure stable contact between the connective tissues of the edges of the flaps. The mesial and distal papilla are stabilized with additional interrupted sutures. Nine months after surgery the PPD is 2 mm (g), the periapical radiograph shows a good bone fill of the one-wall bony defect (h), and surgical re-entry shows formation of new bone (i).

Acknowledgments

The authors thank Dr. Hector Rios for his written contributions to the previous edition of this chapter.

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Lindhe's Clinical Periodontology and Implant Dentistry

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Seventh Edition

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WILEY Blackwell

Volume 2
CLINICAL CONCEPTS

This edition first published 2022

Registered Offices
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Berglundh, Tord, 1954– editor. | Giannobile, William V., editor. | Lang, Niklaus Peter, editor. | Sanz, Mariano (Professor) editor.
Title: Lindhe's clinical periodontology and implant dentistry / edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, Mariano Sanz.
Other titles: Clinical periodontology and implant dentistry
Description: Seventh edition. | Hoboken : John Wiley & Sons, Inc., 2022. | Preceded by Clinical periodontology and implant dentistry / edited by Jan Lindhe and Niklaus P. Lang ; associate editors, Tord Berglundh, William V. Giannobile, Mariano Sanz. 6th edition. 2015.
Identifiers: LCCN 2021028065 (print) | LCCN 2021028066 (ebook) | ISBN 9781119438885 (cloth) | ISBN 9781119438946 (adobe pdf) | ISBN 9781119438953 (epub)
Subjects: MESH: Periodontal Diseases | Dental Implantation | Dental Implants
Classification: LCC RK667.I45 (print) | LCC RK667.I45 (ebook) | NLM WU 240 | DDC 617.6/93–dc23
LC record available at https://lccn.loc.gov/2021028065
LC ebook record available at https://lccn.loc.gov/2021028066

Cover Design: Wiley
Cover Image: Courtesy of William V. Giannobile

Set in 9.5/12pt Palatino by Straive, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

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Part 9: **Examination Protocols**

Chapter 22

Examination of Patients

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Patient's history

As a basis for comprehensive treatment planning and understanding of the patient's needs, social and economic situations, as well as general medical conditions, the history of the patient is a revealing documentation. In order to expedite history taking, a health questionnaire may be filled out by the patient prior to the initial examination. Such a questionnaire should be structured in a way that the professional immediately realizes compromising or risk factors that may modify the treatment plan and hence, may have to be discussed in detail with the patient. The assessment of the patient's history requires an evaluation of the following six aspects: (1) chief complaint, (2) social and family history, (3) dental history, (4) oral hygiene habits, (5) tobacco consumption history and potential drug abuse, and (6) medical history and medications.

Chief complaint and expectations

It is essential to realize the patient's needs and desires for treatment. If a patient has been referred for specific treatment, the extent of the desired treatment has to be defined and the referring dentist should be informed of the intentions for treatment. However, patients reporting by themselves usually have specific desires and expectations regarding treatment outcomes. These may not be congruent with the true assessment of a professional with respect to the clinical situation. Satisfactory individually optimal treatment results may only be achieved if the patient's demands are in balance with the objective evaluation of the disease and the projected treatment outcomes. Therefore, the patient's expectations have to be taken seriously and must be incorporated in the evaluation in harmony with the clinical situation.

Social and family history

Before assessing the clinical conditions in detail, it is advantageous to elucidate the patient's social environment and to feel for his/her priorities in life including the attitude towards periodontal therapy and potential rehabilitation with dental implants. Likewise, a family history may be important especially with respect to forms of periodontitis with a rapidly progressing pattern.

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Dental history

These aspects include an assessment of previous dental care and maintenance visits if not stated by a referring dentist. In this context, information regarding signs and symptoms of periodontitis noted by the patient such as migration and increasing mobility of teeth, bleeding gums, food impaction, and difficulties in chewing have to be explored. Chewing comfort and the possible need for tooth replacement with removable or fixed dental prostheses is determined.

Oral hygiene habits

In addition to the exploration of the patient's routine dental care including an assessment of frequency and duration of daily tooth brushing habits, the knowledge about interdental cleansing devices and additional supportive antiseptics and regular use of fluorides should be assessed. The patient's manual dexterity and his/her cleansing patterns with either manual or power-driven toothbrushes should be evaluated.

History of tobacco use

Since tobacco use has been documented to be the second most important risk factor after inadequate plaque control (Kinane *et al*. 2006; Bassetti *et al*. 2017) in the etiology and pathogenesis of periodontal diseases, the importance of tobacco use counseling cannot be overestimated. Moreover, based on the fact that cigarette smokers display an increased risk for peri-implant diseases and implant loss compared with non-smokers (Strietzel *et al*. 2007; Heitz-Mayfield & Huynh-Ba 2009; Meyle *et al*. 2019), the assessment of the tobacco use history represents an important step in the initial patient evaluation.

Hence, the determination of the tobacco use history including detailed information about exposure time and quantity have to be collected. Further aspects of tobacco cessation counselling are presented in Chapter 27.

Medical history and medications

General medical aspects may be extracted from the health questionnaire constructed to highlight the medical risk factors encountered for routine periodontal and/or implant therapy. The four major complexes of complications encountered in patients may be prevented by checking the medical history with respect to: (1) cardiovascular and circulatory risks, (2) bleeding disorders, (3) infective risks, and (4) allergic reactions. Further aspects are presented in Chapter 24.

In light of the increasing consumption of medications in the aging population, an accurate assessment of the patient's prescribed medications and their potential interactions and effects on therapeutic procedures have to be collected. With respect to treatment planning with dental implants, it may be indicated to contact the patient's physician for detailed information relevant to systemic risks (Bornstein *et al*. 2009; Chappuis *et al*. 2018).

Genetic testing before periodontal and implant therapy

Cytokine gene polymorphisms may modulate the host response to the bacterial challenge and influence susceptibility to periodontal and peri-implant diseases. Based on current evidence, however, it may be considered premature to recommend a systematic genetic screening of patients with periodontal diseases and candidates for implant therapy (Huynh-Ba *et al*. 2007, 2008).

Signs and symptoms of periodontal diseases and their assessment

Periodontal diseases are characterized by color and texture alterations of the gingiva, for example redness and swelling, as well as an increased tendency to bleeding on probing (BoP) in the gingival sulcus/pocket area (Fig. 22.1). In addition, the periodontal tissues may exhibit a reduced resistance to probing perceived as increased probing depth and/or tissue recession. Advanced stages of periodontitis may also be associated with increased tooth mobility as well as drifting or flaring of teeth (Fig. 22-2).

On radiographs, periodontitis may be recognized by moderate to advanced loss of alveolar bone (Fig. 22-3). Bone loss is defined either as "horizontal" or "angular". If bone loss has progressed at similar rates in the dentition, the crestal contour of the remaining bone in the radiograph is even and defined as being "horizontal". In contrast, angular bony defects are the result of bone loss that has occurred at different rates around teeth/tooth surfaces and hence, is defined as "vertical" or "angular" bone loss.

In a histological section, periodontitis characterized by the presence of an inflammatory cell infiltrate within a 1–2 mm wide zone of the gingival connective tissue adjacent to the subgingival biofilm on the tooth (Fig. 22-4). Within the infiltrated area there is a pronounced loss of collagen. In more advanced forms of periodontitis, marked loss of connective tissue attachment to the root and apical downgrowth of the dentogingival epithelium along the root are important characteristics.

Outcomes from experimental and clinical research indicated that periodontal diseases:

- Affect individuals with various susceptibility at different rates (Löe *et al*. 1986; Ramseier *et al*. 2017)
- Affect different parts of the dentition to a varying degree (Papapanou *et al*. 1988)
- Are site specific in nature for a given area (Socransky *et al*. 1984)

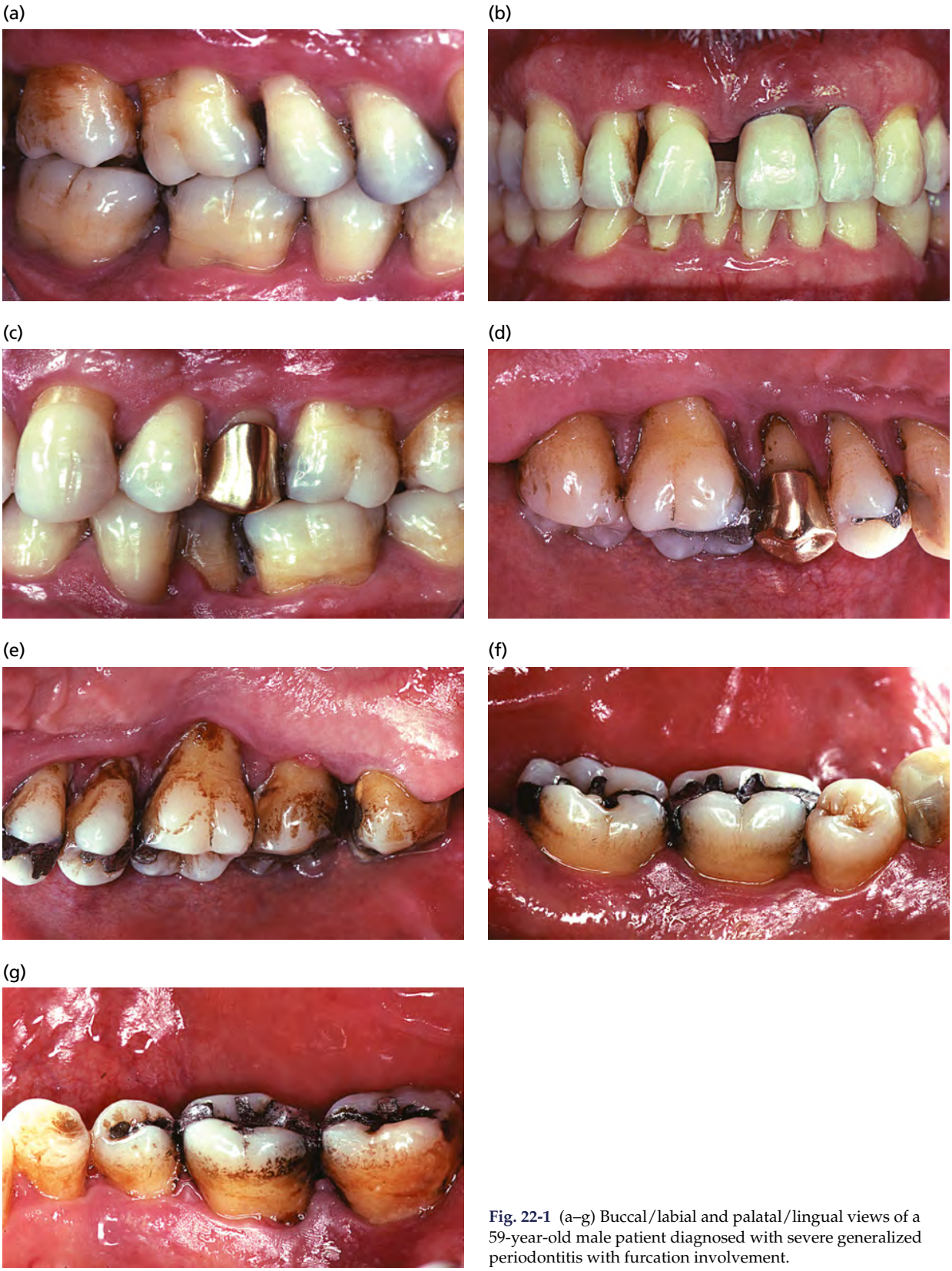


Fig. 22-1 (a–g) Buccal/labial and palatal/lingual views of a 59-year-old male patient diagnosed with severe generalized periodontitis with furcation involvement.

- Are sometimes progressive in character and, if left untreated, may result in tooth loss (Löe *et al*. 1986; Ramseier *et al*. 2017)
- Can be successfully treated and maintained long-term (Hirschfeld & Wasserman 1978; Rosling *et al*. 2001; Axelsson *et al*. 2004).

For effective treatment planning, the location, topography and extent of periodontal lesions should be recognized in all parts of the dentition. It is, therefore, mandatory to examine all sites of all teeth for the presence or absence of periodontal lesions. This, in turn, means that single-rooted teeth should be

examined at least at four sites (e.g. mesial, buccal, distal, and oral) and multirooted teeth at least at six sites (e.g. mesiobuccal, buccal, distobuccal, distooral, oral, and mesio-oral) with special attention to the furcation areas.

Because periodontitis includes inflammatory alterations of the gingiva and a progressive loss of periodontal attachment and alveolar bone, the comprehensive examination must include assessments describing such pathologic alterations.

Figure 22-1 illustrates the clinical status of a 59-year-old patient diagnosed with severe periodontitis.

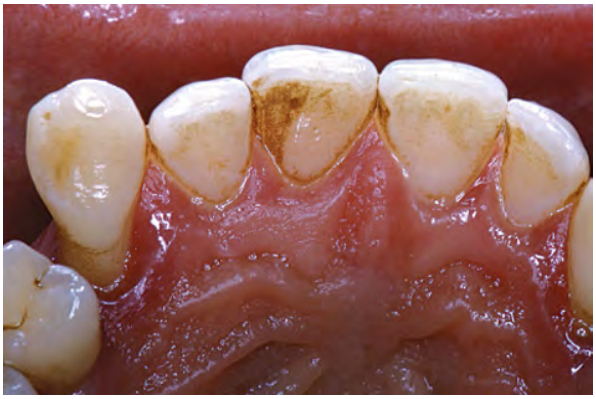


Fig. 22-2 Buccal migration of tooth 13 as a sign of severe periodontitis.

The examination procedures used to assess the location and extension of periodontal disease will be demonstrated by using this case as an example.

Gingiva

Clinical signs of gingivitis include changes in color and texture of the soft marginal gingival tissue and BoP.

Various index systems have been developed to describe gingivitis in epidemiologic and clinical research. They are discussed in Chapter 6. Even though the composition of the inflammatory infiltrate can only be identified on histologic sections, inflamed gingival tissue can be correctly diagnosed on the basis of the tendency to bleed on probing. The symptom BoP to the bottom of the gingival sulcus/pocket is associated with the presence of an inflammatory cell infiltrate. The occurrence of such bleeding, especially in repeated examinations, is indicative of disease progression (Lang *et al*. 1986), although the predictive value of this single parameter remains rather low (i.e. 30%). On the other hand, the absence of BoP yields a high negative predictive value (i.e. 98.5%) and hence, is an important indicator of periodontal stability (Lang *et al*. 1990; Joss *et al*. 1994). Since trauma to the tissues provoked by probing should be avoided if the true vascular permeability changes

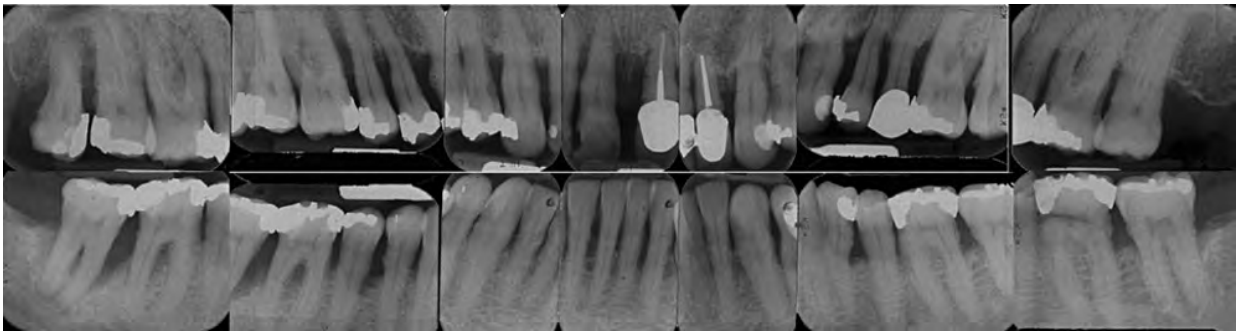


Fig. 22-3 Periapical radiographs of the patient presented in Fig. 22-1.

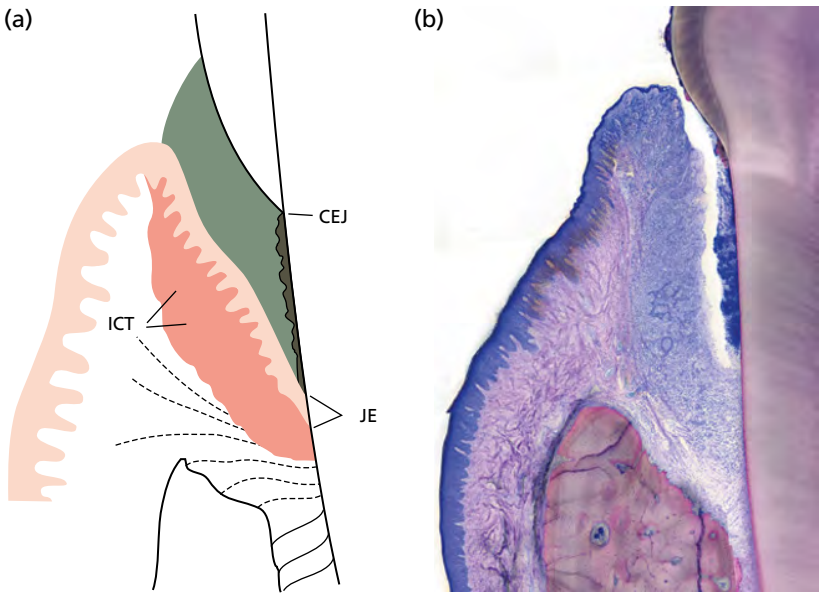


Fig. 22-4 Schematic drawing (a) and histologic section (b) illustrating the characteristics of periodontal disease. Note the zone of infiltrated connective tissue (ICT) lateral to the junctional epithelium (JE). CEJ, cementoenamel junction; JE, junctional epithelium. (Source: Part b courtesy of Professor D. Bosshardt, University of Bern, Switzerland.)

associated with inflammation are to be assessed, a probing pressure of 0.25 N should be applied when assessing BoP (Lang *et al*. 1991; Karayiannis *et al*. 1992). The identification of the apical extent of the gingival lesion is made in conjunction with *pocket probing depth* (PPD) measurements. In sites where "shallow" pockets are present, inflammatory lesions residing in the marginal portion of the gingiva are distinguished by probing in the superficial tissue. When the infiltrate resides in sites with attachment loss, the inflammatory lesion in the apical part of the pocket must be identified by probing to the bottom of the deepened pocket.

Bleeding on probing

A periodontal probe is inserted to the "bottom" of the gingival/periodontal pocket by applying light force and is moved gently along the tooth (root) surface (Fig. 22-5). If bleeding is provoked upon retrieval of the probe, the site examined is considered BoP-positive and hence, inflamed.

Figure 22-6 shows the chart used to identify BoP-positive sites in a dichotomous way at the initial examination. Each tooth in the chart is represented and each tooth surface is indicated by a triangle. The inner segments represent the palatal/lingual gingival units, the outer segments the buccal/labial units, and the remaining fields the two approximal gingival units. The fields of the chart corresponding to the inflamed gingival units are marked in red. The mean BoP score (i.e. gingivitis) is given as a percentage. In the example shown in Fig. 22-6, 104 out of a total number of 116 gingival units bled on probing, amounting to a BoP percentage of 89%. This method of charting not only serves as a means of documenting areas of health and disease in the dentition, but charting during the course of therapy or maintenance will disclose sites which turn healthy or remain inflamed. The topographical pattern will also identify sites with consistent or repeated BoP at various observation periods.

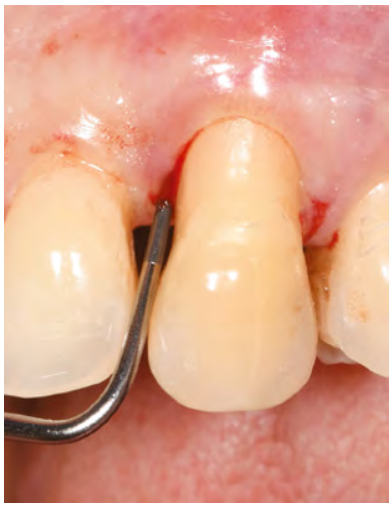


Fig. 22-5 Pocket probing depth in conjunction with bleeding on probing. A graduated periodontal probe is inserted to the "bottom" of the gingival/periodontal pocket applying light force and is moved gently along the tooth (root) surface.

At *implant sites*, BoP is assessed in a similar matter as for all teeth. It has to be realized that BoP-positive peri-implant mucosal sites represent a status of peri-implant mucositis. As for teeth, it has been demonstrated that such peri-implant mucositis sites, like for gingivitis sites, are reversible simply by the removal of biofilm in a systematic way (Salvi *et al*. 2012; Meyer *et al*. 2017). Peri-implant mucositis represents in most cases a precursor stage for the development of peri-implantitis.

Keratinized mucosa at implant recipient sites

In order to maintain health and tissue stability around dental implants, the presence of a minimum width of keratinized mucosa has been postulated. A width of keratinized mucosa <2 mm has been debated in the literature as a contributing factor for impaired plaque control with consequent increase in inflammation around dental implants (Bouri *et al*. 2008; Schrott *et al*. 2009; Crespi *et al*. 2010). The findings of a systematic review, however, indicated that the evidence in support of the need for keratinized mucosa around dental implants in order to maintain health and stability is limited (Wennström & Derks 2012). Nevertheless, the dimensions of the keratinized mucosa in edentulous areas should be evaluated in candidates for implant therapy (Roccuzzo *et al*. 2016).

Periodontal ligament and the root cementum

In order to evaluate the amount of tissue lost in periodontitis and also to identify the apical extension of the inflammatory lesion, the following parameters should be recorded:

- Pocket probing depth (PPD)
- Probing attachment level (PAL)
- Furcation involvement (FI)
- Tooth mobility (TM)

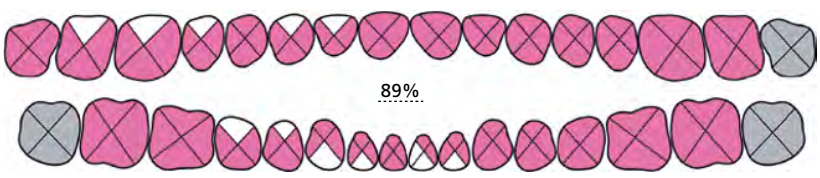


Fig. 22-6 Chart used to identify bleeding on probing-positive sites in a dichotomous way at the initial examination and during maintenance care.

Assessment of pocket probing depth

The probing depth (i.e. the distance from the gingival margin to the bottom of the gingival sulcus/pocket) is measured to the nearest millimeter by means of a graduated periodontal probe with a standardized tip diameter of approximately 0.4–0.5 mm (Fig. 22-7).

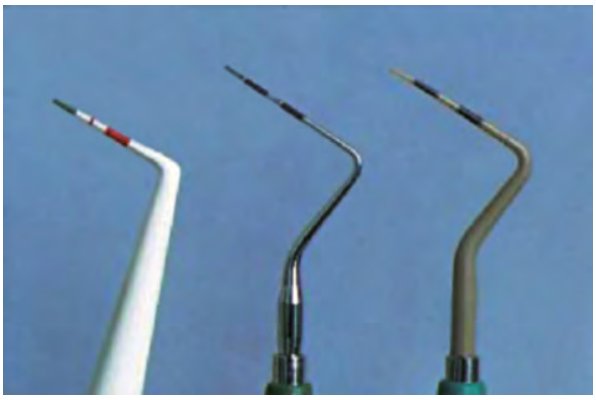


Fig. 22-7 Examples of graduated periodontal probes with a standardized tip diameter of approximately 0.4–0.5 mm.

The pocket depth should be assessed at each surface of all teeth as well as existing implants in the oral cavity. In the periodontal chart (Fig. 22-8), PPD <4 mm are indicated in black figures, while deeper PPD (i.e. ≥4 mm) are marked in red. This allows an immediate evaluation of diseased sites (i.e. red figures) both from an extent and severity point of view. The chart may be used for case presentations and discussions with the patient. For convenience, the therapist may download free of charge a template of the periodontal chart used in the Department of Periodontology at the University of Bern, Switzerland (www.periodontalchart-online.com).

Clinical probing of implant sites represent a sensitive diagnostic procedure for the detection of peri-implant diseases. Clinical probing will leave a

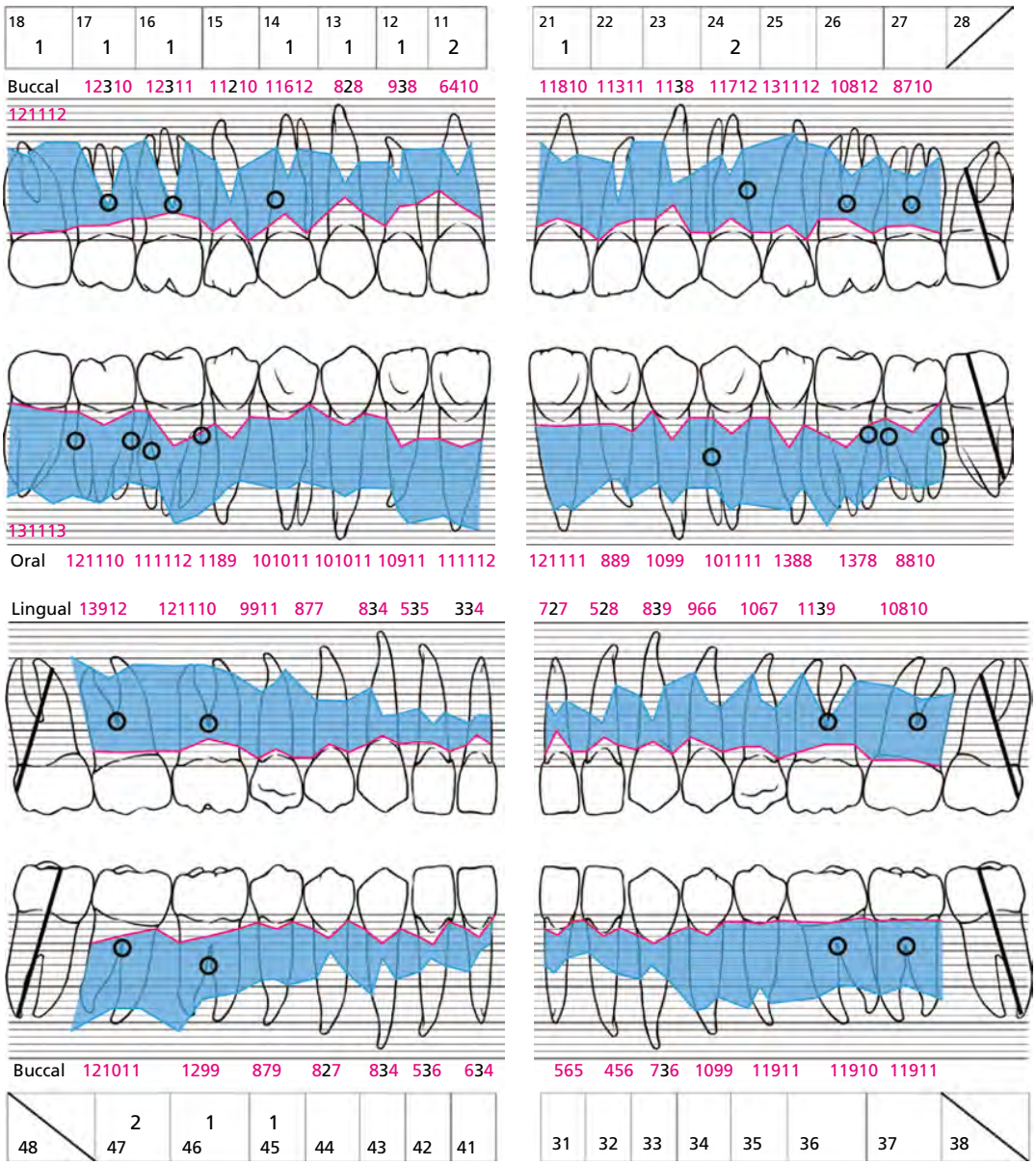


Fig. 22-8 Periodontal chart indicating pocket probing depth (PPD) <4 mm in black figures and PPD ≥4 mm in red figures. This allows an immediate evaluation of diseased sites (i.e. red figures) both from an extent and severity point of view.

short-term trauma to the peri-implant tissue that will repair completely during the course of 5–7 days with a junctional epithelium (Etter *et al*. 2002). Hence, the clinician does not have to worry about damaging the peri-implant soft tissue adhesion mechanism.

Results from PPD measurements will only in rare situations (i.e. when the gingival margin coincides with the cementoenamel junction [CEJ]) give proper information regarding the extent of loss of probing attachment. For example, an inflammatory edema may cause a swelling of the free gingiva resulting in a coronal displacement of the gingival margin without a concomitant migration of the dentogingival epithelium to a level apical to the CEJ. In such a situation, a pocket depth exceeding 3–4 mm represents a "pseudopocket". In other situations, an obvious loss of periodontal attachment may have occurred without a concomitant increase of PPD. A situation of this kind is shown in Fig. 22-9 where multiple recessions of the gingiva can be seen. Hence, the assessment of the PPD in relation to the CEJ is an indispensable parameter for the evaluation of the periodontal condition (i.e. PAL).

Assessment of probing attachment level

PAL may be assessed to the nearest millimeter by means of a graduated probe and expressed as the distance in millimeters from the CEJ to the bottom of the

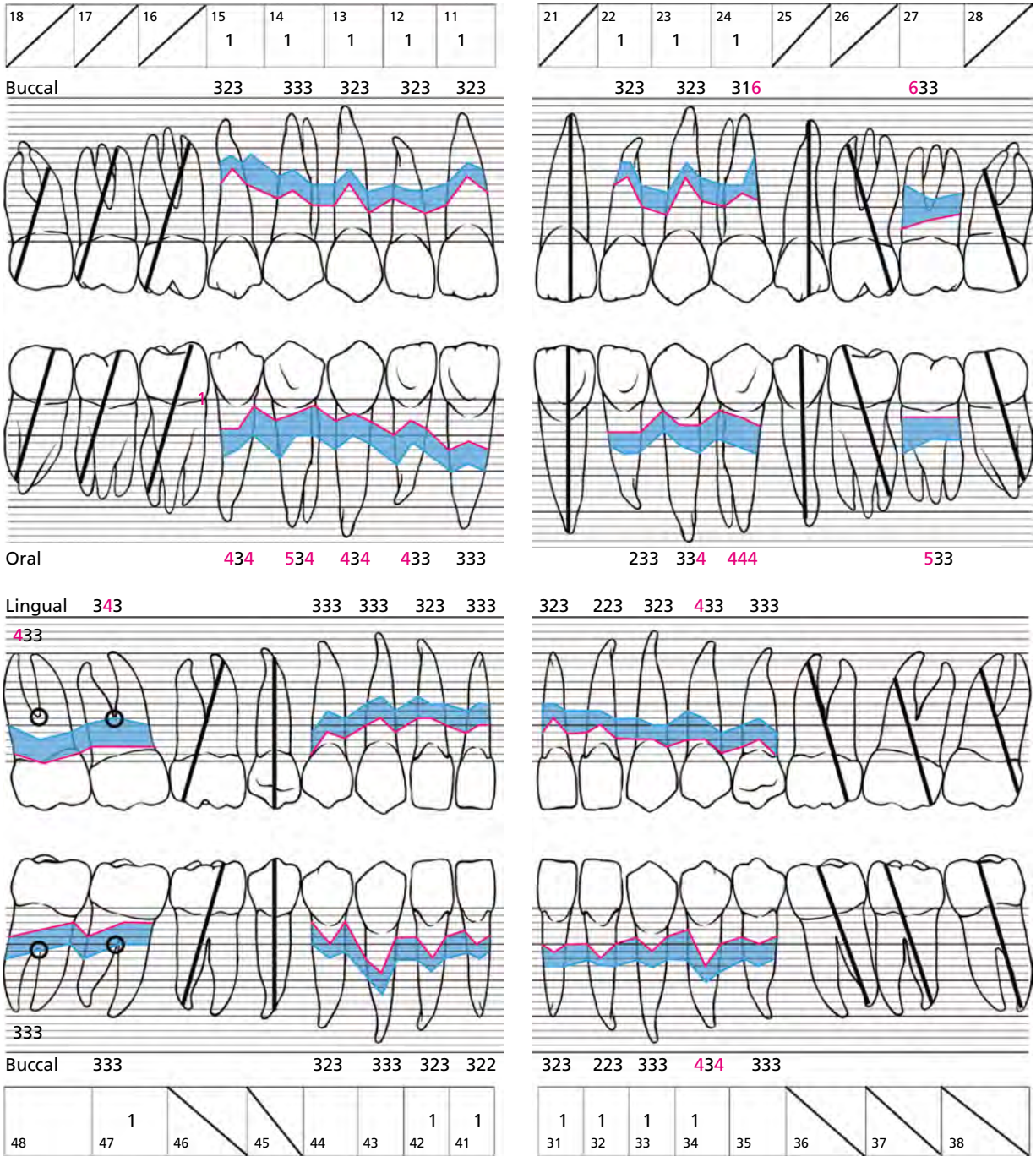


Fig. 22-9 Periodontal chart indicating periodontal attachment loss has occurred without a concomitant increase of probing pocket depth. Multiple buccal/labial as well as palatal/lingual gingival recessions can be seen.

probeable gingival/periodontal pocket. The clinical assessment requires the measurement of the distance from the free gingival margin (FGM) to the CEJ for each tooth surface. After recording this, PAL may be calculated from the periodontal chart (i.e. PPD - distance CEJ–FGM). In cases with gingival recessions, the distance CEJ–FGM turns negative and hence, will be added to the PPD to determine PAL.

Errors inherent in periodontal probing

The distances recorded in the periodontal examination using a periodontal probe have generally been assumed to represent a fairly accurate estimate of the PPD or PAL at a given site. In other words, the tip of the periodontal probe has been assumed to identify the level of the most apical cells of the dentogingival (junctional epithelium) epithelium. Results from research, however, indicated that this is seldom the case (Saglie *et al*. 1975; Listgarten *et al*. 1976; Armitage *et al*. 1977; Spray *et al*. 1978; Robinson & Vitek 1979; van der Velden 1979; Magnusson & Listgarten 1980; Polson *et al*. 1980). A variety of factors influencing measurements made with periodontal probes include: (1) thickness of the probe used, (2) angulation and positioning of the probe because of anatomic features such as the contour of the tooth surface, (3) graduation scale of the periodontal probe, (4) pressure applied on the instrument during probing, and (5) degree of inflammatory cell infiltration in the soft tissue and accompanying loss of collagen. Therefore, a distinction should be made between the histological and the clinical PPD to differentiate between the depth of the actual anatomic defect and the measurement recorded by the probe (Listgarten 1980).

Measurement errors depending on factors such as the thickness of the probe, the contour of the tooth surface, incorrect angulation, and the graduation scale of the probe can be reduced or avoided by the selection of a standardized instrument and careful management of the examination procedure. More difficult to avoid, however, are errors resulting from variations in probing force and the extent of inflammatory alterations of the periodontal tissues. As a rule, the greater the probing pressure applied, the deeper the penetration of the probe into the tissue. In this context, it should be realized that in investigations designed to disclose the pressure (force) used by different clinicians, the probing pressure was found to range from 0.03 to 1.3 N (Gabathuler & Hassell 1971; Hassell *et al*. 1973), and also, to differ by as much as 2:1 for the same dentist from one examination to another. In order to exclude measurement errors related to the effect of variations in probing pressure, so-called pressure sensitive probes have been developed. Such probes enable the examiner to probe with a predetermined pressure (van der Velden & de Vries 1978; Vitek *et al*. 1979; Polson *et al*. 1980). However, over and underestimation of the "true" PPD or PAL may also occur when this type of probing device is employed (Armitage *et al*. 1977; Robinson & Vitek 1979; Polson *et al*. 1980). Thus, when the connective tissue subjacent to the pocket epithelium is infiltrated by inflammatory cells (Fig. 22-10), the periodontal probe will penetrate beyond the apical termination of the dentogingival epithelium, resulting in an overestimation of the "true" depth of the pocket. Conversely, when the inflammatory infiltrate decreases in size following successful periodontal treatment and a concomitant deposition of new collagen occurs within the previously inflamed tissue area, the dentogingival tissue will become more resistant to penetration by the probe. The probe may then fail to reach the apical termination of the epithelium

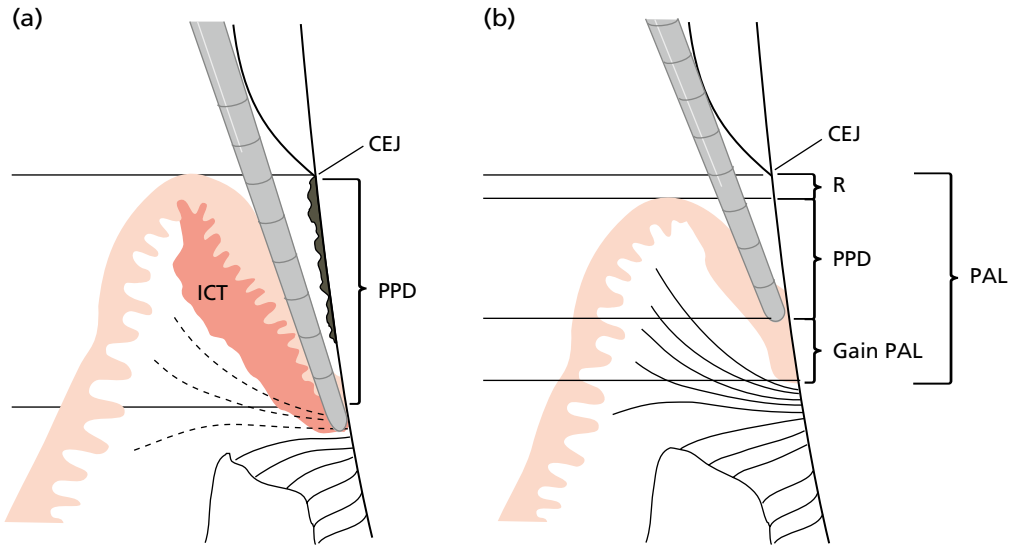


Fig. 22-10 (a) In the presence of an inflammatory cell infiltrate (ICT) in the connective tissue of the gingiva, the periodontal probe penetrates apically to the bottom of the histologic pocket; (b) following successful periodontal therapy, the swelling is reduced and the connective tissue cell infiltrate is replaced by collagen. The periodontal probe fails to reach the apical part of the dentogingival epithelium. CEJ, cementoenamel junction; Gain PAL, recorded false gain of attachment ("clinical attachment"); PAL, probing attachment level; PPD, probing pocket depth; R, recession

using the same probing pressure. This, in turn, results in an underestimation of the "true" PPD or PAL. The magnitude of the difference between the probing measurement and the histologic "true" pocket depth (Fig. 22-10) may range from fractions of a millimeter to a couple of millimeters (Listgarten 1980).

From this discussion it should be understood that reductions in PPD following periodontal treatment and/or gain of PAL, assessed by periodontal probing do not necessarily indicate the formation of a new connective tissue attachment at the bottom of the treated lesion. Rather, such a change may merely represent a resolution of the inflammatory process and may thus occur without an accompanying histologic gain of attachment (Figs. 22-10). In this context it should be realized that the terms "probing pocket depth" (PPD) and "probing attachment level" (PAL) have replaced the previously used terms "pocket depth" and "gain and loss of attachment". Likewise, the term PAL is used in conjunction with "gain" and/or "loss" to indicate that changes in PAL have been assessed by clinical probing.

Current knowledge of the histopathology of periodontal lesions and healing thereof has thus resulted in an altered concept regarding the validity of periodontal probing. However, despite difficulties in interpreting the significance of PPD and PAL measurements, such determinations still give the clinician a useful estimate of the extent of disease involvement, particularly when the information obtained is related to other findings of the examination procedure such as BoP and changes in alveolar bone height.

In recent years, periodontal probing procedures have been standardized to the extent that automated probing systems (e.g. Florida Probe™) have been developed yielding periodontal charts with PPD, PAL, BoP, FI, and TM at one glance (Gibbs *et al*. 1988).

Despite of all the sources of errors discussed, periodontal probing represents a very sensitive method to assess the extent and severity of periodontal lesions. This sensitivity is because periodontal probing has only – if any – false negative values.

Assessment of furcation involvement

The progression of periodontitis around multirooted teeth may involve the destruction of the supporting structures of the furcation area (Fig. 22-11). In order to plan the treatment of such involvement, a detailed and precise identification of the presence and extent of periodontal tissue breakdown within the furcation area is of importance.

FI is assessed from all the entrances of possible periodontal lesions of multirooted teeth, i.e. buccal and/or lingual entrances of the mandibular molars. Maxillary molars and premolars are examined from the buccal, distopalatal and mesiopalatal entrances. Owing to the position of the first maxillary molars within the alveolar process, the furcation between the mesiobuccal and the palatal roots is best explored from the palatal aspect (Fig. 22-12).

FI is explored using a curved periodontal probe with graduations at 3 mm and 5 mm (Nabers furcation probe, Fig. 22-13a). Depending on the penetration depth, the FI is classified as "superficial" or "deep":

- *Class I*: horizontal probing depth ≤3 mm from one or two entrances (Fig. 22-13b).

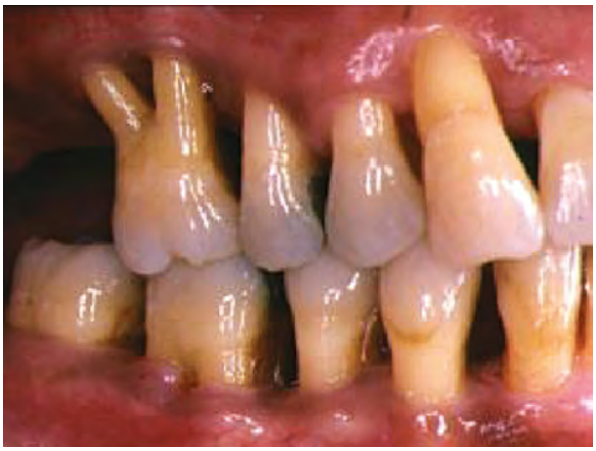
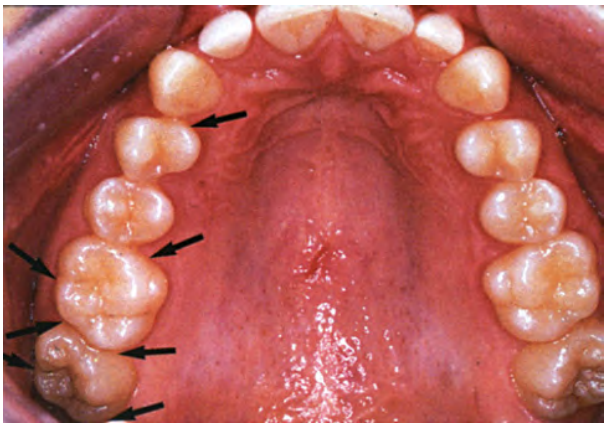


Fig. 22-11 Superficial (tooth 46) and deep (tooth 16) periodontal tissue destruction in the buccal furcation areas.

(a)



(b)

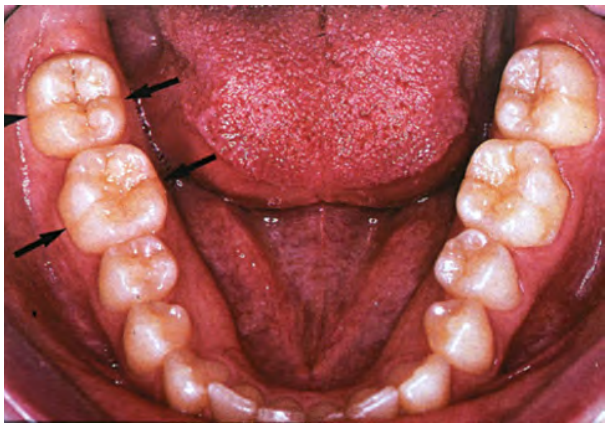


Fig. 22-12 (a, b) Anatomic locations for the assessment of furcation involvement in the maxilla and in the mandible.

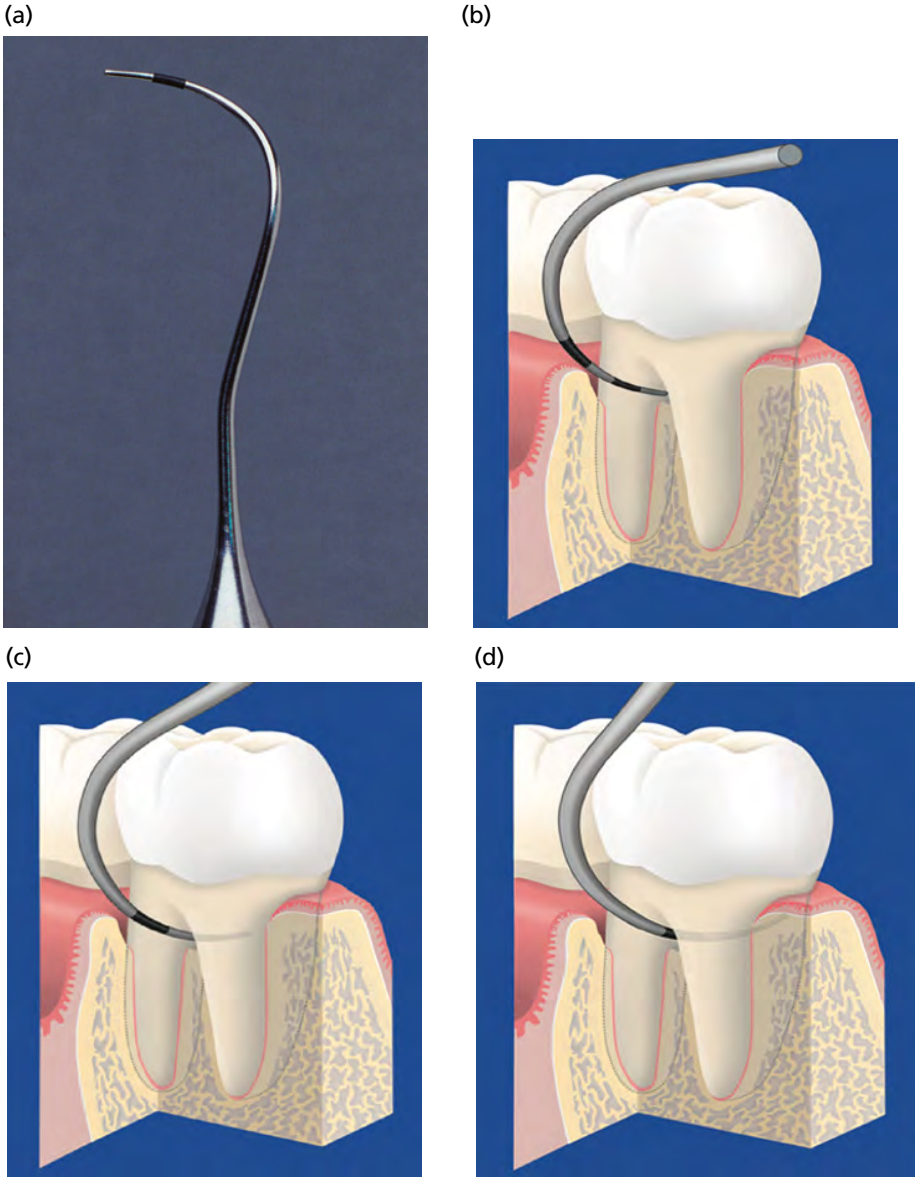


Fig. 22-13 (a) Furcation involvement is explored using a curved periodontal probe with graduations at 3 mm and 5 mm (Nabers furcation probe). (b) Class I: horizontal probing depth ≤3 mm from one or two entrances. (c) Class II: horizontal probing depth >3 mm in at the most one entrance and/or in combination with a FI class I. (d) Class III: horizontal probing depth >3 mm in two or more entrances usually represents a "through-and-through" destruction of the supporting tissues in the furcation.

- *Class II*: horizontal probing depth >3 mm in at the most one entrance and/or in combination with a FI class I (Fig. 22-13c).
- *Class III*: horizontal probing depth >3 mm in two or more entrances usually represents a "through-and-through" destruction of the supporting tissues in the furcation (Fig. 22-13d).

The FI degree is presented on the periodontal chart (Fig. 22-14) together with a description of which tooth surface the involvement has been identified on. The effects of various therapeutic approaches to the management of multirooted teeth with FI has been systematically appraised (Huynh-Ba *et al*. 2009; Salvi *et al*. 2014). A detailed description with respect to the management of furcation-involved teeth is presented in Chapter 33.

Assessment of tooth mobility

The continuous loss of the supporting tissues may result in increased TM. However, trauma from occlusion may also lead to increased TM. Therefore, the reason for increased TM as being the result of a widened periodontal ligament or a reduced height of the supporting tissues or a combination thereof should be elaborated. Increased TM may be classified according to Miller (1950):

- *Degree 0*: "physiologic" mobility measured at the crown level. The tooth shows mobility of 0.1–0.2 mm in the horizontal direction within the alveolus.
- *Degree 1*: increased mobility of the crown of the tooth of at the most 1 mm in the horizontal direction.

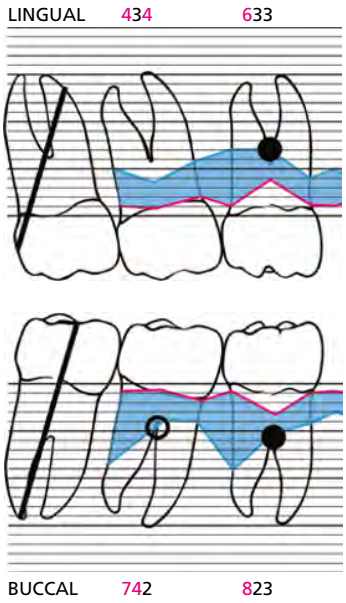


Fig. 22-14 The furcation involvement (FI) shown on the periodontal chart. Open circles represent a superficial FI (i.e horizontal probe penetration ≤3 mm) whereas filled black circles represent a deep FI (i.e. horizontal probe penetration >3 mm).

- *Degree 2*: visually increased mobility of the crown of the tooth exceeding 1 mm in the horizontal direction.
- *Degree 3*: severe mobility of the crown of the tooth in both horizontal and vertical directions and impinging on the function of the tooth.

It must be understood that plaque-associated periodontal disease is not the only cause of increased TM. For instance, trauma may result in tooth hypermobility. Increased TM can frequently also be observed in conjunction with periapical lesions or immediately following periodontal surgery. From a therapeutic point of view it is important, therefore, to assess not only the degree of increased TM, but also the cause of the observed hypermobility (see Chapter 13).

All data collected from measurements of PPD and PAL as well as assessments of FI and TM are included in the periodontal chart (see Fig. 22-8). The various teeth in this chart are denoted according to the two-digit system adopted by the World Dental Federation (FDI) in 1970.

Alveolar bone

Radiographic analysis

Radiographs provide information on the height and configuration of the interproximal alveolar bone (see Fig. 22-3). Obscuring structures such as roots often make it difficult to identify the outline of the buccal and lingual alveolar bony crest. The analysis of the radiographs must, therefore, be combined with a detailed evaluation of the periodontal chart in order to estimate correctly concerning "horizontal" and "angular" bony defects.

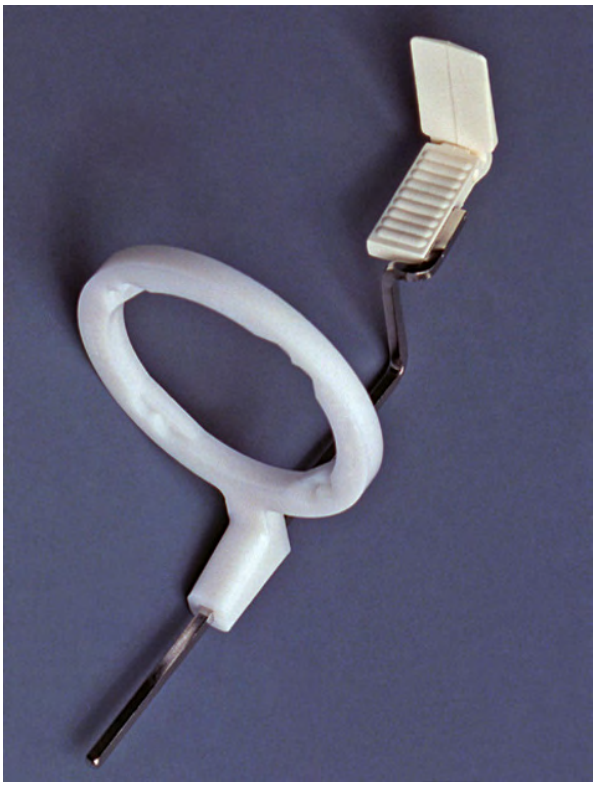


Fig. 22-15 The use of a Rinn filmholder and a long-cone paralleling technique yield reproducible radiographs.

Unlike the periodontal chart, which represents a sensitive diagnostic estimate of the lesions, the radiographic analysis is a specific diagnostic method yielding few false positive results and hence, being confirmatory to the periodontal chart (Lang & Hill 1977).

To enable meaningful comparative analysis, a reproducible radiographic technique should be used. A long-cone paralleling technique (Updegrave 1951) is recommended (Fig. 22-15).

Radiographic evaluation of implant recipient sites

In order to evaluate vertical bone height at potential implant recipients sites, panoramic radiography may be used as a reliable diagnostic tool to determine the preoperative implant length in premolar and molar mandibular areas (Vazquez *et al*. 2013). Furthermore, to determine accurately the bone volume and morphology at future implant recipient sites, cone beam computed tomography (CBCT) may offer valuable information in selected indications such as implant placement in conjunction with sinus floor elevation (Harris *et al*. 2012).

Diagnosis and classification of periodontitis

Based on the information regarding the condition of the various periodontal structures (i.e. the gingiva, the periodontal ligament, and the alveolar bone)

obtained through the comprehensive examination presented above, a classification of the patient regarding his/her periodontal conditions may be given. Four different tooth-based diagnoses may be used to determine the staging and grading of periodontitis.

Gingivitis

This diagnosis is applied to teeth displaying BoP-positive sites. The sulcus depth usually remains at levels of 1–3 mm irrespective of the level of clinical attachment. "Pseudopockets" may be present in cases of slightly increased probing depth without concomitant attachment and alveolar bone loss and presence/absence of BoP. The diagnosis of gingivitis usually characterizes lesions confined to the gingival margin.

Periodontitis

As proposed by the World Workshop on the Classification of Periodontal and Peri-Implant Diseases of 2017 (Tonetti *et al*. 2018), periodontitis is now classified in 1 out of 4 stages and its progression pattern is determined by grading (i.e. Grade A, Grade B, and Grade C). Extent, severity, and complexity will determine the stage of periodontitis affecting the patient (Table 22-1).

Periodontitis Stage I (former mild to moderate periodontitis)

Gingivitis in combination with attachment loss is termed "periodontitis". If the PPD does not exceed 4 mm and the bone loss yields a predominantly horizontal pattern, the classification corresponds to a stage I. Interdental PAL at the site of greatest loss does not exceed 2 mm.

Periodontitis Stage II

In Stage I and II, no teeth have been lost because of periodontitis. For Stage II, the maximum PPD is 5 mm with mostly horizontal bone loss. Interdental PAL at sites of greatest loss may be 3–4 mm.

Periodontitis Stage III (former advanced periodontitis)

In periodontitis Stage III, up to four teeth have been lost because of periodontitis. Interdental PAL at sites of greatest loss is at least 5 mm. In addition to periodontitis Stage II, complexity factors are noted: PPD is up to 6 mm, vertical bone loss is up to 3 mm, FI Class 2 or 3 may be present. Moderate alveolar ridge defects may be observed.

Periodontitis Stage IV

In periodontitis Stage IV, multiple tooth loss because of periodontitis (i.e. ≥5 teeth) jeopardizing the functionality of the dentition is observed. Interdental PAL at the sites of greatest loss is at least 5 mm. The complexity factors noted in addition to periodontitis Stage III, may be: a need for complex rehabilitation because of masticatory dysfunction, secondary occlusal trauma with at least a TM of Degree 3, severe

Table 22-1 Periodontitis stages I–IV according to Tonetti *et al*. (2018).

Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	**Interdental CAL at site of greatest loss**	1–2 mm	3–4 mm	≥5 mm	≥5 mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15–33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss because of periodontitis		Tooth loss because of periodontitis of ≤4 teeth	Tooth loss because of periodontitis of ≥5 teeth
				In addition to stage II complexity:	In addition to stage III complexity:
Complexity	**Local**	Maximum probing depth ≤4 mm	Maximum probing depth ≤ mm	Probing depth ≥6 mm	Need for complex rehabilitation because of:
		Mostly horizontal bone loss	Mostly horizontal bone loss	Vertical bone loss ≥3 mm	Masticatory dysfunction
					Secondary occlusal trauma (tooth mobility degree ≥2)
				Furcation involvement Class II or III	Severe ridge defect
				Moderate ridge defect	Bite collapse, drifting, flaring
					Less than 20 remaining teeth (10 opposing pairs)
Extent and distribution	**Add to stage as descriptor**	For each stage, describe extent as localized (<30% of teeth involved), generalized, or molar/incisor pattern			

CAL, clinical attachment loss. (Source: Tonetti *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

Table 22-2 Periodontitis grades A to C according to Tonetti *et al*. (2018).

Periodontitis grade			Grade A: slow rate of progression	Grade B: moderate rate of progression	Grade C: rapid rate of progression
Primary criteria	Direct evidence of progression	Longitudinal data (radiographic bone loss or CAL)	Evidence of no loss over 5 years	<2 mm over 5 years	>2 mm over 5 years
	Indirect evidence of progression	% bone loss/age	<0.25	0.25–1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectation given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease (e.g. molar/incisor pattern; lack of expected response to standard bacterial control therapies)
Grade modifiers	Risk factors	Smoking	Non-smoker	Smoker <10 cigarettes/day	Smoker ≥10 cigarettes/day
		Diabetes	Normoglycemic/no diagnosis of diabetes	HbAlc <7.0% in patients with diabetes	HbAlc ≥7.0% in patients with diabetes
Risk of systemic impact of periodontitis[a]	Inflammatory burden	High sensitivity CRP (hsCRP)	<1 mg/L	1–3 mg/L	>3 mg/L
Biomarkers	Indicators of CAL/bone loss	Saliva, gingival crevicular fluid, serum	?	?	?

[a] Refers to increased risk that periodontitis may be an inflammatory co-morbidity for the specific patient. CAL, clinical attachment loss; HbA1c, glycated hemoglobin. (Source: Tonetti *et al*. 2018. Reproduced with permission from John Wiley & Sons.)

alveolar ridge defects, bite collapse, drifting and flaring of teeth, less than 20 remaining teeth (i.e. 10 antagonistic pairs).

Grading of the progression pattern of periodontitis

Grading is used as an indicator of the rate of progression of periodontitis and is subdivided in Grade A, Grade B, and Grade C. The primary criteria are either direct or indirect evidence of progression (Table 22-2).

Grade A

This grade marks a slow rate of progression of periodontitis. There is no evidence of PAL loss over 5 years. The progression of radiographic bone loss or PAL is less than 0.25%, divided by the age of the patient. The patient is generally a non-smoker and normoglycemic. The inflammatory burden is less than 1 mg/L of C-reactive protein (CRP).

Grade B

The default Grade B marks a moderate rate of progression with fewer than 2 mm of PAL loss over 5 years. This corresponds to 0.25–1.0% alveolar bone loss divided by the age of the patient. If the patient is a smoker, he/she generally smokes fewer than 10 cigarettes/day. The HbA_{1c} is less than 7.0% in patients diagnosed with diabetes mellitus. The inflammatory burden corresponds to 1–3 mg/L of CRP.

Grade C

Grade C represents a rapid rate of disease progression with at least 2 mm PAL loss over 5 years. The percentage of bone loss divided by age is greater than 1.0. There is a disproportion between periodontal destruction and biofilms deposits. There are specific clinical patterns of destruction suggestive of periods of rapid progression and/or early onset diseases.

Risk factors may include smoking at least 10 cigarettes/day and HbA_{1c} levels of at least 7.0% in patients with diabetes mellitus. The inflammatory burden is greater than 3.0 mg/L of CRP.

Clinicians should initially assume a default value of Grade B and seek specific evidence to shift towards a Grade A or a Grade C.

Moreover, based on pathophysiology, two additional forms of periodontitis are recognized:

1. Necrotizing periodontitis
2. Periodontitis as a direct manifestation of systemic diseases.

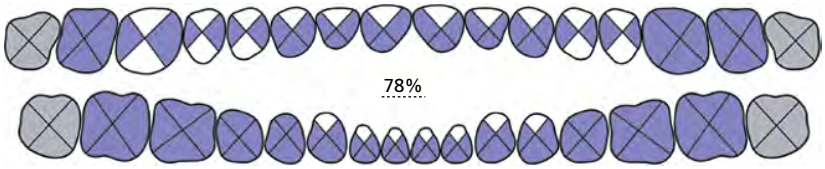


Fig. 22-16 The presence of bacterial biofilms is marked in the appropriate fields in the chart.

Oral hygiene status

In conjunction with examination of the periodontal tissues, the patient's oral hygiene practices must also be evaluated. Absence or presence of bacterial biofilms on each tooth surface in the dentition is recorded in a dichotomous manner (O'Leary *et al*. 1972). The bacterial deposits may be stained with a disclosing solution to facilitate their detection. The presence of biofilms is marked in appropriate fields in the chart shown in Fig. 22-16. The mean biofilm score for the dentition is given as a percentage in correspondence with the system used for BoP (see Fig. 22-6).

Alterations with respect to the presence of biofilm and gingival inflammation are monitored in a simple way by the repeated use of the combined BoP (see Fig. 22-6) and biofilm (Fig. 22-16) charts during the course of treatment. Repeated biofilm recordings alone (Fig. 22-16) are predominantly indicated during the initial phase of periodontal therapy (i.e. infection control) and are used for improving self-performed biofilm control. Repeated BoP charts alone (see Fig. 22-6), on the other hand, are predominantly recommended during supportive periodontal therapy (SPT).

Additional dental examinations

In addition to the assessment of biofilm deposits, retentive factors, such as supra- and subgingival calculus and defective margins of dental restorations, should be identified. Furthermore, the assessment of tooth sensitivity is essential for comprehensive treatment planning. Sensitivity to percussion may indicate acute changes in pulp vitality and lead to emergency treatment prior to systematic periodontal therapy. It is obvious that a complete examination and assessment of the patient will need to include the search for carious lesions both clinically and by means of bitewing radiographs.

A screening for functional disturbances may be performed using a short (i.e. 1–2 minute) test according to Shore (1963). In this test, harmonious function of the jaws with simultaneous palpation of the temporomandibular joints during opening, closing, and excursive movements is verified. Maximal mouth opening is assessed and finally, the lodge of the lateral pterygoid muscles is palpated for muscle tenderness. Further morphologic characteristics of the dentition as well as occlusal and articulating contacts may be identified.

Conclusion

The methods described in this chapter for the examination of patients with periodontal diseases and candidates for implant therapy provide a thorough analysis of the presence, extent, and severity of the disease in the dentition. The periodontal classification of the patient and the correct diagnosis for each individual tooth should form the basis for a pretherapeutic prognosis and the treatment planning of the individual patient (Chapter 25).

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Chapter 23

Diagnostic Imaging of the Periodontal and Implant Patient

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Introduction

Diagnostic imaging is an essential component in dental medicine, which supplements findings from clinical examination, facilitates the planning of non-surgical and surgical procedures, and assists in monitoring of treatment outcomes. Dental practitioners should be familiar with advantages and disadvantages of imaging modalities used in dental medicine prior to performing or also referring a patient for imaging procedures. The selection of an appropriate imaging modality should be based on the underlying condition of each patient including considerations of a potential benefit to a patient, which should comprise the risks of biological effects due to added radiation due to the radiographs taken. This chapter describes basic principles of diagnostic imaging in dental medicine with special emphasis on imaging modalities used for periodontal health/disease assessment and implant treatment planning as well as follow-up.

Basic principles of diagnostic imaging in dental medicine

Modalities

The physical principle of image formation varies among different diagnostic imaging modalities. They can be generally classified into two main categories according to whether the imaging modality is associated with ionizing radiation or not. In dental medicine, diagnostic imaging is primarily used for the evaluation of the health and pathology of hard tissues including teeth and jaws. Therefore, X-ray-based (e.g. ionizing) imaging modalities are predominant in clinical practice. These X-ray-based modalities include periapical radiographs, bitewings, occlusal

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

views, panoramic images, cephalometric views, cone beam computed tomography (CBCT) imaging, and multidetector computed tomography (MDCT) for selected cases. Ultrasound imaging and magnetic resonance imaging (MRI) are non-ionizing techniques, and are frequently used for the observation of biological/pathological changes of soft tissues in clinical medicine, but their use is still relatively uncommon in dental medicine. The non-ionizing nature of these modalities and the favorable soft tissue contrast motivate scientists and clinicians to introduce and adapt ultrasound imaging and MRI for evaluations of dentoalveolar pathologies, especially for periodontal/peri-implant diseases. The following sections provide a brief overview of the basic principles of ionizing and non-ionizing imaging modalities as currently used in dental medicine.

Ionizing modalities

Diagnostic imaging modalities used in dental medicine are mostly associated with ionizing radiation that is produced by the respective X-ray machines used. X-rays emitted from these machines are high energy photons of electromagnetic waves. When penetrating the human body, X-rays ionize electrons from atoms or molecules present in the scanned region and cause an exposure on a photographic film or digital receptor to generate an image (Rout & Brown 2012). According to the location of the X-ray film or digital receptor in relation to the patient's mouth, imaging modalities used in dental medicine can be categorized into intraoral and extraoral techniques.

Intraoral techniques

Periapical radiography

Periapical images are taken using a small size (ranging from 22 × 35 mm to 30.5 × 40.5 mm) X-ray film or digital receptor to capture a two-dimensional (2D) image with a restricted field of view (FOV) depicting two or three adjacent teeth and surrounding bone. The film or digital receptor is ideally positioned deep into the lingual vestibule or palatal vault, parallel to the long axis of the teeth or close to the lingual surface of the teeth, and stabilized by a receptor holding instrument. The central X-ray beam is directed through the external localizing ring of the holding instrument. Ideally, the entire length and periapical region of the observed teeth can be captured in one radiograph. Due to high spatial resolution and low radiation dose, periapical radiography is considered to be the first-line diagnostic imaging modality for the detection of early dentoalveolar pathologies, such as dental caries, periapical lesions, and marginal alveolar bone loss (Mupparapu & Nadeau 2016). Moreover, periapical images are commonly used to observe the morphology of roots, pulpal cavity, impacted teeth, determine the length for endodontic instrumentation, bone levels around teeth, or assess implant osseointegration and monitor peri-implant bone loss (Fig. 23-1).

Bitewing radiography

Bitewing images are taken using an X-ray film or digital receptor with a size similar to that of periapical images. The film or receptor is positioned in the lingual vestibule close to the lingual surface of the maxillary and mandibular posterior teeth. The receptor bite plate is gently fixed by the patient's teeth and the central X-ray beam is aimed through the mandibular premolar contacts or external localizing ring of the holding instrument. Bitewing radiography is able to capture 2D images that depict the coronal portions of the maxillary and mandibular posterior teeth on one side including the level and bone density of interdental alveolar crest. For a sufficient image of the crestal bone the normal size of periapical radiographs might be beneficial compared with narrow sized and long formats. As a result, bitewing radiography is mainly used for early diagnosis of caries and periodontal lesions, for example to detect interproximal/secondary caries and periodontitis (Fig. 23-2).

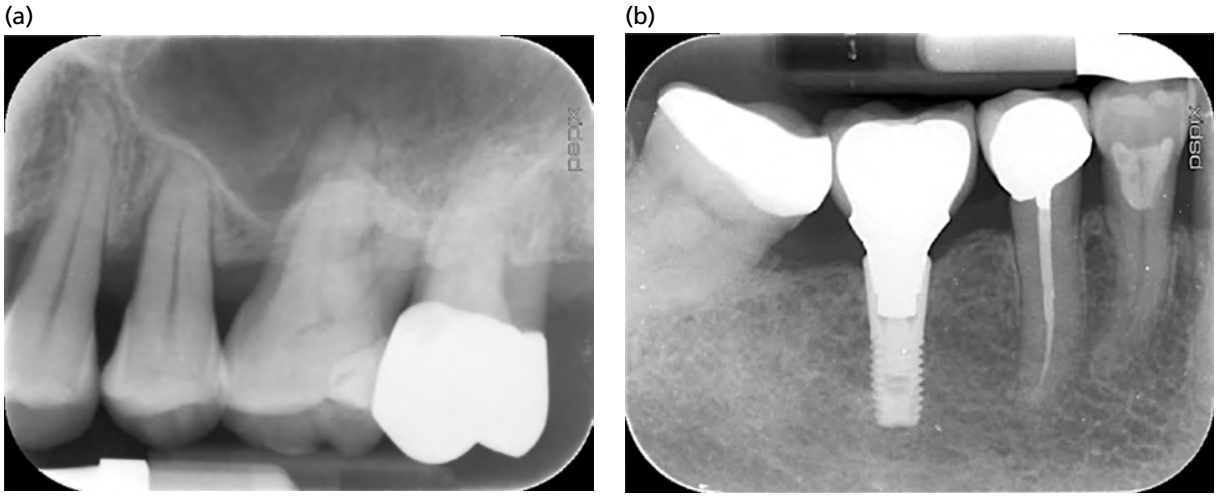

Fig. 23-1 Representative periapical images of the upper and lower jaws. (a) The periapical image of the posterior left maxilla shows mostly horizontal bone loss for the premolars, but also suspected furcation involvement for the molars. (b) The periapical image shows an osseointegrated implant at the site of tooth 46, and an endodontically treated second premolar.

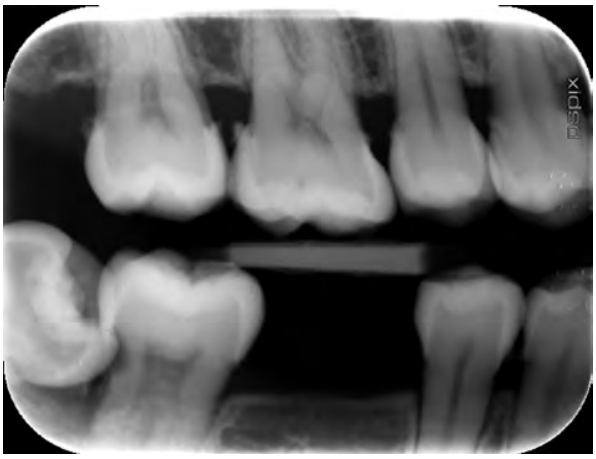

Fig. 23-2 This bitewing radiograph shows an impacted third molar with resorption on the distal surface of tooth 47 (undermining root resorption) and a missing first molar in the posterior right mandible. Furthermore, several calculus deposits on the mesial and distal surfaces of the upper posterior teeth can be observed.

Occlusal radiography

Occlusal images are taken using a large size (58 × 77 mm) X-ray film or digital receptor placed between the upper and lower teeth to capture a 2D image depicting the maxillary/mandibular teeth and arches, and palate/floor of the mouth. Occlusal radiography is less frequently used, but useful to locate supernumerary, unerupted, and impacted teeth, radiolucent/radiopaque lesions (e.g. cysts or sialoliths) in the region of jaws, palate, and floor of the mouth, and assess potential fractures in the anterior maxilla and mandible (Fig. 23-3). Small size X-ray film or digital receptor can be used in children with deciduous teeth to get a comfortable overview of the anterior teeth of the maxilla. Occlusal images can measure the width of the mandible, which was previously considered to be useful for the planning of implant treatment. However, due to the nature of 2D images, they can only display the width of the mandibular base and not of the alveolar process. Therefore, occlusal radiography is seldom recommended for implant patients nowadays with the wide availability of three-dimensional (3D) imaging techniques such as CBCT (Mallya & Lam 2019).

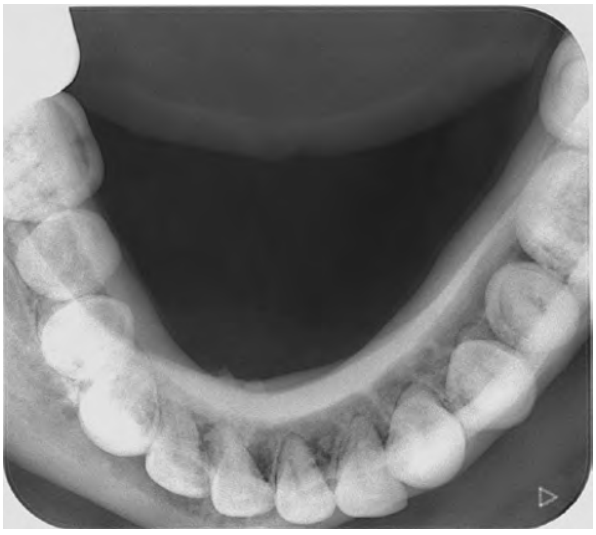

Fig. 23-3 The width of the mandibular base can be estimated on an occlusal image, but the alveolar process cannot be distinguished (vertical dimension).

Extraoral techniques

Extraoral techniques differ from intraoral techniques in that the films and receptors used are positioned outside the mouth/body of the patients. Extraoral techniques are able to capture images with a large FOV, depicting entire jaws or parts of the skull, which is useful to assess the general dental status of patients, and for the overall treatment planning process as well as imaging adjacent vital/endangered anatomical structures.

Panoramic radiography

Panoramic radiography is one of the most common extraoral imaging techniques used in dental medicine. Panoramic images are taken by using a rotation of the X-ray source and image receptor around the patient's head, which generates a curved image layer depicting the teeth, maxilla, mandible, and temporomandibular joints (TMJs). It can provide an overall view of the dentoalveolar structures in 2D for diagnostic and treatment purposes on one single image. The panoramic view is widely used as a routine and initial radiographic examination to evaluate the deciduous or permanent dentition, the position of impacted teeth and especially mandibular third molars in relation to the mandibular canal, bone levels, intraosseous lesions (such as cysts and tumors), and TMJs (Fig. 23-4). For patients where intraoral X-rays are not possible due to discomfort or difficulty in mouth opening, panoramic radiography is an alternative to acquire a useful diagnostic image. The limitations of panoramic views include low spatial resolution, image magnification and distortion, and the superimposition of the structures, such as cervical spine, soft tissues, and air spaces (Fig. 23-5). These ultimately limit the diagnostic accuracy of panoramic radiography. New techniques of panoramic radiography provide different "sharp layers" and are able to generate images with beneficial views with reduced superimposition concerning special indications.

Cephalometric radiography

Cephalometric radiography is mainly used in the field of orthodontics and orthognathic surgery. This technique is able to capture an image with a large FOV depicting the craniofacial region of patients. It can be taken by using a lateral or posteroanterior cephalometric projection to identify dental, skeletal, and soft tissue anatomic landmarks for the planning of orthodontic treatment and orthognathic surgery (Fig. 23-6). Cephalometric radiography is relatively seldom used in the field of periodontology and oral implantology.

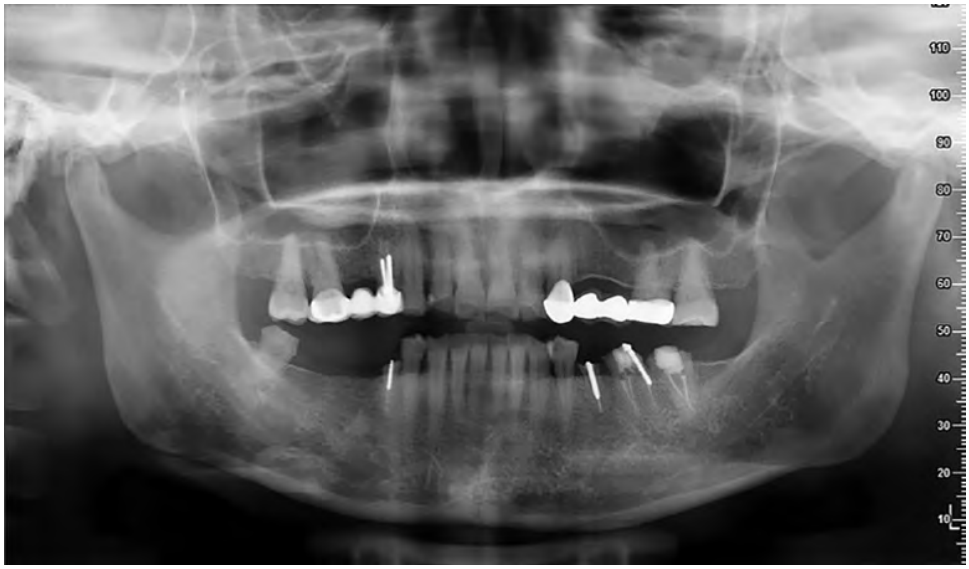

Fig. 23-4 This panoramic view shows an overview of the dental and maxillofacial structures including the remaining teeth in the upper and lower jaws, the bone condition at the edentulous sites, the maxillary sinuses including lower aspects of the orbit and the temporomandibular joints.

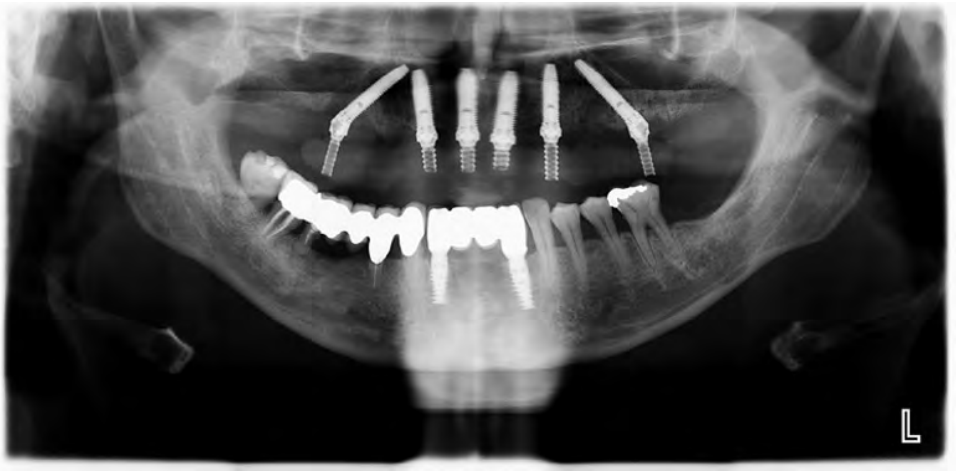

Fig. 23-5 This panoramic view exhibits image distortion and superimposition artifacts of the cervical spine and air spaces that limit the diagnostic validity to evaluate the condition of the implants in the anterior maxilla and mandible.

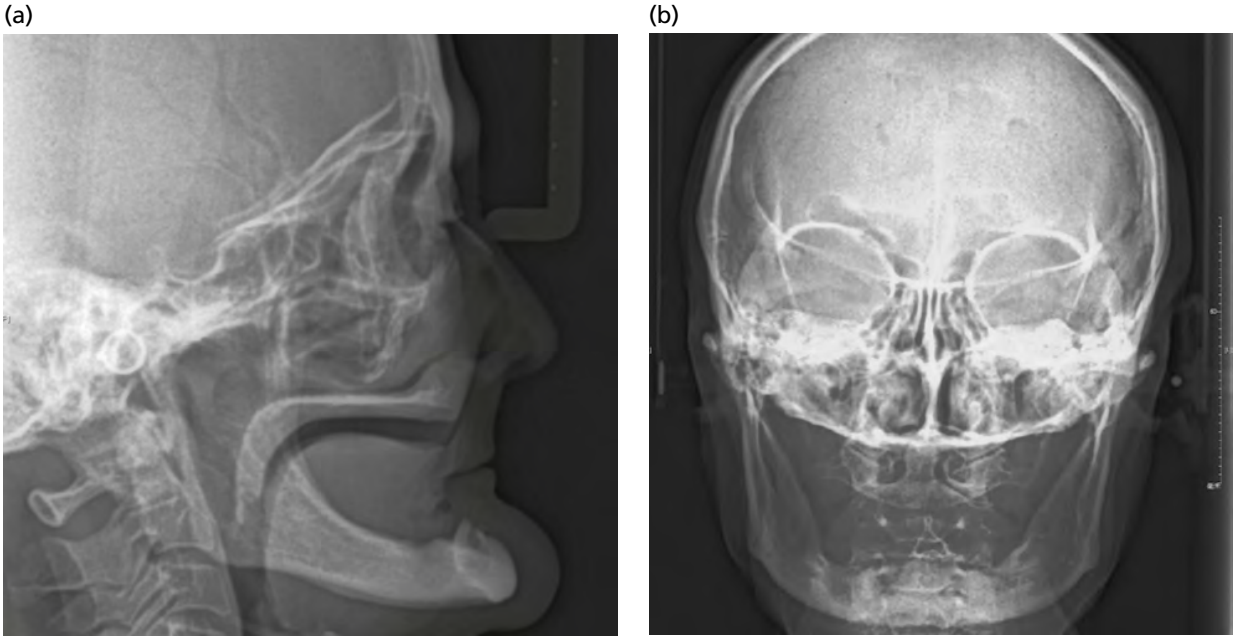

Fig. 23-6 (a) Lateral and (b) posteroanterior cephalometric projections can show jaw dimensions, the relative position of the maxilla and mandible towards each other, and the facial profile. For completely edentulous patients, such information has been proposed to be helpful for treatment planning purposes of, for example, a full-arch implant rehabilitation.

Multidetector computed tomography

MDCT is one of the most common 3D imaging techniques used in medicine. MDCT units use fan-beam X-rays to capture multiple axial slices by continuously scanning from the top to bottom of the region of interest during image acquisition. The series of axial slices captured can be reconstructed into 3D images, which allows for the visualization and assessment of anatomic structures at different planes (Fig. 23-7). However, mainly due to the higher radiation dose, costs, and impaired availability and access in private practice, MDCT imaging is not a commonly used 3D imaging modality in dental medicine. Nevertheless, compared with CBCT, MDCT imaging has relatively superior soft tissue contrast resolution that can show density differences between certain types of soft tissues, which may be helpful for the evaluation of different soft tissue masses in the dental and maxillofacial region (Mallya & Lam 2019).

Cone beam computed tomography

Since the initial description of CBCT in 1998 in the field of dentistry, it has become an established 3D imaging technique, and continues to gain popularity in dental medicine (De Vos *et al*. 2009; MacDonald 2017). Because CBCT imaging uses a cone beam instead of a fan beam to capture images in one single rotation around the patient's head, the radiation dose of one CBCT scan is usually lower than an MDCT scan (Pauwels *et al*. 2015). The high spatial resolution of CBCT images is beneficial to visualize anatomical structures accurately and identify pathological changes in the dental and maxillofacial region (Fig. 23-8). Although the spatial resolution of CBCT images is still inferior to 2D images, it is reported that the spatial resolution of CBCT is twice to eight times higher than that of MDCT (Mallya & Lam 2019). Thus, the CBCT imaging modality is more frequently used in dental medicine compared with MDCT. However, the radiation dose of one CBCT scan is still considerably higher than that of conventional 2D imaging modalities. CBCT examination is only recommended for patients when clinical examination and conventional 2D images do not contribute sufficient diagnostic information (ICRP 2007; Carter *et al*. 2008; Horner *et al*. 2012). The clinical applications for CBCT include all fields in dental medicine but are mainly for the evaluation of the hard tissue including teeth and jaws. However, CBCT imaging has its limitations with respect to metallic artifacts and low contrast resolution (Koong 2015) as well as with movement artifacts (Spin-Neto *et al*. 2018). Low contrast resolution limits the visibility of soft tissue and lower density osseous structures on CBCT images. On the other hand, metal artifacts from dental restorations may influence the visibility of adjacent anatomic structures (Fig. 23-9).

Non-ionizing modalities

Imaging techniques used in dental medicine are mostly based on X-rays resulting in ionizing radiation exposure to patients. Although the biological effects of ionizing radiation stemming from dental X-ray devices have been considered almost negligible, repeated radiation exposures may be related to an increased risk of developing salivary gland tumors (Preston-Martin & White 1990), thyroid cancer (Memon *et al*. 2010), and meningioma (Longstreth *et al*. 2004). Therefore, there is increasing interest in the application of imaging modalities that do not employ ionizing radiation in order to prevent unnecessary radiation exposure to patients and to provide alternative imaging modalities for diagnostic purposes in the dentomaxillofacial region (Boeddinghaus & Whyte 2018).

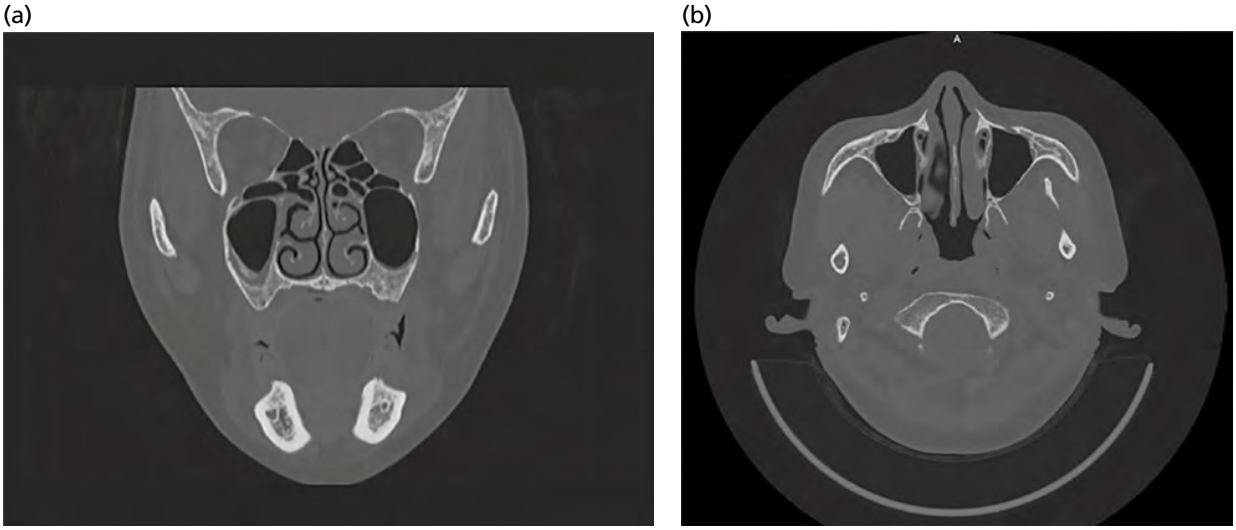

Fig. 23-7 The superior soft tissue contrast resolution of MDCT scans enables the visualization and differentiation of facial muscles with the surrounding soft tissues. (a) Coronal slice. (b) Axial slice.

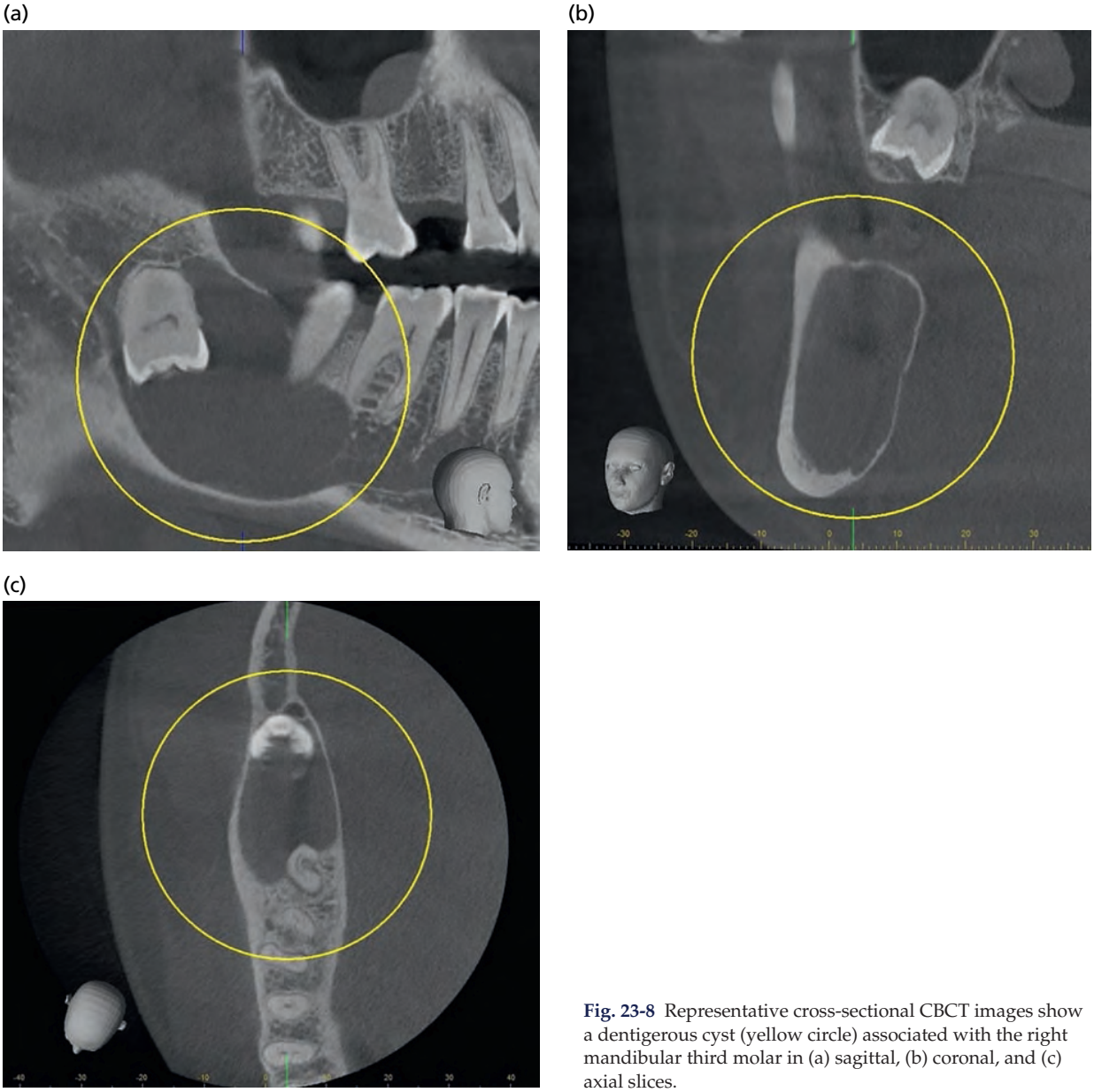

Fig. 23-8 Representative cross-sectional CBCT images show a dentigerous cyst (yellow circle) associated with the right mandibular third molar in (a) sagittal, (b) coronal, and (c) axial slices.

Ultrasound

Ultrasound imaging is a non-ionizing diagnostic modality that is based on the application of ultrasound and is frequently used in clinical medicine. A transducer emits sound waves of vibratory frequencies in the range of 1–20 MHz that pass through or interact with tissues of different acoustic impedance. Subsequently, the reflected sound waves are detected by the transducer, and eventually display a real-time cross-sectional 2D image (Shriki 2014). Although ultrasound imaging has been widely used for diagnosis of disease and image-guided surgery in clinical medicine, because of the size of the ultrasound transducer its application in dental medicine has been mostly limited to examining major salivary glands, superficial mass lesions, cervical lymph nodes, masticatory and neck muscles, maxillofacial fractures, and the TMJ (Mupparapu & Nadeau 2016). With the introduction of smaller intraoral transducers, ultrasound imaging may be a promising imaging modality to visualize the gingiva and the surface contour of the alveolar bone (Fig. 23-10) (Caglayan & Bayrakdar 2018). In addition, ultrasound images are not affected by metal artifacts, which may be very helpful for the evaluation of peri-implant bone resorption.

Magnetic resonance imaging

MRI is a revolutionary imaging technique that has been used in medicine since the 1980s; it does not employ ionizing radiation. This technique directs a radiofrequency pulse into the patient, who is placed in static magnetic fields generated by the MRI unit. This results in the hydrogen nuclei of the atoms in

the body of the patient to absorb resonance energy. As the radiofrequency pulse is turned off, the energy stored in the hydrogen nuclei is released. The scanner of the MRI unit detects the released energy and converts the energy to an electrical signal that is used for image reconstruction (Mallya & Lam 2019). In the dental and maxillofacial region, MRI can be used to evaluate the morphology and function of the TMJ, specifically for the diagnosis of disk pathologies including displacement or joint effusion (Koong 2015; Mupparapu & Nadeau 2016). Other potential applications of MRI include the evaluation of the floor of the mouth, salivary glands, tongue, and paranasal sinuses (Fig. 23-11). Although MRI has no known biological effects and is particularly useful in the evaluation of soft tissue, it is rarely used in general dental practice. This is because MRI units are relatively expensive and not widely accessible to dental practitioners. Patients with cardiac pacemakers, insulin pumps, and claustrophobia are not eligible for an MRI examination. Furthermore, MRI-generated images are severely affected by metal artifacts (Fig. 23-12), which limits its application for the evaluation of dentoalveolar pathology (Gunzinger *et al*. 2014). Imaging with MRI in dentistry using special coils has been attempted to acquire high-resolution images for various dental indications in a more reasonable acquisition time (Flugge *et al*. 2016).

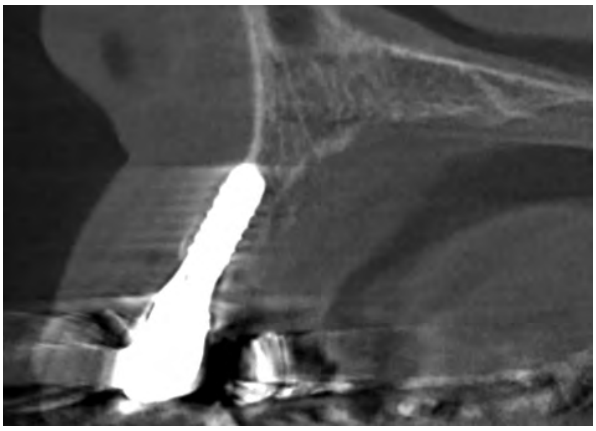

Fig. 23-9 Metal artifacts from a titanium dental implant and corresponding restoration may influence the visibility of buccal and oral bone on CBCT scans. Thus, the diagnostic validity for assessment of peri-implant bone conditions in CBCTs might be limited.

Radiation hazards and radiation dose protection

Diagnostic imaging modalities used in dental medicine are mainly based on X-rays. Ionizing radiation from X-rays may induce biological damage at a cellular level. Damage to the chromosome structures is of particular importance as there is a chance that irreparable chromosome damage may cause radiation-induced cell death, heritable mutations, and carcinogenesis (Omar *et al*. 2015). Thus, dental practitioners should have a clear understanding of the principle of radiation hazards and radiation dose protection measures.

Biological risks of radiation

The biological risks of radiation include deterministic and stochastic effects (Firetto *et al*. 2019). Deterministic effects are adverse effects that occur only when patients are exposed to ionizing radiation with a dose exceeding specific threshold values. Below this threshold dose, deterministic effects will not occur. However, if the threshold is exceeded, the severity of the deterministic effects increases with an increase of radiation dose. Relevant deterministic effects (the corresponding threshold values

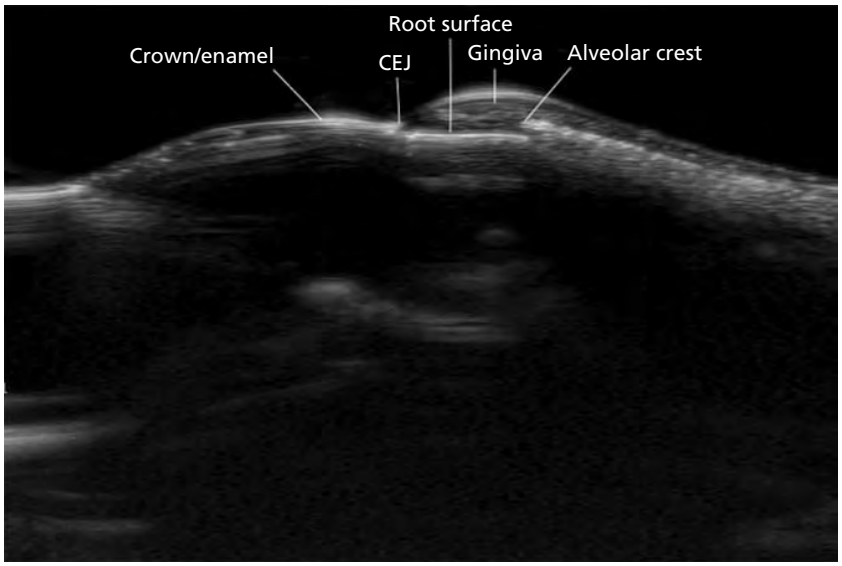

Fig. 23-10 Representative ultrasound image shows superficial anatomical landmarks on the buccal aspect of an upper right canine including the morphology of the gingiva and level of the alveolar crest.

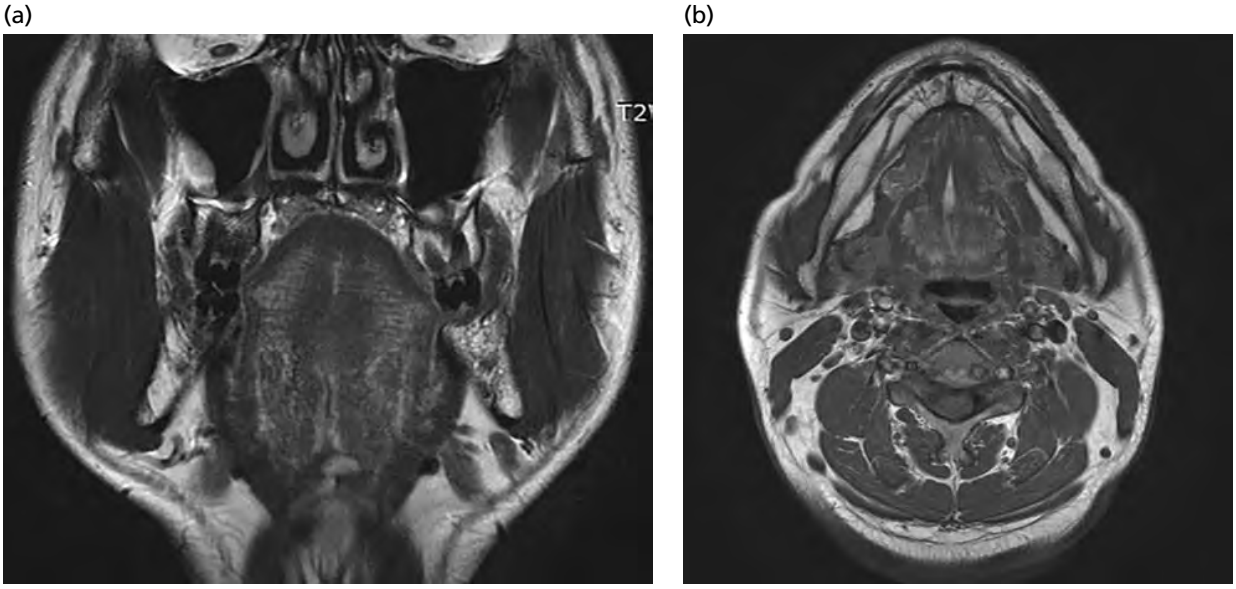

Fig. 23-11 Representative magnetic resonance images exhibiting facial soft tissues and more specifically the fibres of the tongue and also masseter muscles. (a) Coronal slice. (b) Axial slice.

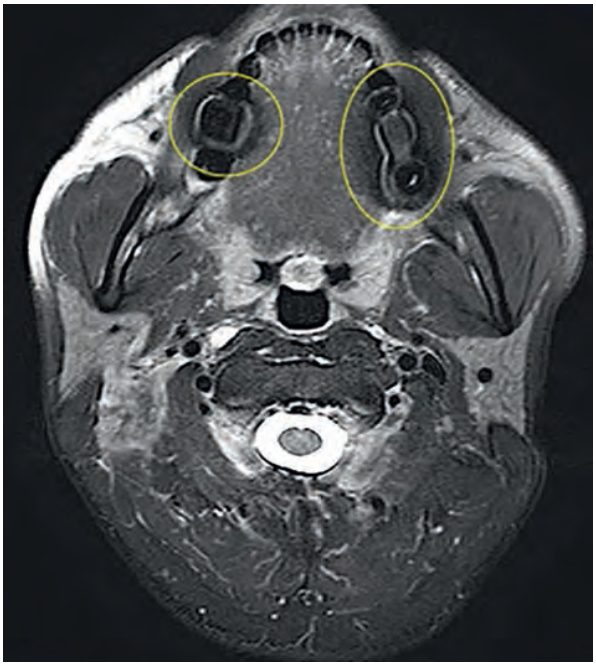

Fig. 23-12 Axial magnetic resonance image shows multiple hyperintense rings in the signal void (yellow circles) due to metallic artifacts around dental restorations, which influence the visibility of the adjacent anatomical structures.

in grays) include fetal abnormality (0.1–0.5 Gy), sterility (2–3 Gy), skin erythema (2–5 Gy), hair loss (2–5 Gy), and irreversible skin damage (20–40 Gy) (Dendy & Heaton 1999). Theoretically, the threshold values are significantly higher than the diagnostic radiation doses used in medical and dental examination.

On the other hand, when X-ray ionized electrons hit the chromosome structure, it may result in sublethal DNA damage. Damaged DNA may subsequently cause DNA mutation, and then develop to specific cancers, such as leukemia, thyroid cancer, salivary gland tumors, breast cancer, and brain or nervous system neoplasias. Occurrences of radiation-induced cancers are considered as stochastic effects. They can often occur years after radiation exposure. Compared with deterministic effects, the occurrence of stochastic effects is not linked to a specific dose threshold as a DNA mutation may be caused by a single X-ray exposure with the smallest radiation dose. Besides, it is generally accepted that there is a positive correlation between the risk of stochastic effects and radiation dose (Ludlow *et al*. 2008; Mallya & Lam 2019). The higher the radiation dose, the higher the risk of stochastic effects. As a result, stochastic effects are more related to radiation exposure in diagnostic imaging.

Principles of radiation dose protection

In the general population, radiation exposure is primarily attributed to natural background radiation and artificial radiation sources including medical exposure and consumer products. Medical exposure is reported as the largest artificial radiation source and represents approximately 14% of the total annual dose of ionizing radiation for individuals (Bornstein *et al*. 2019). MDCT has been reported to comprise 47% of the total annual medical imaging exposure in the USA (ICRP 2007). In dental medicine, CBCT imaging is more frequently used than MDCT. The radiation dose from CBCT imaging is reported to be up to 15 times less than MDCT, although it is still higher than that of conventional 2D dental radiographic imaging procedures (ICRP 2007; Ludlow & Ivanovic 2008; Loubele 2009). Epidemiological studies suggest that radiation exposure from dental procedures (2D or 3D) may be related to an increased risk of developing salivary gland tumors (Preston-Martin & White 1990), thyroid cancer (Memon *et al*. 2010), and

meningioma (Longstreth *et al*. 2004). Therefore, radiation risk should be minimized by adopting radiation dose protection principles including justification of patient exposures, optimization of patient dose, and dose limitation during radiological procedures.

Justification

The most effective way to protect patients from unnecessary ionizing radiation is to avoid unnecessary exposures. The principle of justification is that an imaging examination should be performed only when the benefit to a patient exceeds the risk of radiation exposure (Federal Guidance Report No. 9 1976; ICRP 2007). This means that clinicians should firstly obtain a patient's medical history and the results of the clinical examination prior to referring a patient for imaging. An imaging examination should be considered only when clinical examination cannot provide sufficient diagnostic information. Also of importance is an effective communication of any specific request for the imaging examination between the clinician and the operator who takes responsibility for the imaging examination to avoid any re-exposure. Generally, the determination of the type of diagnostic imaging modality should be considered based on the reason for referral, location, size, and characteristics of the anatomic structure/pathological changes, and the radiation dose to the patient. For periodontal evaluation, conventional intraoral radiography is the first choice to assess marginal bone loss of the teeth in question. Due to higher radiation doses, CBCT imaging should only be suggested in selected cases, such as furcation lesions. Although panoramic radiography allows dental practitioners to have an overview of the condition of remaining teeth and their supporting bone, a relatively low spatial resolution and potential image superimposition limit its application for diagnostic purposes in periodontology. For implant treatment planning purposes, CBCT has seen increased use and popularity as an adjuvant and even a primary imaging modality (Horner *et al*. 2012; Al-Ekrish 2018). The 3D information of CBCT compensates for the low spatial resolution of this technique. Intraoral or panoramic views are considered to be more appropriate imaging modalities for the assessment and monitoring of osseointegration following implant insertion and during follow-up.

Optimization

Once referral for an imaging examination has been justified, the next step is to ensure the examination is effectively performed in accordance with the principle of optimization that is also known as the As Low As Reasonably Achievable (ALARA) or As Low As Diagnostically Acceptable (ALADA) concept (ICRP 2007; Jaju & Jaju 2015). ALARA was established in 1977 to designate the optimization of X-ray doses in order to minimize radiation dose exposure. Almost a decade ago, the ALADA concept has been introduced with an emphasis on using as low a dose as possible to obtain diagnostically acceptable images instead of just "beautiful" images (Schulze 2012; Jaju & Jaju 2015). The implementation of the ALADA concept in dental practice includes determining a suitable diagnostic imaging modality to suit the patient's specific needs, using radiation detectors with maximum sensitivity, selecting appropriate exposure parameters, using shielding devices, and selecting a radiographic projection in which radiosensitive organs receive the minimum dose. As the radiation dose of MDCT/CBCT imaging is higher than conventional 2D imaging, much attention is now being paid to reducing radiation exposure from MDCT/CBCT. Reducing the FOV size can reduce the exposed area of the patient's body, which is the most straightforward measure to reduce radiation dose (Davies *et al*. 2012). In addition, reducing the FOV size improves image quality by reducing image noise and artifacts. Therefore, the FOV size should be selected carefully ideally to cover only the region of interest. For example, patients who need implant treatment for one missing tooth in a site with sufficient bone volume should not be referred for a CBCT scan with full coverage of the craniofacial region. In addition, novel low-dose scanning protocols are also considered as an option to reduce radiation exposure without an unacceptable loss of image quality for diagnostic and treatment purposes (Yeung *et al*. 2019a). This concept has already found recognition in various dental disciplines, specifically in pediatric dentistry (such as evaluation of orofacial clefts and impacted teeth), orthodontics (such as cephalometric analysis), endodontics (such as detection of periapical bone loss), oral implantology (such as implant planning), and oral and maxillofacial surgery (such as assessment of mandibular third molars and TMJs). Low-dose scanning protocols are available in some CBCT units, which provide pre-set dose reduction settings to reduce radiation exposure. Alternatively, manually adjusting imaging parameters including reducing the tube current (mA), exposure time(s), resolution (i.e. increasing voxel size), the number of projections, and/or adopting a partial rotation mode (e.g. 180° instead of 360° rotation) can also be applied for dose reduction.

Dose limitation

Radiation dose limitation is a constant safety issue in radiology, especially for occupationally exposed individuals. Unlike patients who can get direct benefit from medical exposures for diagnostic and treatment purposes, clinical staff who take responsibility for operating radiographic imaging equipment are at high risk of excessive exposure to ionizing radiation. In order to protect any member of clinical staff or individuals staying in dental settings from unnecessary occupational and public exposure, the principle of dose limitation should be strictly followed. According to the statement of the International Commission on Radiological Protection, the annual

dose for occupationally exposed individuals should not exceed 20 mSv of whole-body radiation exposure (ICRP 2007). Personnel protection including reduction of the chance of potential exposure from the primary X-ray beam and scattered radiation, and monitoring of the accumulated exposure level among occupationally exposed staff should be strictly implemented. Dental clinics equipped with an X-ray-based imaging device should meet the radiation shielding requirements based on local national regulations. The dose limitation of medical exposure is not applicable to patients who are referred for the imaging examination as these exposures are intentionally performed for diagnostic and treatment purposes. However, the use of shielding devices, such as protective lead aprons and thyroid collars, can effectively protect the thyroid gland and the trunk of the patient's body from primary and scattered radiation.

In addition, multiple institutions including the NCRP (National Council on Radiation Protection and Measurements) and EURATOM (European Atomic Energy Community) have recommended the use of so-called dose reference levels (DRLs) to standardize dose values for medical and dental diagnostic imaging. DRLs are acceptable upper limits of dose exposure values that should not be exceeded for standard diagnostic imaging procedures on patients as defined by the use of standard dimensions/phantoms (Schafer *et al*. 2014). Generally, a DRL is set based on the third quartile (75% percentile) of field measurements performed in a large number of establishments. For example, the NCRP recommends a national DRL of 1.6 mGy entrance skin dose for periapical and bitewing radiography (Mallya & Lam 2019). The use of DRLs provides a good framework regarding dose exposures for specific indications for the operator who takes responsibility for the imaging examination, and will very likely be a field with more focus in the future due to the growing availability of CBCT in dental medicine. Based on a national survey from Switzerland initiated by the Federal Office of Public Health (FOPH/ BAG), five DRLs for CBCT use for the most common indications for dental and ENT practice have been proposed (Deleu *et al*. 2020).

Diagnostic imaging in periodontology

Diagnosis of periodontal diseases should be based on data gathered from both clinical and imaging examinations. Patients with clinical symptoms and/or signs of periodontal diseases should be referred for an imaging examination to evaluate the supporting bony structures of the affected teeth. Diagnostic imaging is mainly used to identify the presence of bone destruction and also to assess bone defect morphology. Pathological changes confined to the soft tissue alone including dental plaque-induced gingivitis and non-plaque-induced gingival lesions or acute inflammatory lesions, such as acute periodontal abscess, are usually not seen on X-ray-based diagnostic images due to the absence of bone destruction. This section describes general recommendations on various diagnostic imaging modalities used for the evaluation of periodontal defects.

General recommendations

Two-dimensional modalities

Intraoral 2D images are currently deemed as the standard imaging modality to complement clinical findings for periodontal evaluation (Tonetti & Sanz 2019). Bitewing and periapical radiography are the two main 2D imaging modalities used for evaluation of the condition of the supporting bone. Bitewing radiography is usually more accurate in the evaluation of periodontal bone loss because the X-ray projection is more perpendicular to the long axis of the teeth. This leads to less distortion and superimposition of the image. However, bitewing radiography can only depict the most coronal portion of the alveolar bone due to its limited FOV (Fig. 23-13). The application of normal sized periapical radiographs as bitewing formats should be preferred instead of long and narrow sized radiographs. The advantage of this format is the visualization of slightly more bone and a more perpendicular projection for the whole format. Nevertheless, this limits the use of bitewing radiography in patients with moderate to severe periodontal bone defects exceeding the middle third of the root involved. In contrast, periapical radiography has the advantage of depicting the full length of the tooth, which is more suitable for the evaluation of the extent of periodontal bone destruction. A full-mouth intraoral X-ray examination is recommended for patients with clinical symptoms and/or signs of general periodontitis or periodontitis-susceptible patients (Fig. 23-14) (Tonetti & Sanz 2019). Panoramic radiography can also offer an overview of teeth and

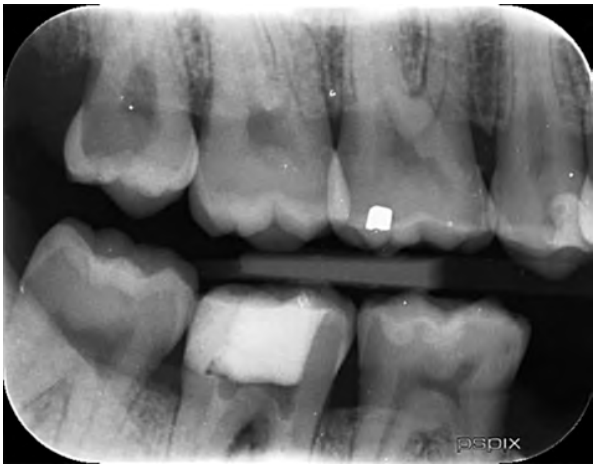

Fig. 23-13 This bitewing radiograph exhibits a radiolucency in the region of the furcation of tooth 47. Unfortunately, this finding is not be entirely visible due to the limited field of view of the radiograph.

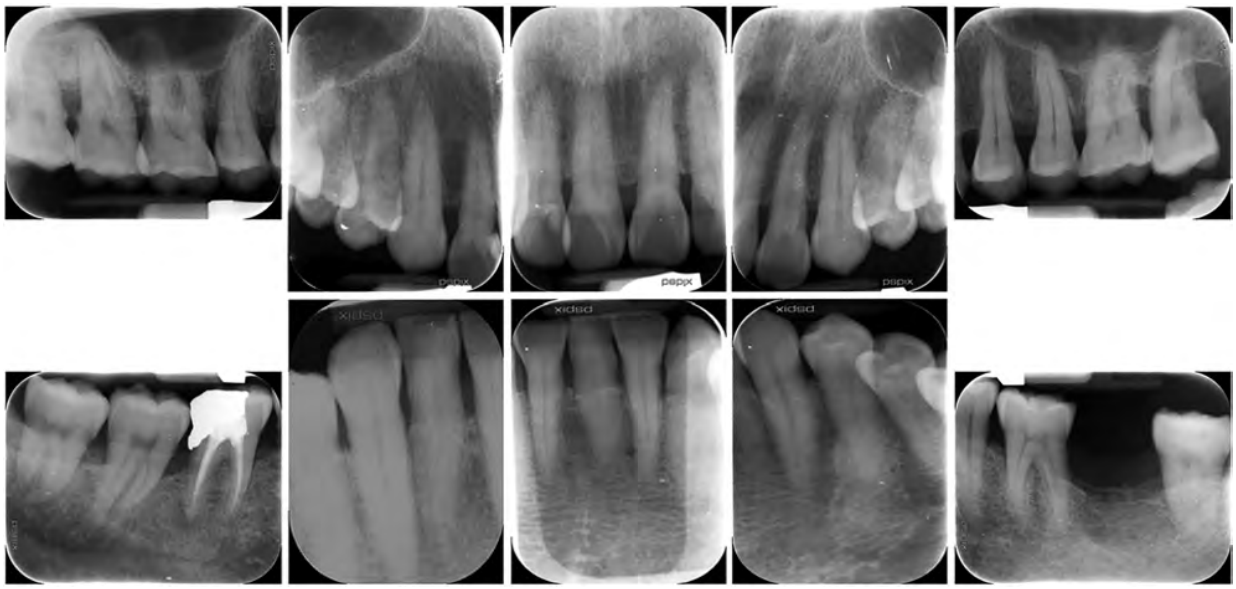

Fig. 23-14 An example of a full-mouth intraoral X-ray examination for periodontal diagnostics that consists of 10 periapical images, in this case demonstrating all teeth and their supporting bony structures. Overlap of teeth and difficulty in correctly placing the film or sensor might limit the visibility of interradicular bone in some areas. As an incidental finding, an apical lesion is visible here on the distal root of the first right mandibular molar (tooth 46).

the supporting bone in one single image. The lower spatial resolution, the vertical magnification of teeth, and superimposition of the image may lead to an incorrect estimation of the periodontal bone destruction. New technology for panoramic radiographs is available and offers different "sharp layers" so that the best possible image can be chosen or is automatically focused. For the ALARA principle, existing panoramic radiographs should be used. Therefore, the application of additional periapical radiographs depends on the clinical examination and the visualization of all regions on the panoramic radiograph.

Plaque-induced inflammatory periodontal bone loss originates at the alveolar crest. In the initial phase, a reduced density of the cortical bone of the interradicular alveolar crest and an erosion of the crest with a diffuse border may be observed in 2D images. As periodontitis progresses, the loss of supporting bone with/without a widened periodontal ligament space may occur and aggravate. The presence of bone loss is identified based on the level of the interradicular alveolar crest in relation to the cementoenamel junction (CEJ). In healthy subjects, the level of the interradicular alveolar crest should be located at 0.5–2.0 mm apically to the CEJ level of adjacent teeth, whereas the distance between the two levels in patients with periodontitis at the involved site is greater than 2.0 mm. Radiologically, the development of periodontitis can be classified, based on the degree of bone loss, into four stages (Mallya & Lam 2019) (Fig. 23-15):

- *Stage I:* The bone loss is less than 15% of the tooth root length
- *Stage II:* The bone loss is between 15% and 33% of the tooth root length
- *Stage III:* The bone loss extends to the middle-third of the tooth root
- *Stage IV:* The bone loss extends beyond the middle-third of the tooth root.

Bone defects can be categorized as horizontal or vertical bone loss. Horizontal bone loss usually involves multiple adjacent teeth, presenting the level of the interradicular alveolar crest parallel with an imaginary line passing through the CEJ levels of the involved teeth (Fig. 23-16). Vertical bone loss is often centered on one tooth more than the adjacent tooth, presenting an uneven and oblique bone destruction morphology. In some cases, an increased distance between the CEJ level and the interradicular alveolar crest may not be attributed to periodontal bone loss. For example, this distance on supraerupted or passively erupted teeth is greater than on healthy teeth, which results from the coronal movement of the teeth and not from the loss of supporting bone.

Two-dimensional imaging examination may be able to identify an intrabony defect. According to the condition of the buccal and oral cortical plates around an intrabony defect, these bone defects can be classified into three-walled, two-walled, and one-walled. A three-walled defect is defined as an intrabony defect enclosed by the buccal and oral cortical plates and interradicular alveolar bone. A two-walled bony defect is defined as an intrabony defect surrounded by either buccal or oral cortical plate and interradicular alveolar bone, and a one-walled bony defect is characterized by the absence of both buccal and oral cortical plates. For three-walled and two-walled bony defects, a reduced density of the alveolar bone with/without a slightly reduced level of the alveolar crest may be observed at the root

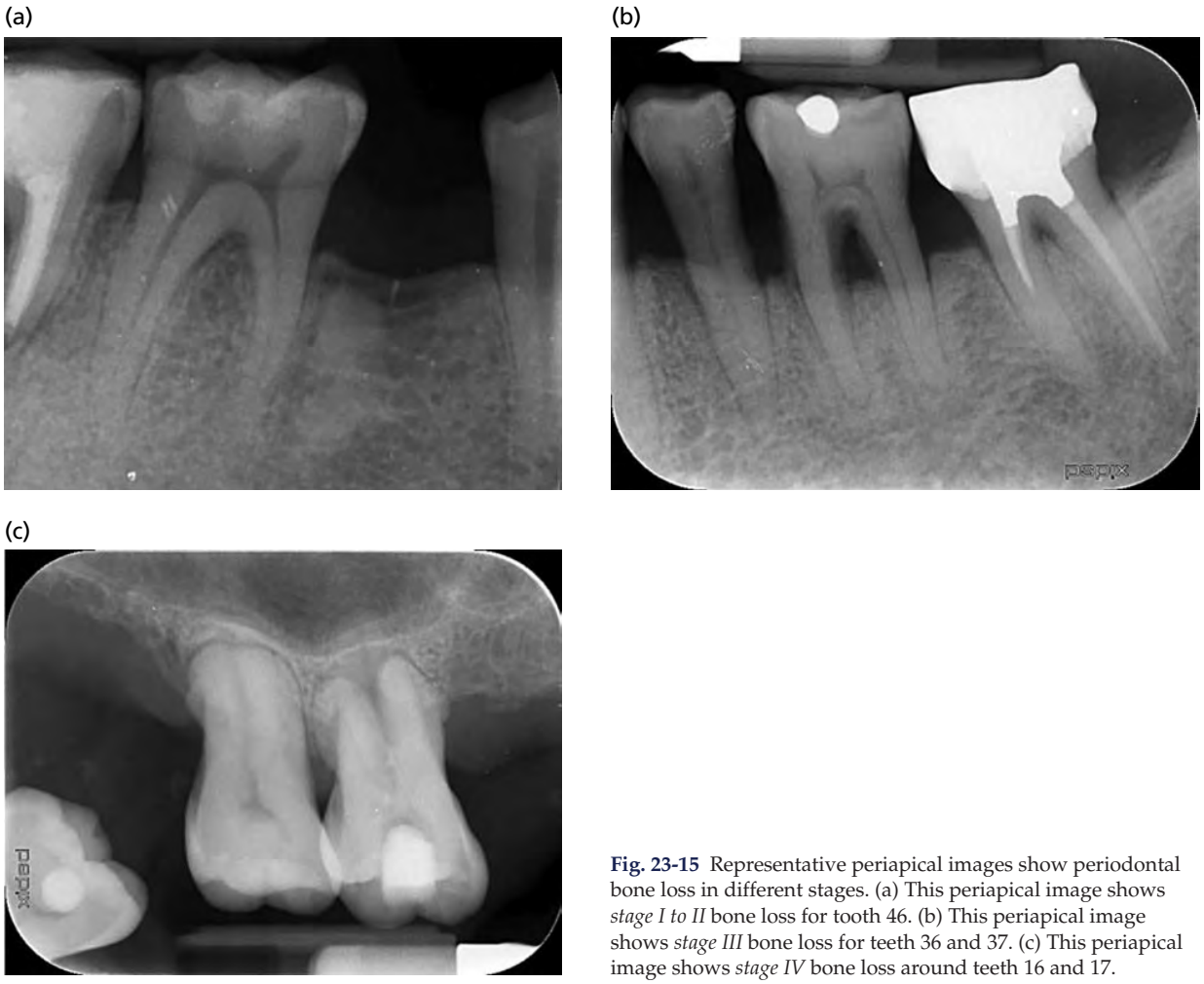

Fig. 23-15 Representative periapical images show periodontal bone loss in different stages. (a) This periapical image shows *stage I to II* bone loss for tooth 46. (b) This periapical image shows *stage III* bone loss for teeth 36 and 37. (c) This periapical image shows *stage IV* bone loss around teeth 16 and 17.

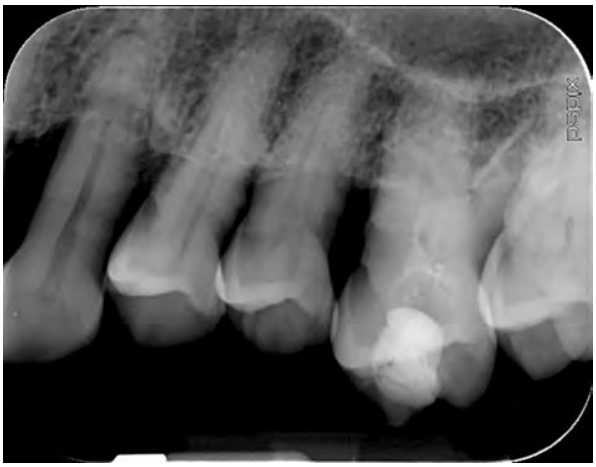

Fig. 23-16 The periapical image shows a reduced interradicular alveolar crest level affecting multiple adjacent teeth in the left posterior maxilla including the canine, premolars, and also first molar (e.g. horizontal bone loss).

surface on 2D images (Fig. 23-17). The exact contour of the bone destruction may not be clearly exhibited on 2D images as the intrabony defect is superimposed by either the buccal or oral cortical plate. Therefore, 3D diagnostic imaging is considered as a more appropriate option for the evaluation of three- and two-walled intrabony defects. However, due to the loss of both buccal and oral cortical plates, a one-walled intrabony defect can be clearly observed on 2D images (Fig. 23-17). Alternatively, a three- or two-walled bony defect may be identified on 2D images through inserting a gutta-percha tip into the periodontal pocket prior to X-ray exposure. The image of the inserted gutta-percha can point out the bottom level of the bone destruction. The interdental crater is a specific two-walled bony defect between adjacent teeth. The morphology of the interdental crater is a trough-like depression enclosed by the buccal and oral cortex and the root surface of the adjacent teeth. The imaging feature of an interdental crater on 2D images may present as a reduced density of the alveolar bone apically to the alveolar crest in connection with an increased density of alveolar bone apically to the bottom of the crater. This may not be clearly exhibited on 2D images as the defect is superimposed by the buccal and oral cortex, and thus a 3D imaging examination

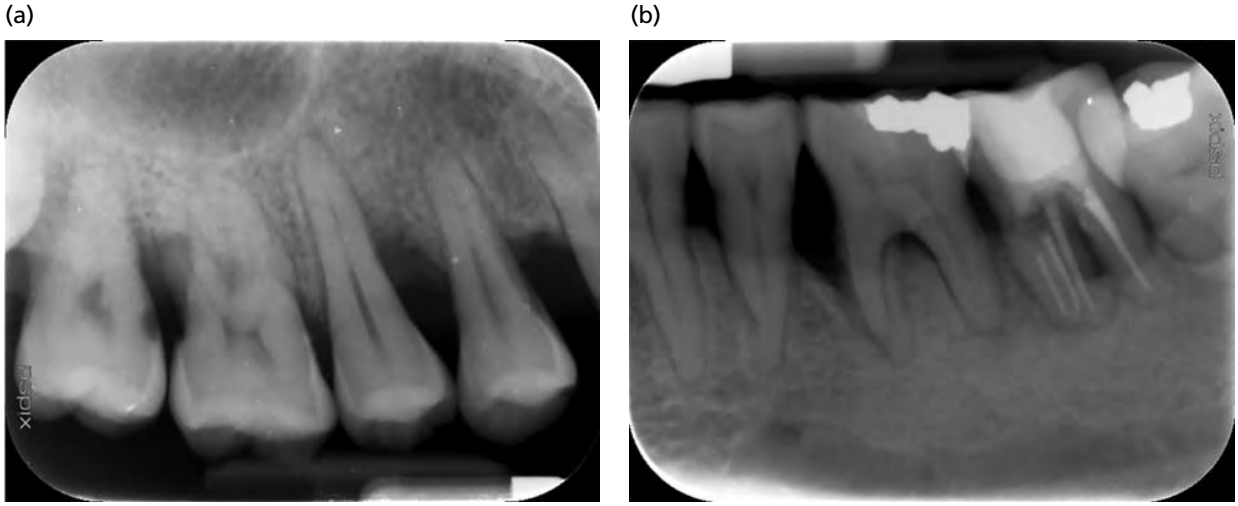

Fig. 23-17 Representative examples of bony defects around teeth as depicted in intraoral radiographs. (a) This periapical image exhibits a two-walled defect enclosed by the mesial surface of tooth 15, interradicular alveolar bone, and oral cortical plate. (b) This periapical image exhibits a one-walled defect enclosed by the mesial surface of tooth 36 and interradicular alveolar bone.

can be needed for the diagnosis of interdental craters (Vandenberghe *et al*. 2008).

Furcation defects are a relatively complex form of periodontal disease occurring in multirooted teeth. Due to the anatomic characteristics of multirooted teeth, the furcation region easily accumulates periodontal pathogenic bacteria, but on the other hand it is difficult to gain access for treatment. This leads to furcation defects being considered as the most common reason for the loss of molars (Nibali *et al*. 2016). Therefore, early diagnosis of furcation defects is crucial for the treatment outcome and in consequence also for the survival of the treated teeth. When periodontal pathogenic bacteria invade the furcation of multirooted teeth, a slight widening of the periodontal ligament space in the furcation region may be observed on 2D images. As the progression of periodontitis destroys more supporting bone, an increase of the radiolucent area in the furcation region may be detected (Fig. 23-18). In maxillary molars, the widening of the periodontal ligament space and the bone destruction in the furcation area may be superimposed by the palatal root. In this case, periapical radiography using an angulated technique is recommended to reveal such "hidden" furcation defects. Besides, the occurrence of an inverted "J" shaped radiolucency is a typical imaging feature for furcation defects between adjacent maxillary multirooted teeth. The hook of the "J" shaped radiolucency is caused by the bone destruction extending into the furcation region of a maxillary multirooted tooth (Fig. 23-19). On 2D images, however, relatively well-defined furcation defects are usually only seen when the buccal and oral cortical plates are destroyed. If one of these cortical plates is preserved, the furcation defect may only present as an area with decreased bone density. Therefore, CBCT is considered as a more accurate imaging examination to assess the extent and morphology of furcation defects (Walter *et al*. 2016).

For endo-perio lesions, 2D images can exhibit radiolucent defects extending from the alveolar crest to the apex of a tooth root, which reflects contiguity of periodontal and periapical inflammatory lesions (Fig. 23-20). Although it is considered that the larger radiolucent area is more likely to be the origin of perio-endo lesions, it cannot be evaluated by the imaging examination alone. Thus, the evaluation of the origin of perio-endo defects should be based on the morphology of the defect as well as clinical findings (Shenoy & Shenoy 2010).

In brief, due to the high spatial resolution and low radiation dose, intraoral 2D imaging examination is the first choice for the assessment of periodontal diseases. Besides, the 2D images are commonly used as a baseline record of the periodontal condition including the level of the alveolar crest, width of the periodontal ligament space, and density of the alveolar bone for comparison with follow-up images. However, 2D imaging modalities have several limitations. The bone deconstruction located at the buccal and oral side of the involved teeth cannot be clearly exhibited on 2D images. Additionally, dense buccal and/or oral cortical plates may affect the evaluation of the interproximal bone defects. This may cause misdiagnosis of the supporting bone condition and thus lead to a lower detection rate of periodontal bone defects (Vandenberghe *et al*. 2008). Furthermore, non-standardized follow-up radiographs could mimic bone healing or bone loss due to the deviation in X-ray projection angulation. This may result in a faulty assessment of the supporting bone conditions.

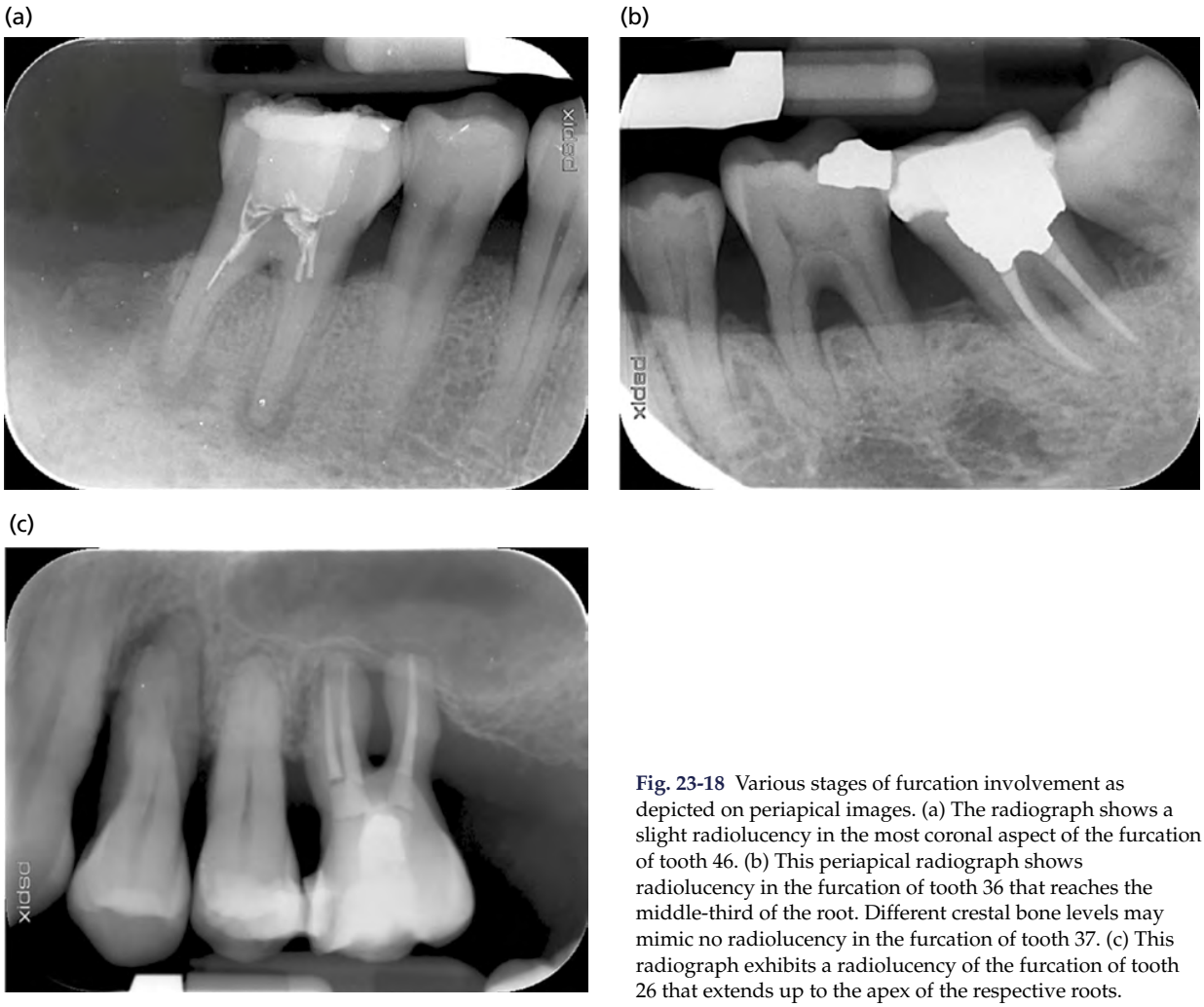

Fig. 23-18 Various stages of furcation involvement as depicted on periapical images. (a) The radiograph shows a slight radiolucency in the most coronal aspect of the furcation of tooth 46. (b) This periapical radiograph shows radiolucency in the furcation of tooth 36 that reaches the middle-third of the root. Different crestal bone levels may mimic no radiolucency in the furcation of tooth 37. (c) This radiograph exhibits a radiolucency of the furcation of tooth 26 that extends up to the apex of the respective roots.

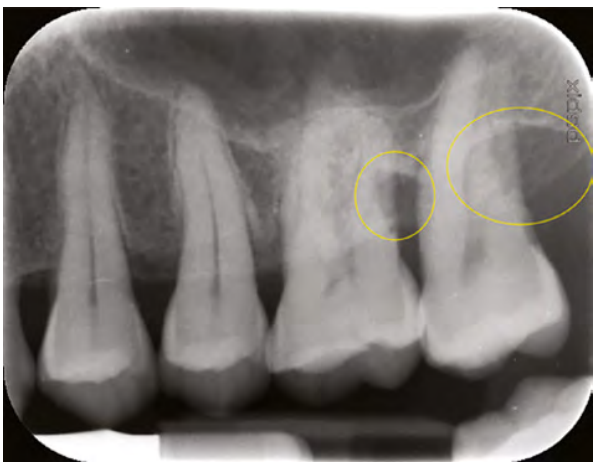

Fig. 23-19 A periapical image demonstrating a radiolucent triangle superimposed over the distal roots of tooth 26 and demonstrating the hooks of the "J" shaped radiolucency on the distal root of tooth 27, both of which indicate bone destruction extending into the furcation of the respective regions (yellow circles).

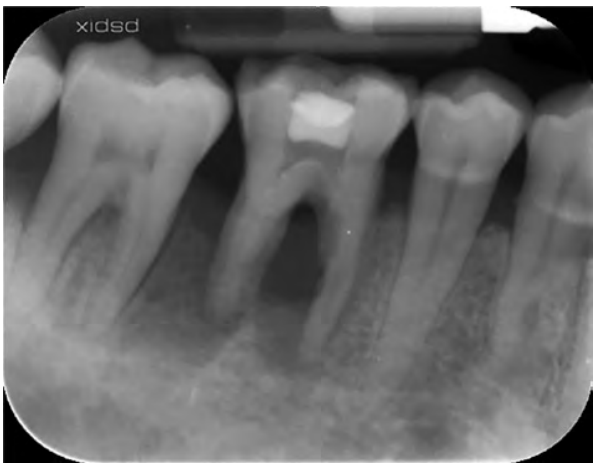

Fig. 23-20 This periapical image shows an extended radiolucency from the alveolar crest to the periapical region of tooth 46. This points towards the presence of periodontal and periapical inflammatory pathologies (perio-endo lesion).

Three-dimensional modalities

MDCT and CBCT as 3D imaging modalities allow cross-sectional views that display the architecture of all types of bone defects. This increases the accuracy in the evaluation of the presence, severity, and morphology of periodontal bone destruction (Misch *et al*. 2006; Mol & Balasundaram 2008,; Choi *et al*. 2018). A clear understanding of the 3D morphology of periodontal bone destruction and the involved roots is of great importance for treatment planning and will also influence the treatment outcome. As a result, 3D imaging modalities are recommended for the assessment of complex bone defects, especially for the intrabony and furcation defects in maxillary molars (Walter *et al*. 2009, 2010) (Fig. 23-21). Nevertheless, according to the principles of radiation dose protection, MDCT and CBCT are not recommended for routine preoperative imaging procedures in periodontology (ICRP 2007). Patients that present with clinical symptoms and signs of periodontal disease should initially be referred for 2D imaging. MDCT/CBCT is recommended only when 2D images cannot provide sufficient diagnostic information in the evaluation process of periodontal defects. Although it is reported that radiation doses for MDCT using low-dose protocols may be in the range of doses for CBCT imaging (Almashraqi *et al*. 2017), CBCT is still currently the most widely used 3D imaging modality for dental medicine and specifically for periodontal evaluations. The scanning protocol and the FOV of a CBCT examination should be determined based on the clinical and previous (2D) imaging findings on an individual case basis. Although CBCT imaging has several advantages for the evaluation of periodontal bone defects, it cannot be used to assess the condition of the gingiva. Moreover, a CBCT examination is not recommended for follow-up and monitoring of periodontal patients. In general, a follow-up

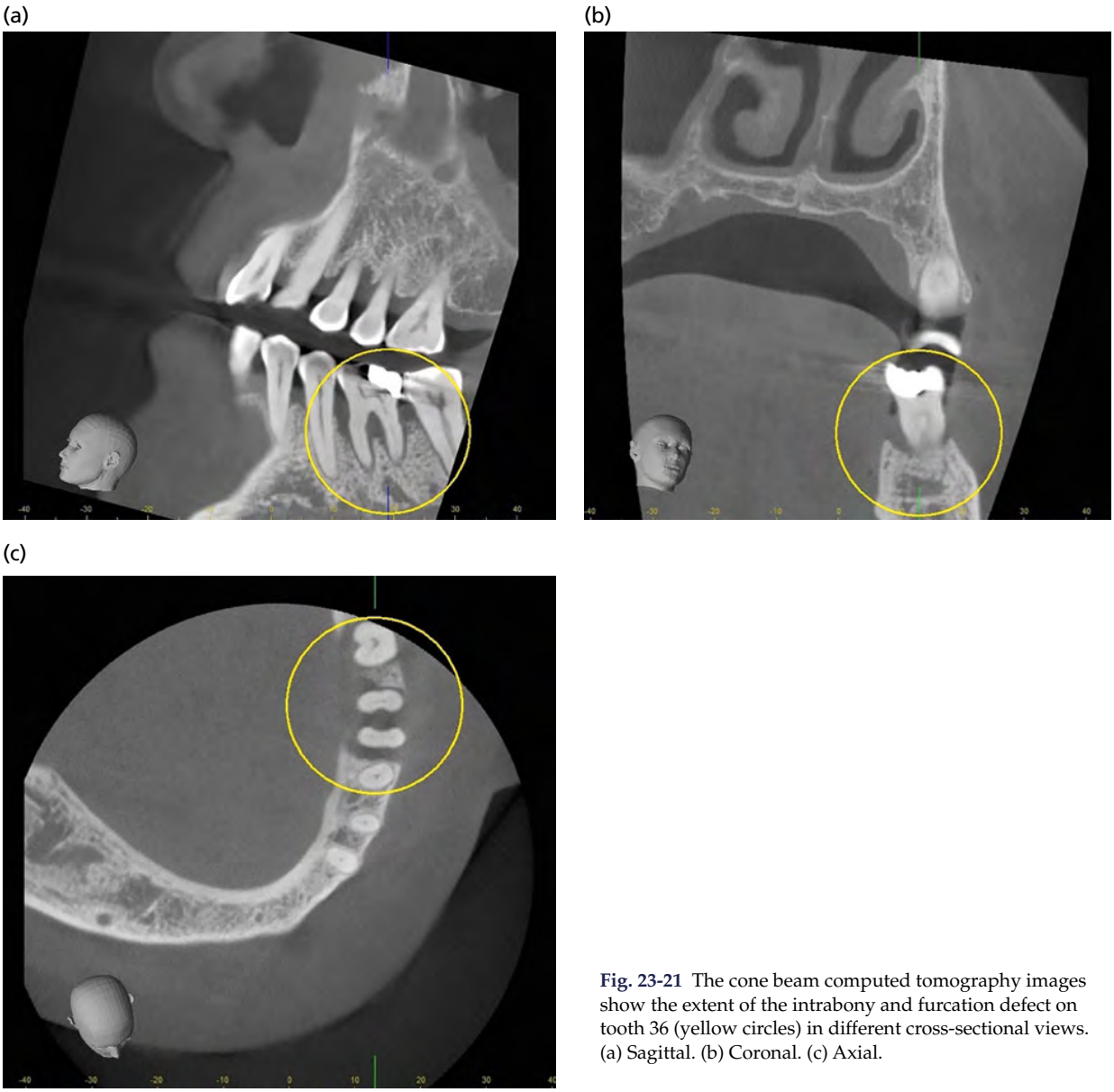

Fig. 23-21 The cone beam computed tomography images show the extent of the intrabony and furcation defect on tooth 36 (yellow circles) in different cross-sectional views. (a) Sagittal. (b) Coronal. (c) Axial.

examination should be done using 2D images to reduce the accumulated dose of radiation exposure. It is worth noting that the presence of periodontal bone loss detected in both 2D and 3D images only exhibits bone destruction and cannot indicate disease activity (Koong 2015). The bone loss may result from previous disease (history of periodontal disease) that has been controlled by appropriate treatment. As a result, the decision for any imaging modality must be based on current clinical findings.

Future trends and developments

Ultrasound

Patients with a high risk for periodontal diseases or those that have experienced periodontal treatment may need regular imaging during follow-up. Doing so will inevitably increase the accumulated dose of radiation exposure to the patient. Ultrasound imaging is a promising modality that does not employ ionizing radiation, with potential for real-time diagnostic workup and follow-up evaluations in patients with periodontal diseases. Before the advent of intraoral ultrasound transducers, ultrasound imaging was only feasible for assessing major salivary glands and superficial masses in the head and neck region, but not for periodontal diseases. Currently, small-footprint and high frequency (40-MHz) transducers designed especially for periodontal evaluation are under development, which will allow for non-ionizing, real-time, and chair-side imaging of the periodontal soft tissue, underlying alveolar bone surfaces, and buccal or oral bone defects (Chifor *et al*. 2015, 2019). Ultrasound can display the gingival thickness, gingival sulcus depth, and several relevant landmarks including the levels of alveolar bone crest, CEJ, and free gingival margin. These are of diagnostic value to assess the periodontal condition, especially to screen for and detect early forms of periodontitis. Furthermore, ultrasound is not affected by metallic materials commonly used for dental restorations or orthodontic purposes. This may increase diagnostic accuracy in the evaluation of buccal and oral bone loss at the most coronal position in close proximity to metal restorations or around orthodontic bone screws. During maintenance phases, ultrasound imaging is also useful to evaluate the stability of periodontal soft and bone tissues.

However, ultrasound imaging also has several limitations. Firstly, ultrasound can only exhibit the morphology of the gingiva and surface contour of the supporting bone and tooth portion not covered by bone. It is unable to depict periodontal bone defects covered by buccal or oral bone plates, such as three-walled intrabony and furcation defects, as ultrasonic waves cannot traverse bone tissue. Moreover, the interpretation of ultrasound images is subjective and dental practitioners may find interpretation difficult. Therefore, ultrasound images should be interpreted by appropriately trained clinical staff. These limitations may discourage the clinical use of ultrasound imaging in periodontology.

Magnetic resonance imaging

During periodontal evaluation, the health or disease of the gingiva is generally assessed through clinical examination because conventional X-ray-based imaging modalities are incapable of adequately depicting soft tissue. In contrast to ultrasound imaging, MRI can provide 3D observations of the periodontal soft tissue (Fig. 23-22). In addition, signal intensity changes in the investigated soft tissue using MRI reflect an increased water content, which can help to distinguish inflamed from healthy tissue, and assists in assessing the extent of inflammation (Mallya & Lam 2019). With different MRI sequences, one may also distinguish between infectious- and tumor-induced inflammation in soft and bone tissues (Schara *et al*. 2009). Although there is currently limited evidence for the application of MRI in the evaluation of periodontal disease (Gaudino *et al*. 2011; Ruetters *et al*. 2019), it is reported that MRI may provide sufficient spatial resolution and contrast to characterize inflamed gingiva and periodontal ligament for early diagnosis of gingivitis to an extent that cannot be matched by other imaging modalities used in dental medicine (Mallya & Lam 2019). Moreover, MRI may be helpful in evaluating the healing process (e.g. the degree of inflammation) in the gingiva and periodontal ligament after periodontal treatment. However, there are some limitations when considering MRI for periodontal evaluation (Mendes *et al*. 2020). Firstly, patients with cardiac pacemakers, insulin pumps, and claustrophobia are not suitable

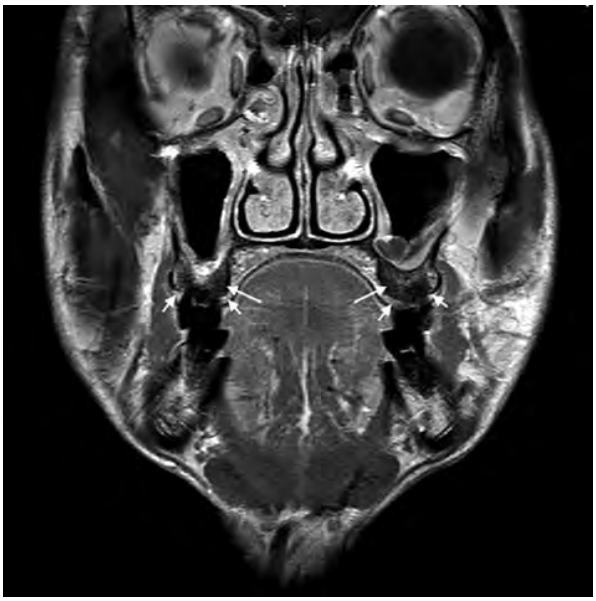

Fig. 23-22 The coronal cut of a magnetic resonance image shows the outline of the alveolar crest (long arrows). Based on this, the thickness of the gingival tissue (short arrows) can be estimated.

candidates for MRI scans. Secondly, several metallic materials used for dental restorations or orthodontic treatment may cause metal artifacts that affect the visibility and detectability of periodontal lesions. Furthermore, MRI units are relatively expensive and not as easily accessible to dental practitioners compared with conventional 2D and 3D X-ray-based imaging units. In addition, the operation of an MRI unit is much more sophisticated so that the scanning should be performed by qualified operators only. In spite of these limitations, MRI should be considered as a promising imaging modality because of its non-ionizing nature and superior soft tissue contrast. A specific user-friendly MRI unit designed for use in dental medicine may become a helpful diagnostic imaging tool to visualize pathology in the gingiva and supporting bone tissue.

Diagnostic imaging and artificial intelligence in periodontology

Digitally coded images generated in medicine that contain diagnostically important patient information are easily converted into computer language, and are thus considered as ideal to bridge the gap between medicine and artificial intelligence (AI) (Hung *et al*. 2020a; Leite *et al*. 2020). Following the processes of determination of the region of interest, identification of lesions, and classification of lesions, pathological changes on images may be automatically diagnosed using AI diagnostic algorithms and modeling. In periodontology, changes in bone density and continuity of the surface contour of the supporting bone could both contribute to the development of AI models for evaluation of periodontal bone defects. Currently, some research groups have proposed test models to automatically or semiautomatically identify and/or measure the degree of periodontal bone destruction (Lin *et al*. 2015, 2017). Moreover, an AI model has been reported to be able to predict the outcome of periodontal treatment (i.e. classifying periodontally compromised teeth into hopeful or hopeless teeth) (Lee *et al*. 2018). Interestingly, most of the proposed AI models were computed based on 2D intraoral images, mainly periapicals. These models can only identify interdental bone defects with evident bone loss because of a lack of 3D information for the entire supporting bone. Future trends for AI models built for periodontal diagnosis and treatment planning should exploit 3D images from CBCT, MDCT, and MRI to realize and implement automated classification of periodontal bone defects, calculation of the volume of bone loss, or propose treatment recommendations.

Diagnostic imaging in oral implantology

In oral implantology, diagnostic imaging is widely used for treatment planning, prosthetic evaluation, and follow-up examinations. The following section describes general recommendations on various diagnostic imaging modalities used in the pre-, intra-, and postoperative phases, and for special considerations including image-guided implant surgery, block grafting procedures, and zygoma implants.

General recommendations for implant treatment planning purposes

Using preoperative imaging examinations, implant surgeons expect to obtain diagnostic information about the condition of the bone at a future implant site, which cannot be evaluated by clinical examination only. A selection of appropriate diagnostic imaging modalities for each individual case is critical to achieve an optimal treatment outcome and minimize intra-/postoperative complications. The presence/absence of dentoalveolar pathology at the proposed implant site should be evaluated using preoperative imaging. Patients with periapical lesions of adjacent teeth, cystic lesions, or bone necrosis are suggested to receive corresponding treatment prior to implant placement. If a patient is considered as a suitable candidate for implant treatment, surgeons can proceed to assess the quantity of available bone at the edentulous site and to evaluate adjacent critical anatomic structures to determine the adequate surgical technique including position(s) and dimension(s) of the proposed implant(s).

Two-dimensional modalities

Before 3D imaging modalities were introduced into and available in dental medicine, the combination of various 2D diagnostic images including periapical, occlusal, and panoramic radiographs was recommended for the evaluation of the vertical, bucco-oral, and mesiodistal dimensions of the alveolar ridge for implant treatment purposes. These imaging techniques were also used to visualize neighboring vital anatomical landmarks such as the mandibular canal or maxillary sinus. However, occlusal images were subsequently considered inappropriate to evaluate the bucco-oral dimension as they can only depict the bucco-oral dimension of the mandibular body, but not that of the alveolar ridge, which is actually more relevant for dental implant insertion. Currently, periapical radiographs and panoramic views are still considered as the main 2D imaging modalities for implant treatment planning purposes (Al-Ekrish 2018).

Periapical radiography

Due to a restricted FOV, periapical radiography is mainly used to assess the alveolar bone condition of a single or two adjacent edentulous sites prior to dental implant treatment, but seldom used for patients with multiple missing teeth. Periapical radiography can provide an initial assessment regarding the healing of extraction sockets, the presence of retained roots, remaining pathologies, and also the presence of

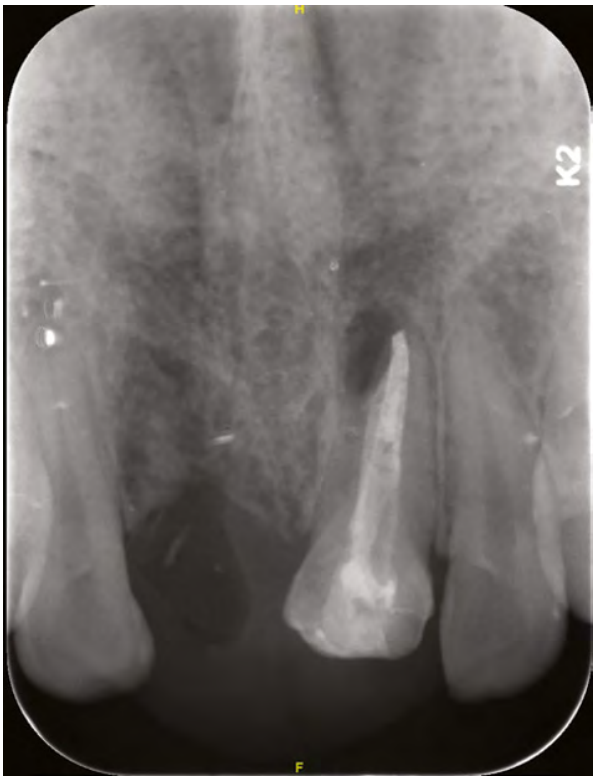

Fig. 23-23 This periapical image shows a reduced bone level at the edentulous site of the former tooth 11, and an apical radiolucency at the root-filled tooth 21.

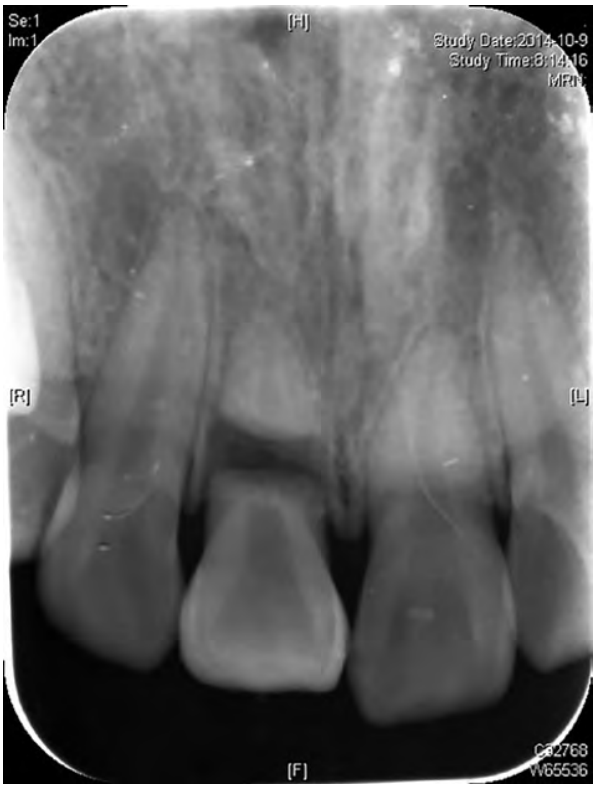

Fig. 23-24 This periapical image shows a wide fracture line on the root of tooth 11.

periapical lesions of adjacent teeth (Fig. 23-23). Based on its high spatial resolution, periapical radiography is an excellent tool for the assessment of bone structure, clearly displaying trabecular bone at the edentulous sites. Moreover, periapical radiography can provide a useful initial view to evaluate the condition of traumatized anterior teeth when evaluating the prognosis of anterior maxillary teeth (Fig. 23-24). However, periapical radiography cannot provide cross-sectional views to display bucco-oral dimensions of the alveolar ridge at a proposed implant site. Furthermore, the distortion and magnification of a periapical image limits accurate linear distance measurements between the adjacent teeth and distances between the alveolar crest and boundaries of critical anatomic structures, such as the floor of the nasal cavity and maxillary sinus, lingual undercuts of the mandible, or the upper limit of the inferior mandibular canal. Therefore, periapical images should be interpreted with caution and always in combination with clinical findings, especially for cases with limited bone volume at the edentulous sites.

Panoramic views

For patients with multiple missing teeth or a completely edentulous maxilla/mandible, panoramic images are considered as the first-line imaging modality to provide an estimate of the condition of the remaining teeth and/or bone volume (Mallya & Lam 2019). Moreover, the broad FOV depicted by panoramic images is able to visualize the entire floor of the nasal cavity and maxillary sinus, inferior mandibular canal, and mental foramen, which is helpful for the assessment of the vertical bone dimensions at all edentulous sites (Fig. 23-25). This is valuable information for the planning process of multiple implants in one single image. Similar to periapical images, panoramic views cannot provide accurate linear measurements, information about bucco-oral dimension of the alveolar ridge, and 3D evaluation and special visualization of critical anatomical structures. Using a standardized metallic ball – for example with a diameter of 5 mm – during panoramic image taking can help clinicians to assess bone dimensions by helping to calculate the magnification factor of panoramic images. Furthermore, the presence of superimposition artifacts of the spinal cord in panoramic images can affect the assessment of the anterior edentulous site in the maxilla and mandible.

Three-dimensional modalities

Three-dimensional diagnostic imaging modalities including MDCT and CBCT allow for an accurate visualization of anatomical structures or pathological changes in the maxillofacial region, and therefore are recommended when periapical and panoramic radiographs are both unable to provide sufficient diagnostic information for implant treatment planning. Considering the similar measurement accuracy between MDCT and CBCT as well as their cost-effectiveness, radiation dose, and availability, CBCT is more frequently used in implant dentistry (Bornstein *et al*. 2017).

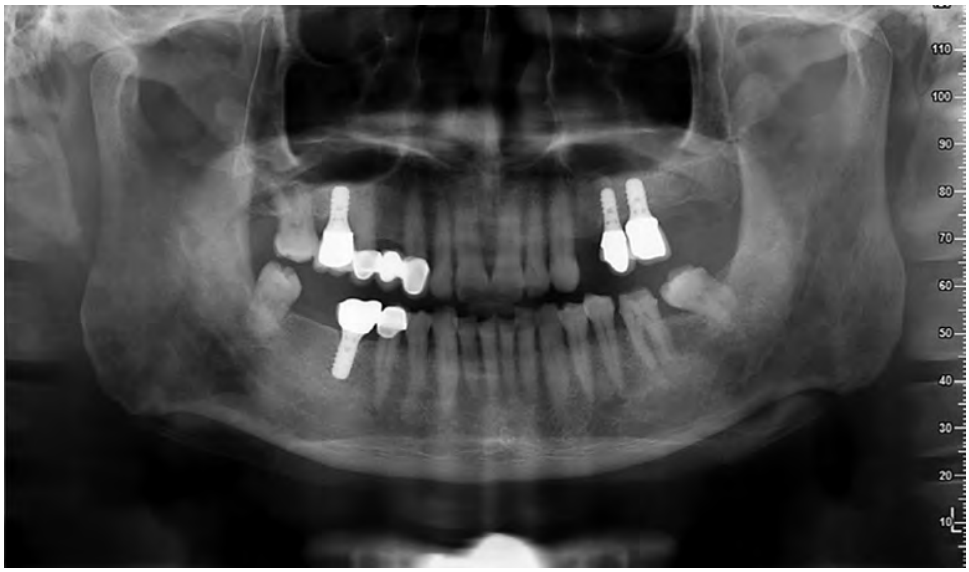

Fig. 23-25 The panoramic view enables an overview of all edentulous regions including an initial assessment of the available vertical bone dimensions. Furthermore, peri-implant bone conditions of already inserted implants and vital anatomical structures, including the mandibular canal or maxillary sinuses, can be evaluated.

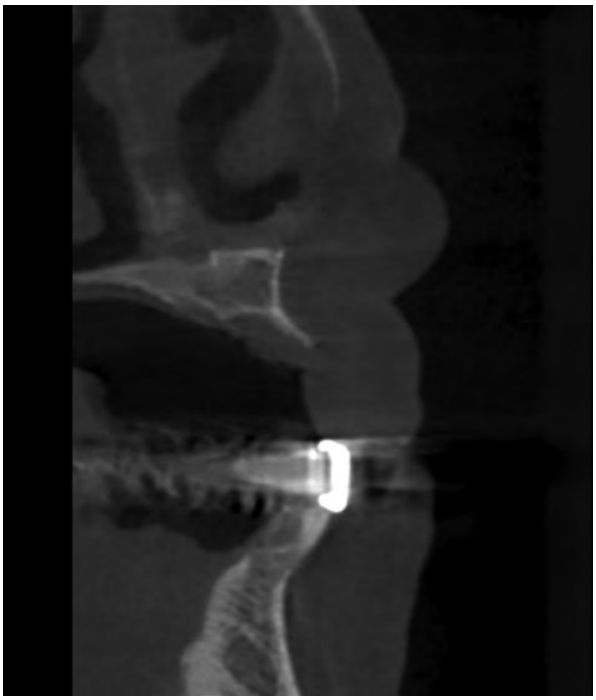

Fig. 23-26 The sagittal cone beam computed tomography plane shows the residual bone height in the anterior maxilla in a patient with an edentulous maxilla. A severely resorbed alveolar crest with a so-called knife-edged morphology can be seen.

In the anterior maxilla, the residual bone height (RBH) is considered as the vertical distance between the alveolar crest and the floor of nasal cavity, which is usually measured on sagittal or coronal CBCT planes (Fig. 23-26). The RBH in the anterior maxilla is usually sufficient in patients for the placement of conventional dental implants. Insufficient RBH in the anterior maxilla is mainly seen in patients with severe periodontitis or maxillary hypoplasia, or patients having experienced trauma or surgery. The residual bone width (RBW) in the anterior maxilla is the bucco-oral dimension of the alveolar ridge, which is also usually measured on sagittal CBCT planes. Compared with the RBH, the RBW in the anterior maxilla is frequently insufficient for implant placement without any simultaneous or staged bone augmentation procedures due to natural buccal ridge concavity or buccal bone resorption after tooth extraction. A knife-edged alveolar ridge is not infrequently observed in this region and presents as a narrow alveolar crest along with a relatively wide alveolar base (Fig. 23-26). In order to achieve an ideal aesthetic gingival contour around an implant placed in the anterior maxilla, the level of the alveolar crest at the edentulous site in relation to the level of the proposed implant shoulder and also the neighboring teeth should be carefully assessed during preoperative CBCT examinations. Furthermore, the nasopalatine canal is also a critical anatomic structure in proximity to the maxillary central incisors (Fig. 23-27). The morphology and dimensions of the nasopalatine canal vary considerably, but generally males present with higher values than females. A large nasopalatine canal may occupy the space needed for a planned implant at the site of the maxillary central incisor necessitating complex grafting procedures (Urban *et al*. 2015).

In the posterior maxilla, the maxillary sinus is the main anatomic structure that may affect the planning of implant treatment. The RBH in the posterior maxilla is the distance between the alveolar crest and the floor of the maxillary sinus, which is usually measured on coronal CBCT planes (Fig. 23-28). The RBW in the posterior maxilla is the bucco-oral dimension of the alveolar ridge, which is also measured on coronal CBCT planes. Due to resorption of the alveolar crest following loss of the posterior teeth, the RBH in the posterior maxilla is frequently insufficient for the placement of dental

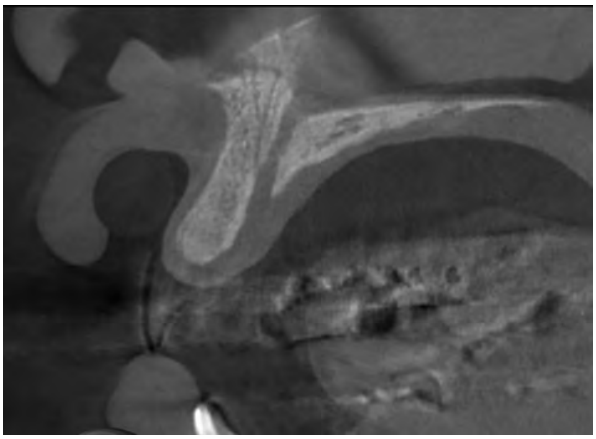

Fig. 23-27 The sagittal cone beam computed tomography view taken between teeth 11 and 21 exhibits the nasopalatine canal and its relation to the alveolar ridge.

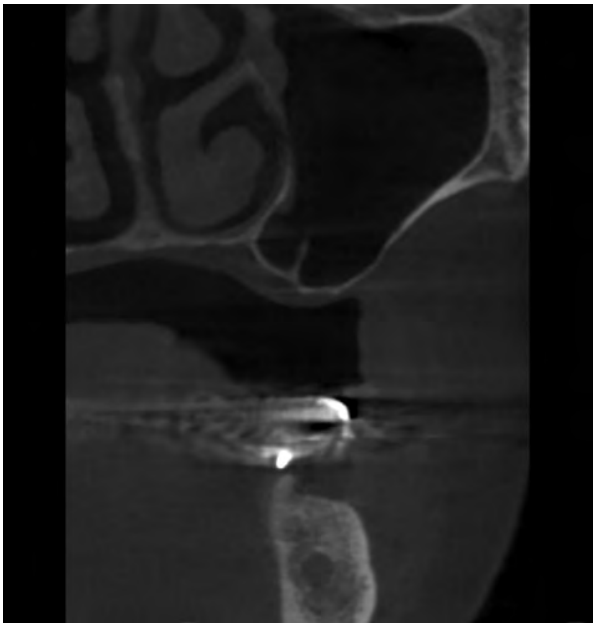

Fig. 23-28 The coronal cone beam computed tomography view shows a severely atrophic posterior maxilla, nicely pneumatized conditions of the maxillary sinus, and a septum located on the floor of the sinus. Furthermore, the outline of the mandibular canal can clearly be seen in the lower jaw.

implants with regular lengths (e.g. 8–10 mm). For those cases, sinus floor elevation (SFE) procedures including the lateral window and transcrestal osteotome approaches are recommended prior to or simultaneously with implant placement (Danesh-Sani *et.al* 2016). Before performing SFE procedures, the condition of the maxillary sinus needs to be assessed. Furthermore, the RBH at the edentulous site, morphology of the maxillary sinus floor (e.g. a flat floor or presence of maxillary sinus septum), and the presence/absence of sinus pathologies should be evaluated and diagnosed on CBCT images (Vogiatzi *et al*. 2014; Bornstein *et al*. 2016). Sinus pathologies such as a mucosal thickening, mucous retention cysts, accessory maxillary ostia, and obstruction of the primary maxillary ostium can be clearly detected on CBCT images (Fig. 23-29). These sinus pathologies were reported to have an association with maxillary sinusitis that may eventually result in postoperative infection and early implant loss following SFE procedures (Yeung *et al*. 2019b; Hung *et al*. 2020b). The thickness of the lateral wall of the maxillary sinus and the presence including location of the superior alveolar artery should be specifically assessed prior to any lateral window approach. The superior alveolar artery may course through the outer/inner surface of the sinus wall or be present inside the bone itself (Fig. 23-30). The course of the artery may complicate the preparation of the bony window, and even result in severe intra- or postoperative hemorrhages (Danesh-Sani *et al*. 2017). It has been reported that cutting a superior alveolar artery of a diameter greater than 2 mm may very likely cause severe bleeding (Guncu *et al*. 2011). Therefore, the presence and exact location of the superior alveolar artery in relation to the lateral sinus wall should be thoroughly assessed on CBCT scans prior to SFE surgery. The preoperative FOV of the posterior maxilla should contain the alveolar bone of all potential implant sites, the adjacent alveolar bone, and the lower third of the maxillary sinus without mandatory inclusion of the primary ostium.

The anterior mandible has been considered as a relatively safe zone for implant placement due to a lack of critical anatomical structures. However, penetrating the lingual cortex of the alveolar ridge in the anterior mandible with a surgical bur may damage the sublingual and submental arteries. This damage may result in immediate or delayed life-threatening hemorrhaging as the tongue will be pushed back towards the throat, with a risk of suffocation (Tomljenovic *et al*. 2016). Therefore, the morphology of the alveolar ridge and mandibular base of the patient should be carefully evaluated on CBCT images to prevent penetration of the lingual cortex during the drilling procedure (Fig. 23-31). The preoperative FOV of the anterior mandible should contain at least the region of both mental foramina including the whole vertical height of the mandible.

In the posterior mandible, the mandibular canal and mental foramen are the main anatomical landmarks that affect implant placement. The RBH in the posterior mandible is calculated as the distance between the alveolar crest and upper boundary of the mandibular canal, which is usually measured on coronal CBCT planes (see Fig. 23-28). The morphology of the mandibular canal and mental foramen can be clearly observed on CBCT images. The location of the mental foramen of patients with a severely atrophic mandible is often located close to the crest of the alveolar ridge (Fig. 23-32). In these cases, an incision on the alveolar ridge or detachment of the mucosa may injure the mental nerve, resulting in postoperative paresthesia. Furthermore, the location of the sublingual fossa should also be carefully assessed to prevent penetration of the lingual cortex during the drilling procedure, which will result in similar consequences to those observed in the anterior mandible (Fig. 23-33).

Although MDCT imaging is not frequently used for implant treatment planning today, it is considered as a useful tool specifically to evaluate the density

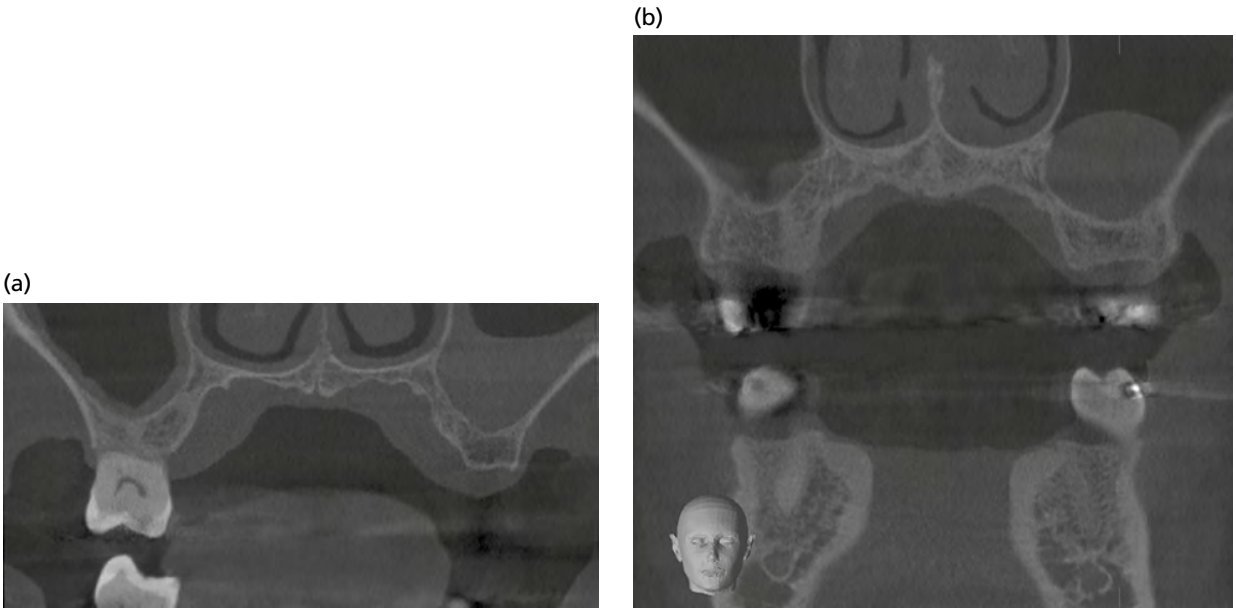

Fig. 23-29 (a) Slight and severe mucosal thickening can be respectively seen in the right and left maxillary sinuses. (b) A dome-shaped mucosa configuration on the floor of the left maxillary sinus can be seen, which is typical for a mucosal retention cyst. In the right maxillary sinus, the mucosal thickening seems to be confined to the floor.

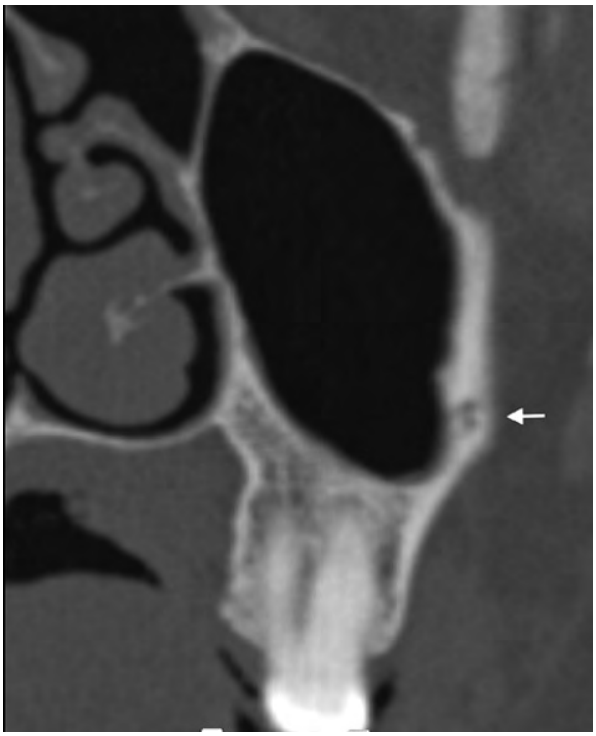

Fig. 23-30 The bony canal for the superior alveolar artery (arrow) can be seen in the lateral wall of the maxillary sinus.

of alveolar bone at a proposed implant site. The Hounsfield Unit (HU) is a standardized index with values proportional to the degree of X-ray attenuation by the body tissue. HUs are routinely used in MDCT for evaluating the degree of bone calcification or tissue densities (Razi *et al*. 2019). For CBCTs grey level values are used rather than HUs, which correspond to the X-ray intensity at that location during a particular exposure of the sensor. However, the applicability of grey levels in CBCT for bone density evaluation is hampered owing to excessive scattered radiation, artifacts, and noise resulting from the use of a cone-shaped beam in CBCTs (Pauwels *et al*. 2015). Thus, the quantitative evaluation of bone density on CBCT images is not recommended, especially to compare the differences in the grey level values in different CBCT units (Corpas Ldos *et al*. 2011; Razi *et al*. 2019). If there is a need to assess bone density, MDCT imaging should be recommended.

Preoperative FOV of the posterior mandible should contain the region of the potential implant sites including the adjacent teeth or bone and the whole vertical height of the mandible. If necessary or discussed for implant treatment planning, the donor site of autogenous block grafts should be also visualized.

For implant treatment planning with merged intraoral scans the complete crowns of the adjacent teeth should be visualized as the respective tooth cusps are frequently used as landmarks for matching of CBCT/MDCT and intraoral scans. See the section "Guided implant surgery" for more details and recommendations regarding diagnostic imaging for guided implant surgery.

Recommendations during and after implant placement (follow-up)

Diagnostic images taken during implant surgery are mainly used to evaluate drill position or dealing with intraoperative complications. Postoperative radiographic examinations are usually performed for prosthetic purposes (e.g. to check abutment/crown fit), and to evaluate the status of the placed dental implants during follow-up and maintenance (e.g. assess peri-implant bone conditions). Postoperative radiographs should be taken with the modality of follow-up, which is mostly 2D radiographs (see later).

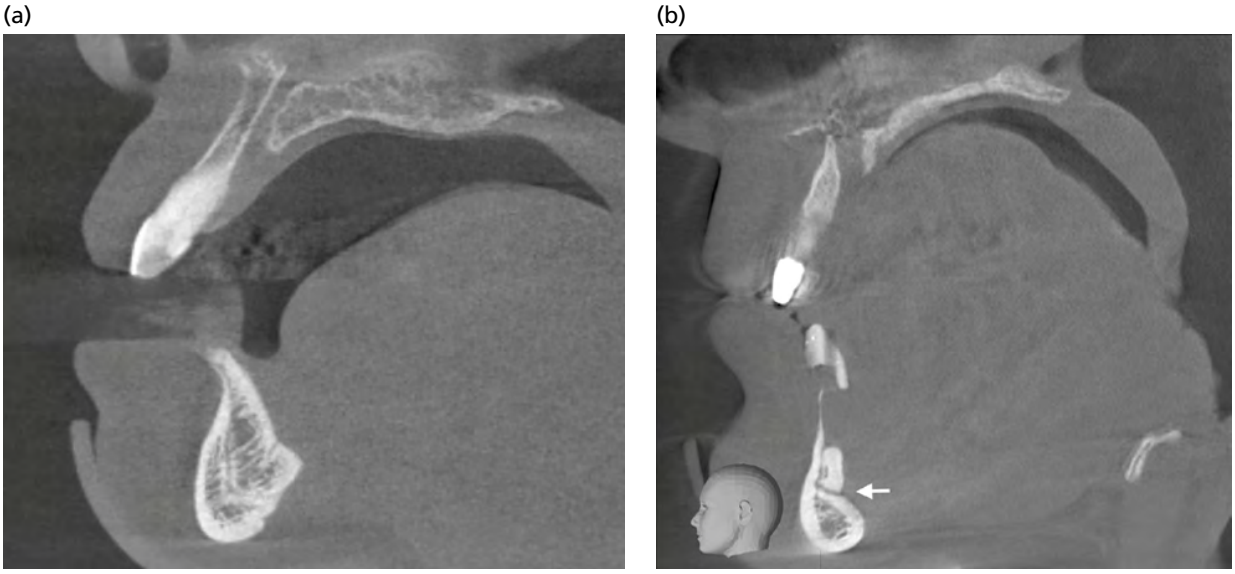

Fig. 23-31 Different morphologies and anatomical landmarks of the mandibular alveolar ridge as seen in cone beam computed tomography (CBCT) scans. (a) The sagittal CBCT image shows a narrow ridge and a wider alveolar base (pyramidal shape). (b) The CBCT image shows a thin, razor-edged remaining alveolar crest and a lingual canal in the symphyseal region (white arrow).

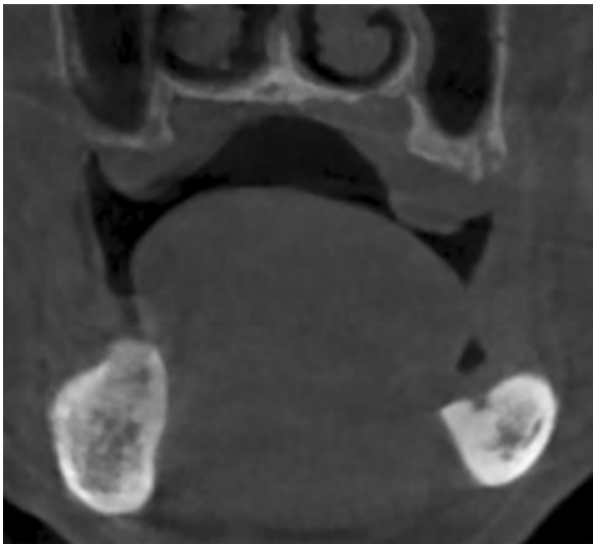

Fig. 23-32 The cone beam computed tomography scan (coronal view) exhibits a severely atrophic posterior mandible especially on the left resulting in the mental foramen to be located at the cranial aspect of the residual alveolar ridge.

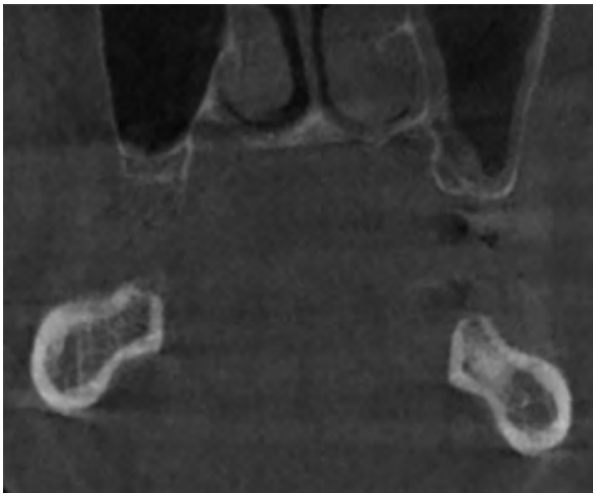

Fig. 23-33 This cone beam computed tomography scan (coronal view) shows extensive sublingual fossae on the lingual surface of the mandibular base on both sides. This morphology of the mandible might be a limiting factor for prosthetically driven implant placement.

Two-dimensional modalities

Often, postoperative diagnostic images are taken immediately after surgery to serve as a baseline record of the placed implants. Nevertheless, it has to be mentioned that there is no evidence available showing any benefit to the patient to justify routine 2D or 3D imaging after intervention, when there is no sign or symptom of any potential complication. Due to the high spatial resolution, periapical radiography is recommended as the optimal imaging modality used to record the level of the alveolar crest around the placed implants and the interface between the implant and bone tissue. Panoramic radiography is also commonly used for documentation, especially for patients who have received multiple implants. If there are more than five intraoral radiographs one should consider choosing a panoramic radiograph for radiation protection purposes (Dula *et al*. 2001). However, the level of the alveolar crest and bone density may not be accurately assessed in panoramic images owing to the lower spatial resolution and the distortion, magnification, and overlapping phenomena.

For a novice implant surgeon, intraoperative periapical and even segmented panoramic images might be helpful to evaluate the correct position of the pilot drill (Fig. 23-34). These images allow the surgeon to correct an inappropriate drill position before the remaining osteotomy steps. Occasionally, it is possible for patients to accidentally swallow or aspirate

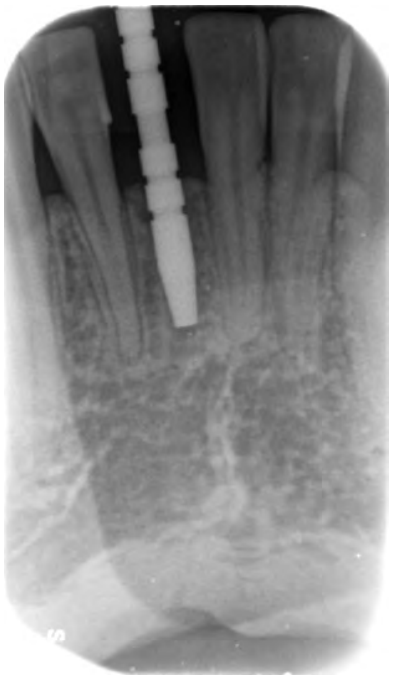

Fig. 23-34 The periapical image shows insertion depth and also the position of the prospective implant with the help of a paralleling guide pin.

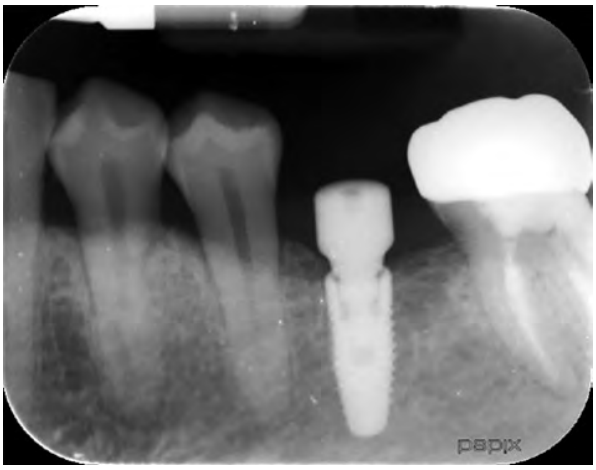

Fig. 23-35 This periapical image highlights an incomplete seating of the healing abutment on the inserted implant presenting as a radiolucent gap between the implant and the abutment.

tiny instruments (such as a screwdriver or a cover abutment) used in implant surgery. If this occurs, the patient should be referred for a chest X-ray to determine whether the instrument was aspirated into the lung.

During the prosthetic phase, periapical and bitewing images are regularly used to assess correct osseointegration of the placed implant and the seating of a prosthetic abutment, frame, or prosthesis (Figs. 23-35, 23-36, 23-37, 23-38). After placement of a prosthesis, a periapical image is recommended to serve as a record for comparison with follow-up images.

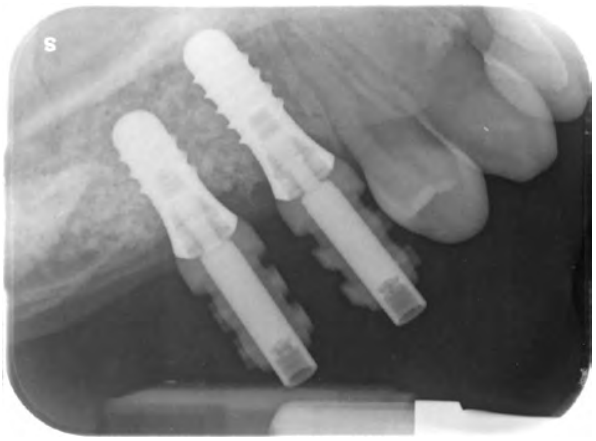

Fig. 23-36 This periapical image shows the seating of the impression posts on the implants presenting as close marginal contact between the implant and the posts.

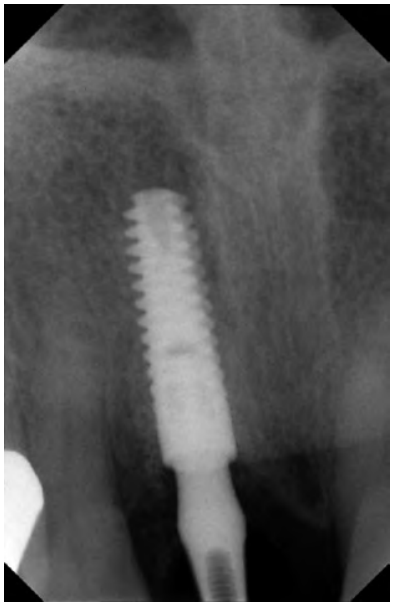

Fig. 23-37 The periapical image shows complete seating of the final abutment on the implant presenting as close marginal contact between the implant and the abutment.

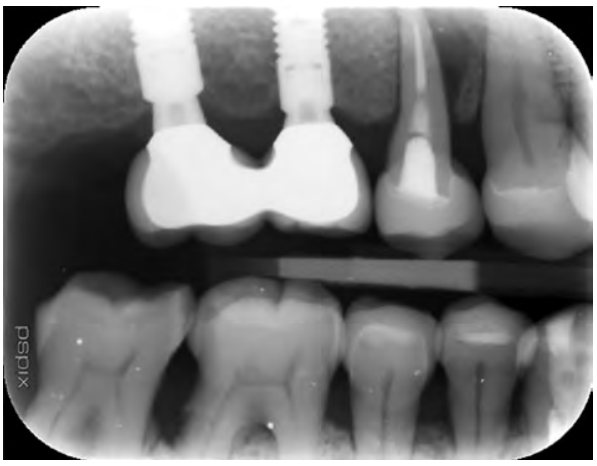

Fig. 23-38 The bitewing radiograph shows complete seating of the prosthesis (splinted crowns) on the implants presenting as a close marginal contact between the implants and the prosthesis.

In the maintenance phase, annual imaging examination of the marginal bone loss is recommended for implant patients. This recommendation is of particular relevance for patients with present risk factors such as tobacco smoking, inefficient oral hygiene use, or a history of periodontitis. Periapical radiographs are considered as the optimal imaging modality for follow-up. Justification for follow-up has to be based on clinical parameters like probing depth and inflammatory scores.

Three-dimensional modalities

MDCT/CBCT imaging is not recommended for routine follow-up examinations due to the high radiation dose, costs, and also implant-related artifacts. The severity of implant-related artifacts increases as the distance between two implants decreases, and thus the bone area between adjacent implants is difficult to assess. The reason for referrals for a MDCT/CBCT examination during and after implant surgery commonly results from the occurrence of intraoperative/postoperative complications, such as the displacement of an implant (for example into the maxillary sinus or damage of the mandibular canal), implant fracture, ailing/failing implants, and special cases of peri-implantitis (Fig. 23-39). For cases when 3D imaging seems appropriate, CBCT scans are usually recommended.

Peri-implant disease

Peri-implant disease includes peri-implant mucositis and peri-implantitis. Peri-implant mucositis is described as the presence of inflammation in the mucosa around dental implants without supporting bone loss. Peri-implantitis is defined as the phase following peri-implant mucositis, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone tissue. Once the presence of peri-implantitis is identified, surgeons may consider resective and regenerative peri-implant treatment, or explantation and replacement of the implant. Periapical radiography and CBCT are the most common diagnostic imaging modalities to evaluate peri-implant bone defects. It is reported that periapical radiography and CBCT imaging exhibit comparable diagnostic accuracy in the assessment of peri-implant bone defects. Both modalities present a clinically acceptable diagnostic accuracy with sensitivity and specificity rates ranging from 59% to 67% for the detection of peri-implant bone defects (Bohner *et al*. 2017). Size and type of peri-implant bone defect are considered as influencing factors associated with diagnostic accuracy. Due to a higher spatial resolution, periapical radiography is considered more useful to detect small defects (Dave *et al*. 2013), but it may only be used to detect such bone defects at the mesial and/or distal sites of implants. In contrast, CBCT imaging can evaluate all types of peri-implant bone defects due to its 3D nature (Fig. 23-40). Although decreasing the voxel size of CBCT images can increase image quality that may be helpful to detect a small bone defect, it will also increase the dose of radiation exposure to the patient. However, metal artifacts seen on CBCT images that present as bright streaks radiating from the metallic restoration and implant and darkening of certain areas may hamper the evaluation of the status of implant osseointegration and bone defects around implants. Therefore, there is a general consensus that the status and condition of peri-implant

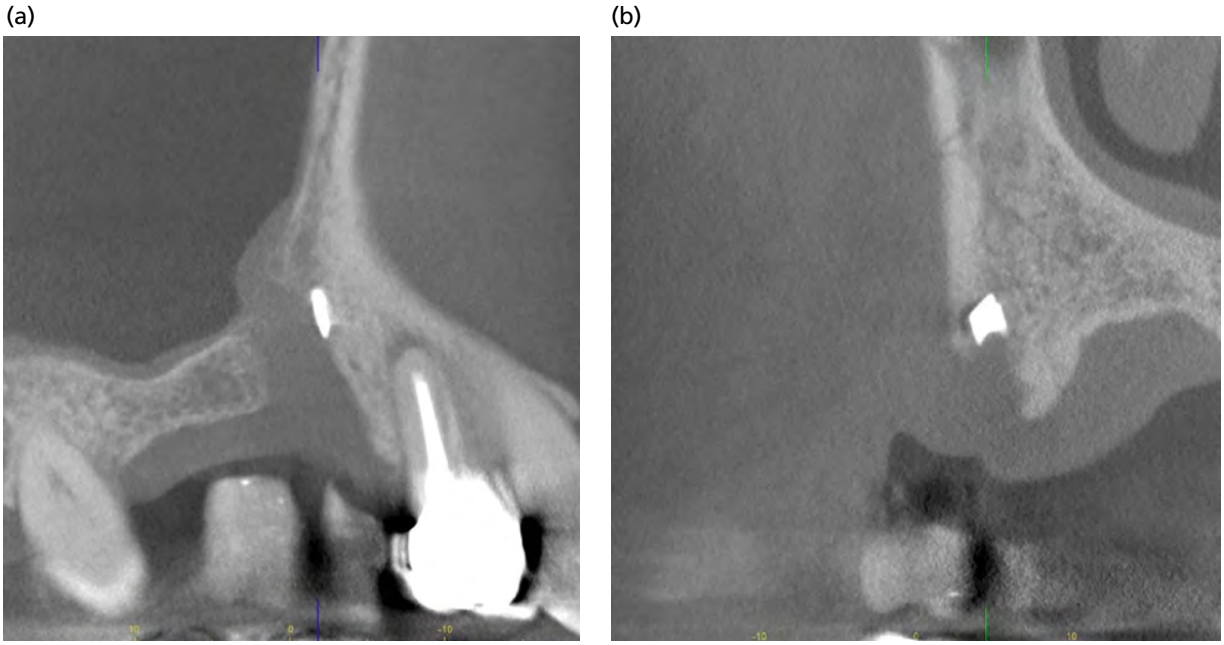

Fig. 23-39 The cone beam computed tomography images show a fragment of the implant remaining in the extraction socket in different cross-sectional views. (a) Sagittal. (b) Coronal.

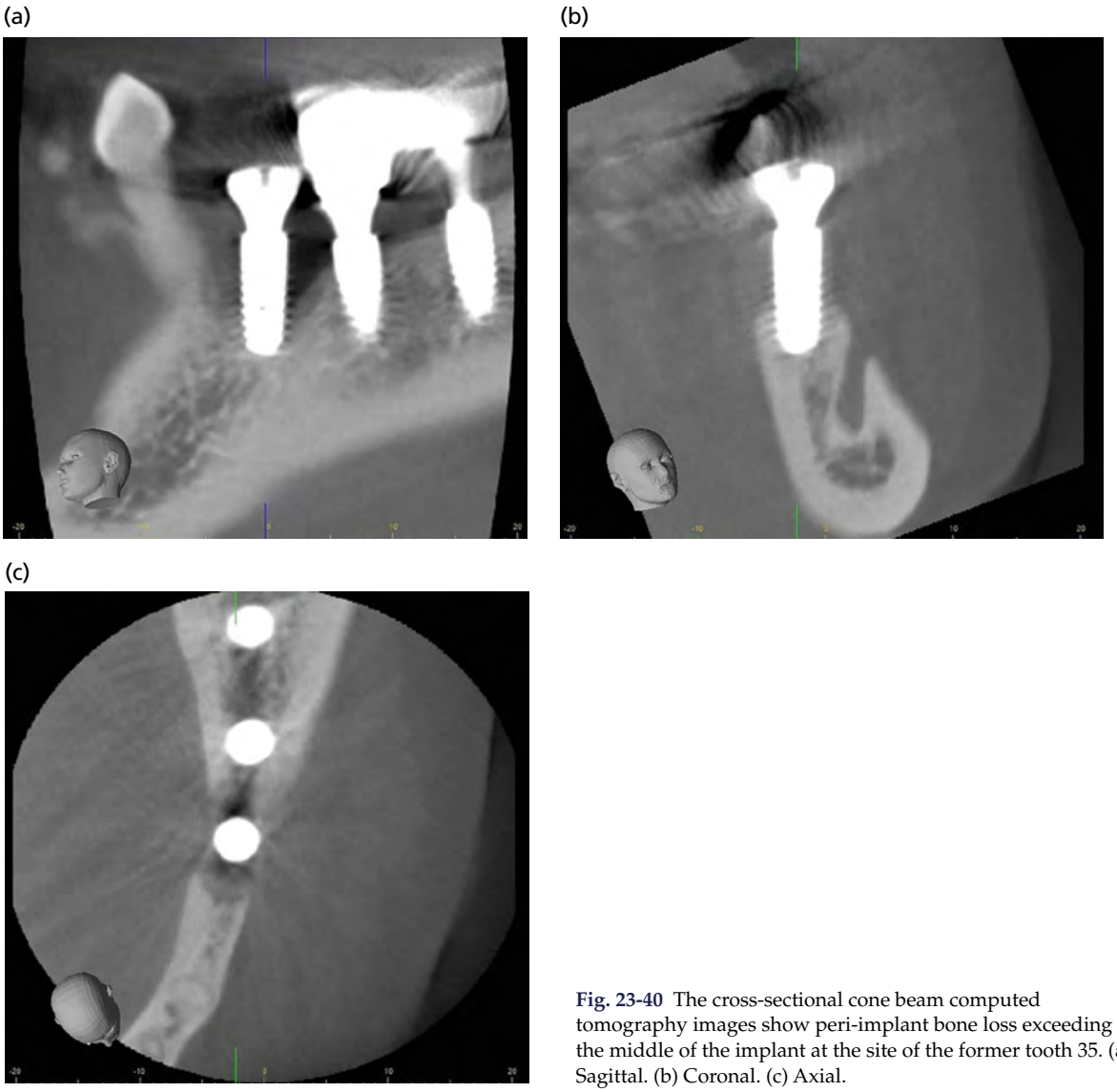

Fig. 23-40 The cross-sectional cone beam computed tomography images show peri-implant bone loss exceeding the middle of the implant at the site of the former tooth 35. (a) Sagittal. (b) Coronal. (c) Axial.

bone should be evaluated ideally by using periapical images (Fig. 23-41). A uniform radiolucent lining may be clearly observed around an ailing/failing implant (Fig. 23-42). A CBCT examination is recommended when 2D imaging does not suffice in patients with clinical signs and symptoms of peri-implant disease, and where the added imaging information might be influential for treatment planning. Therefore, the use of CBCT scans for the evaluation of peri-implant disease should be carefully assessed based on the ALARA/ALADA principle to protect patients from unnecessary exposure to ionizing radiation.

Recommendations for special indications and techniques

Guided implant surgery

Preoperative implant planning is essential to achieve an optimal treatment outcome. The accurate placement of dental implants in the planned position is one of the biggest concerns for surgeons. In the past several years, the conventional plaster-based surgical stent was frequently used to guide surgical implant placement. However, plaster-based surgical templates are mainly recommended for marking the entry point at the planned implant and also to control its angulation. Recent developments in the digital workflow, CAD/CAM technologies, and also real-time surgical navigation techniques have greatly increased the use and also acceptance of guided implant surgery, and it is widely considered as a reliable and accurate method to place implants as much in line with the planned position as possible (Nickenig *et al*. 2010; Wang *et al*. 2018; Zhou *et al*. 2018; Pellegrino *et al*. 2019). Diagnostic images are the basis of modern guided implant surgery as they provide essential imaging information. Guided implant surgery can be categorized into static and dynamic techniques. The static guided surgery technique is defined as the use of a computer-aided design and manufacturing (CAD-CAM) surgical

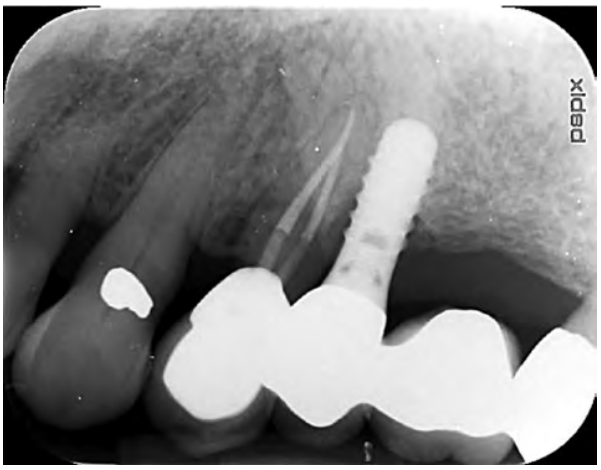

Fig. 23-41 The periapical radiograph exhibits bone loss at the mesial and distal aspects of the implant.

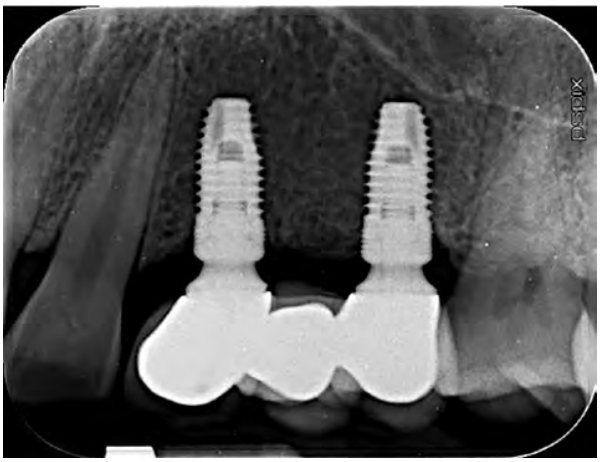

Fig. 23-42 The periapical radiograph shows a uniform radiolucent lining around both implants. Also noteworthy is the incomplete seating of the bridge work on the implants.

template to guide implant placement. The CAD-CAM surgical template is first designed virtually in the respective implant planning software using 3D image datasets including preoperative CBCT images, intraoral scan images, and/or images of the patient's stone model. A fusion of these images in the implant planning software can provide information about the contour of the soft tissue and bony structures to plan the exact future implant position. Moreover, the operator can manually set up the missing teeth or dentition in the software. This information allows implant surgeons to virtually design the position of the proposed implants taking into consideration the bone and soft tissue condition and the position of the prosthesis, thus perfectly adhering to the concept of prosthetic-driven implant planning. For completely edentulous patients, a specific double CBCT scan technique is commonly used to acquire sufficient information. This technique requires one scan of the patient wearing a complete denture embedded with several radiopaque makers, and another scan of the complete denture. Merging of the two CBCT images allows 3D evaluation of the position of the artificial teeth on the denture, bony structures, and the soft tissue contour in between.

To ensure maximum accuracy of the CAD-CAM surgical template, most of the commercially available implant planning software require that the slice thickness of the images should be less than 1 mm. Some software programs do not allow the loading of 3D image datasets with slice thicknesses that are too large. The slice thickness of CBCT images generally is between 0.1 mm and 0.4 mm, which meets the requirements of all available software. On the other hand, the slice thickness of MDCT ranges from 0.625 mm to 2.5 mm. Reducing the slice thickness of MDCT will significantly increase radiation dose. As a result, CBCT is recommended as the main imaging modality used for producing CAD-CAM surgical templates.

Dynamic guided implant surgery is a novel and emerging technique that allows for a complete 3D visualization of trajectories for implant placement through real-time analysis of the position of the surgical bur in relation to the planned trajectories exhibited on CT/CBCT images (Hung *et al*. 2016, 2017a). The application of this technique only needs one preoperative CT/CBCT scan of the patient who is wearing several invasive/non-invasive registration markers in the maxillofacial region. Subsequently, the CT/CBCT scan is used for planning of the implant placement trajectory. During surgery, the infrared camera of the navigation system keeps tracking the location of the patient and surgical instruments through the reflective registration markers in the reference array. The reference array functions to register the patient and surgical instruments to the CT/CBCT data, which enables real-time guided drilling procedures by exhibiting the trajectory, surgical instruments, and adjacent anatomic structures on the CT/CBCT images (Fig. 23-43) (Mandelaris *et al*. 2018; Wu *et al*. 2019).

Block grafting procedures

Autogenous block grafting is considered as a gold standard procedure to reconstruct severely deficient alveolar ridges in both the bucco-oral and vertical dimensions (Sakkas *et al*. 2017). Intraorally, the most common donor sites include the maxillary tuberosity, mandibular symphysis, retromolar area, and mandibular ramus. Before the surgery, the size of the deficiency should be carefully assessed to help harvest a similarly sized bone block from the donor site. Furthermore, critical anatomical structures in the proximity of the donor and recipient sites should also be carefully assessed to avoid intraoperative and postoperative complications, such as severe bleeding or paresthesia. Potential 3D diagnostic imaging of the donor and recipient sites for such cases comprises MDCT and CBCT. A second MDCT/CBCT scan around 6 months after the block grafting surgery is often also recommended to evaluate bone graft integration prior to implant placement.

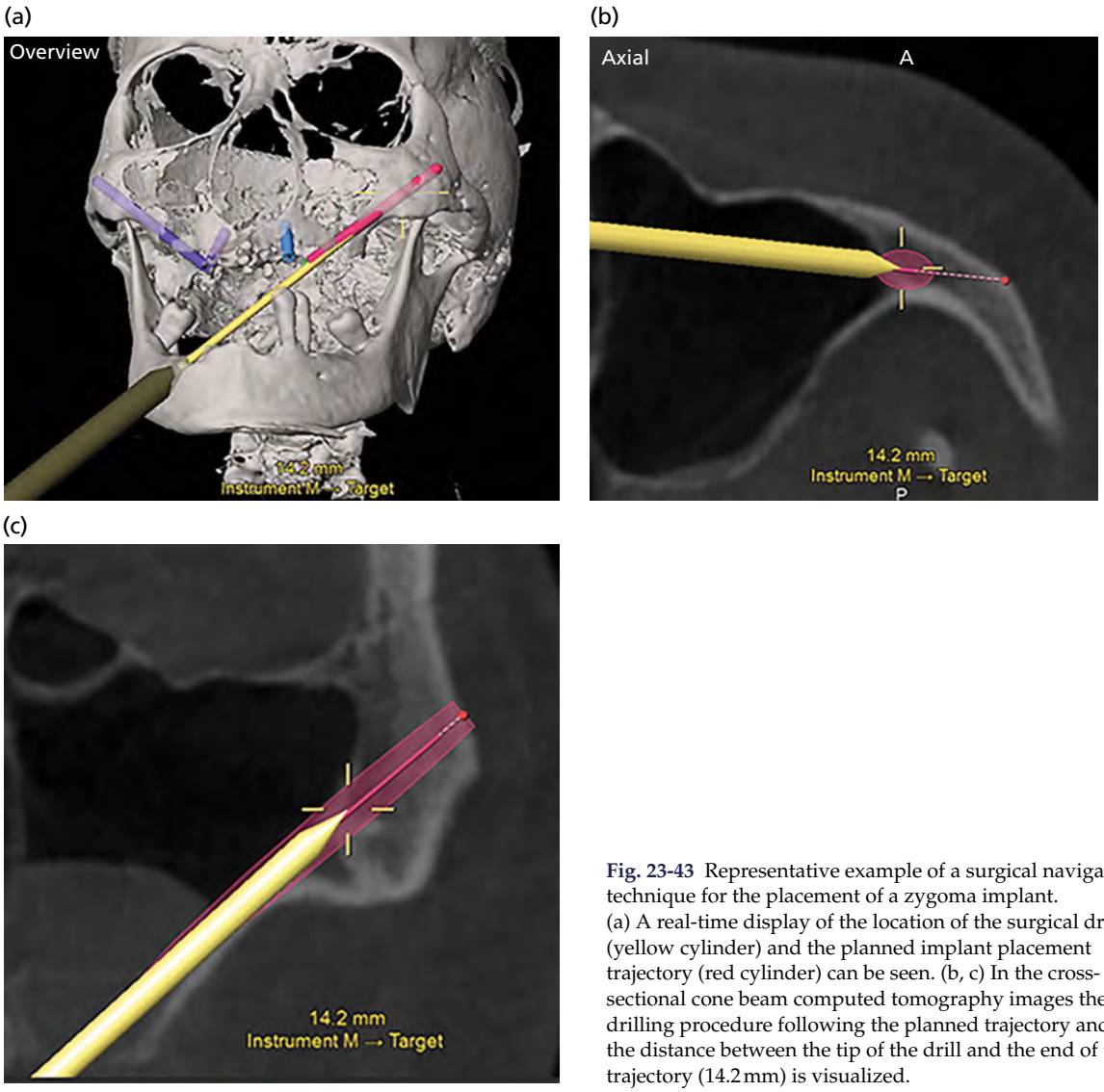

Fig. 23-43 Representative example of a surgical navigation technique for the placement of a zygoma implant. (a) A real-time display of the location of the surgical drill (yellow cylinder) and the planned implant placement trajectory (red cylinder) can be seen. (b, c) In the cross-sectional cone beam computed tomography images the drilling procedure following the planned trajectory and the distance between the tip of the drill and the end of the trajectory (14.2 mm) is visualized.

Zygoma implants

Zygoma implants are an alternative option for completely edentulous patients with severely atrophic maxilla where the placement of the conventional implants without major additional bone augmentation procedures is not feasible or possible. The planning for the zygoma implant trajectory should be made by the use of an implant planning software and MDCT/CBCT image datasets. The implant trajectory generally passes through the alveolar ridge, maxillary sinus, and zygomatic bone. An imaging evaluation only on coronal, sagittal, and axial planes of MDCT/CBCT scans cannot clearly display the complex trajectory, which may increase the risk of intraoperative complications, such as penetrating into the infratemporal fossa or lateral wall of the orbit. Thus, by using implant planning software a 360-degree observation along the axis of the planned implant is possible. This can also exhibit the portion of the implant inserted into the zygoma to optimize the bone–implant contact area and overall stability, which may be associated with the survival of the implant (Hung *et al*. 2017b). Furthermore, the presence of zygomatic nerves inside the zygoma should also be preoperatively observed on MDCT/CBCT images to avoid postoperative paresthesia. For patients with severely reduced width of the alveolar ridge, the coronal portion of a zygoma implant is very likely to lack buccal bone coverage. In this case, a flattening of the alveolar ridge, an additional horizontal bone augmentation procedure, or a more palatal placement of the implant should be considered. The relationship of the middle portion of the implant towards the lateral wall of the maxillary sinus can be classified as an intrasinus, through-sinus, or extrasinus situation (Fig. 23-44). For intrasinus and through-sinus situations, assessment of health or pathology of the maxillary sinus is mandatory prior to surgery.

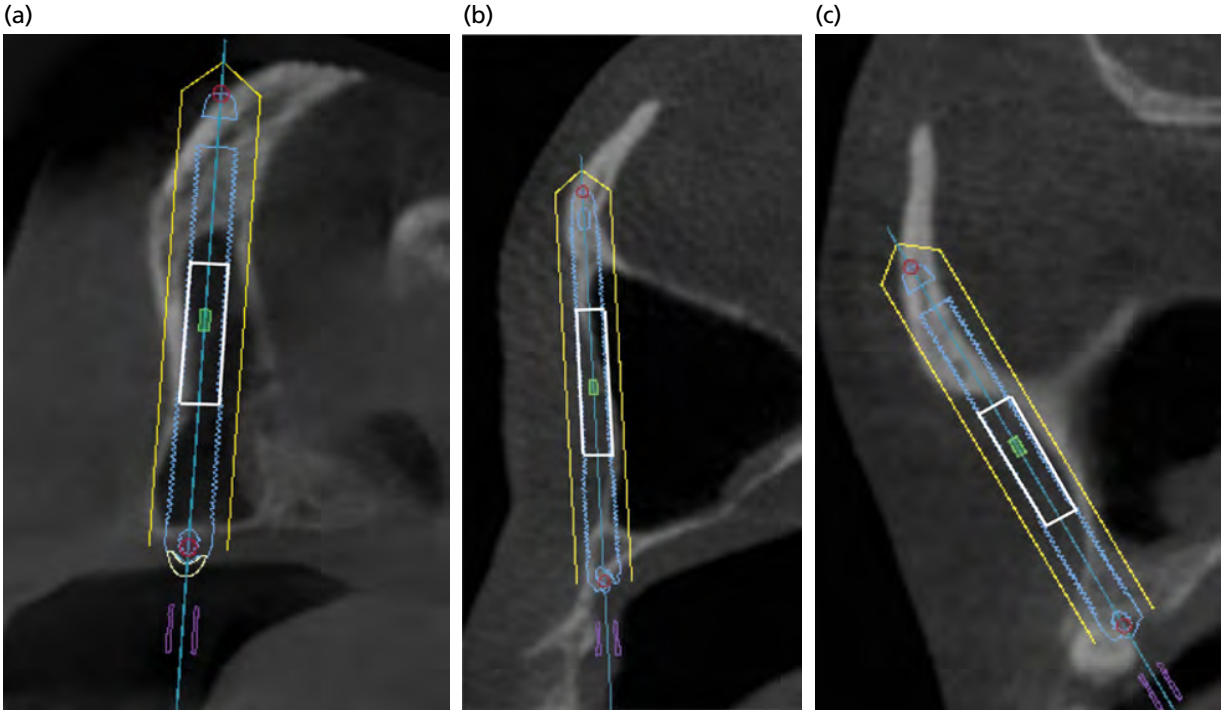

Fig. 23-44 Cross-sectional cone beam computed tomography images demonstrating the relationship of the middle portion (white rectangle) of the zygoma implant towards the lateral wall of the maxillary sinus: (a) intrasinus, (b) through-sinus, and (c) extrasinus situation.

Future trends and developments

Ultrasound

With the advent of intraoral transducers for ultrasound, research and potential applications in various fields of dental medicine have been boosted (Bhaskar *et al*. 2018). For the preoperative phase in oral implantology, ultrasound imaging is emerging as a promising tool to evaluate the phenotype of soft tissue (e.g. gingivae). In addition, ultrasound imaging has been suggested as a chairside screening device for an initial assessment of the surface morphology and buccooral dimension of the alveolar ridges at edentulous sites. In the intraoperative phase, ultrasound imaging may be used to identify the location and morphology of critical structures located on the surface of jaws, such as the greater palatine foramen, the mental foramen in edentulous patients with severely atrophied mandibles, or lingual foramina. During maintenance, ultrasound imaging may be useful to monitor marginal bone loss to identify potential peri-implantitis at an early stage without the use of conventional X-rays. All these are promising clinical applications of ultrasound imaging in oral implantology, but there is still a clear need for more research and device modifications to withstand the test of implementation in daily practice in the near future.

Magnetic resonance imaging

In the past decade, the application of MRI in implantology treatment has been mainly reported for the detection and evaluation of the mandibular canal and the neurovascular bundle from the adjacent trabecular bone, when it cannot be clearly identified on panoramic views, MDCT, or CBCT scans (Gray *et al*. 2003). However, the long imaging time of up to 30 minutes, inadequate spatial resolution with a slice thickness of 2–4 mm, the footprint of the devices, the technical expertise needed to run and maintain MRI devices, their high general cost, and also severe metal artifacts due to oral restorations, limit the application in dental medicine and more specifically for implant treatment purposes. More recently, novel MRI protocols developed for planning of implant treatment have been proposed. These protocols have shown to be able to reduce the imaging time to less than 10 minutes and also to increase the spatial resolution. These improvements put MRI on the map as a possible alternative imaging modality to evaluate the quality and quantity of bone and soft tissues at edentulous sites including anatomical landmarks of neighboring teeth such as the CEJ (Flugge *et al*. 2016; Ludwig *et al*. 2016). In addition, an MRI dataset has been reported to be promising for the production of a CAD-CAM surgical template with a comparable accuracy to a CBCT-based template (Mercado *et al*. 2019). Moreover, it is reported that the diagnostic accuracy of MRI in the evaluation of peri-implant bone defects is comparable with CBCT (Hilgenfeld *et al* 2018). Based on the non-ionizing nature of MRI, these novel possibilities in the field of implantology treatment are promising and certainly warrant further research.

Diagnostic imaging and artificial intelligence in implantology

Currently, potential applications of AI techniques in the field of implant treatment are still at an early developmental phase. AI models proposed for automated identification of changes in bone density may have potential for the diagnosis of jawbone lesions prior to implant placement or be helpful when planning for immediate loading procedures. In addition, AI models proposed for automated tooth detection and numbering on dental X-rays may be helpful to identify edentulous sites for potential future implant insertion (Tuzoff *et al*. 2019). Furthermore, AI may assist or perform automated measurements of residual alveolar ridge dimensions at edentulous sites, and also proceed with the placement of virtual implants on 3D images. This could simplify manual procedures, such as the marking of critical anatomical structures and the placement of implants on the respective images in conventional digital treatment planning workflows. After importing 3D image datasets of the patient, including intraoral scans and 3D radiographic scans such as CBCTs to an AI planning program, it could autogenerate several planning options, and the implant surgeon may then choose the best, adjusting the position of the planned implant(s) to confirm the final plan prior to production of a CAD-CAM surgical template.

On the other hand, automated identification of bone destruction around dental implants during the maintenance phase may be helpful for the (early) diagnosis of peri-implantitis. Deep learning techniques may be capable of analyzing information stored in each pixel of 2D or 3D images to help detect lesions that cannot be seen by the human eye.

Conclusions and future outlook

Unlike other dental treatment, such as tooth extraction and caries removal, periodontology and implantology treatment require a relatively long treatment and follow-up period. During this period, several imaging examinations may be required for diagnosis, treatment planning, postoperative evaluation, and follow-up assessments. A lifetime follow-up including respective radiographs to assess the periodontal/peri-implant bone condition may be necessary for patients who are susceptible to periodontal disease. Therefore, dental practitioners should always follow ALARA/ALADA principles to reduce radiation dose exposure for each imaging examination to minimize the accumulated dose to the patient. Although MDCT and CBCT allow for the visualization and assessment of anatomic structures or pathological changes in 3D with high diagnostic accuracy and precision, 2D imaging examinations are still considered as the baseline and standard of care. Thus, 3D imaging modalities should only be chosen if conventional imaging techniques do not provide sufficient information for diagnosis and treatment planning purposes in individual cases. The application of non-ionizing imaging modalities, including ultrasound and MRI, could eventually eliminate radiation dose exposures to the patient for periodontal and implant-related purposes. However, for the time being, such techniques are still limited mostly due to cost, availability, and lack of evidence.

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Chapter 24

Patient-Specific Risk Assessment for Implant Therapy

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Introduction

From a patient's perspective the successful implant is esthetically acceptable, comfortable, low-cost, and functional. Practitioners usually discuss implant success in terms of level of marginal bone and absence of deep probing depths and mucosal inflammation. Although the two sets of criteria are not in conflict, they emphasize different points of view. During the consultation visit, before any care is delivered, the practitioner should discuss, based on patient-centered outcomes, what can be expected from placement of implants.

A final comprehensive treatment plan should be presented to the patient that includes all recommended dental therapy and alternative treatment options. The patient should also be informed about the sequence of the clinical procedures, risks and costs involved, and the anticipated total treatment time. This discussion between practitioner and patient is critically important in lowering the overall risk of treatment problems. Patients who understand what will be done, and why, are more likely to cooperate with the recommended treatment.

Systemic factors

Patient-based risk assessment begins with taking comprehensive medical and dental histories as well as conducting a complete examination of the candidate for implant therapy (see Chapter 22). A comprehensive medical history should include past and present medications and any substance used or abused. A standard medical history form filled out and signed by the patient is an efficient way to collect basic information (Fig. 24-1). This should always be followed by an interview to explore in more detail any potential medical risks of implant therapy. If any uncertainties remain regarding the patient's health after the interview, a written medical consultation should be obtained from the patient's physician.

Medical conditions

Osteoporosis

Osteoporosis is a complex group of systemic skeletal conditions characterized by low bone mass and microarchitectural deterioration of bone tissue.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

Osteoporotic bone is fragile and has an increased susceptibility to fracture. Primary osteoporosis is a common condition and is diagnosed when other disorders known to cause osteoporosis are absent. Secondary osteoporosis is diagnosed when the condition is related to, or occurs as a consequence of, osteoporosis-inducing circumstances. These might include diet (e.g. starvation, calcium deficiency), congenital conditions (e.g. hypophosphatasia, osteogenesis imperfecta), drugs (e.g. alcohol abuse, glucocorticoids), endocrine disorders (e.g. Cushing's syndrome), and certain systemic diseases (e.g. diabetes mellitus, rheumatoid arthritis). Osteoporosis is assessed using bone densitometry in which a patient's bone mass or bone mineral density (BMD) is determined. BMD refers to grams of bone mineral per square centimeter of bone cross-section and is expressed in units of g/cm^2.

Scientific evidence indicates that there are no convincing findings that dental implant placement is contraindicated in the osteoporotic patient (Otomo-Corgel 2012). Implants placed in individuals with osteoporosis appear to successfully osseointegrate and can be retained for years (von Wowern & Gotfredsen 2001). However, in cases of secondary osteoporosis there are often accompanying illnesses or conditions that increase the risk of implant failure (e.g. poorly controlled diabetes

Health history / personal data
Please complete in capital letters

b UNIVERSITÄT BERN
Medical Faculty
School of Dental Medicine
Department of Periodontology

☐ Mr ☐ Mrs

Surname: _____ Given name: _____

Street: _____ Postal code, Home address: _____

Birthdate (DD. MM. YYYY): _____ E-Mail-Address: _____

Telephone (Home): _____ Business: _____ Mobile: _____

Nationality: _____ Visitor Visa Type: ☐ B ☐ C ☐ Ci ☐ G ☐ L ☐ N ☐ F ☐ S

Profession: _____ Employer: _____

☐ Private Insurance ☐ Accident Insurance ☐ Additional Insurance ☐ Social assistance

Surname, Given name of parent or legal guardian by minors:

_____ *Birthdate:* _____

Referred by: _____

Your physician: _____

Please answer the following questions. All answers will be held in strict confidence.

1. Did you recently receive medical treatment or were hospitalized? ☐ yes ☐ no
   When yes, for which reason? _____
2. Are you currently taking medication? ☐ yes ☐ no
   When yes, which medication? _____
3. Do you suffer from any of the following diseases or disorders?
   ☐ Heart or cardiovascular disease ☐ High blood pressure ☐ Stroke
   ☐ Respiratory diseases ☐ Glaucoma ☐ Kidney disease
   ☐ Rheumatic fever ☐ Diabetes ☐ Epilepsy
   ☐ Osteoporosis ☐ Other _____
4. Have you ever had a severe infection? ☐ yes ☐ no
   ☐ Hepatitis ☐ Tuberculosis ☐ HIV
5. Do you have allergies? ☐ yes ☐ no
   When yes, which one(s) _____
6. Do you experience prolonged bleeding after tooth removal or a cut wound? ☐ yes ☐ no
7. Do you take blood thinners? ☐ yes ☐ no
8. Do you carry a medical alert card? ☐ yes ☐ no
9. Do you have a joint replacement? ☐ yes ☐ no
10. Have you suffered or are you suffering from a disease, which is not listed above? ☐ yes ☐ no
    When yes, which one(s) _____
11. Have you ever had a medical emergency during a dental appointment? ☐ yes ☐ no

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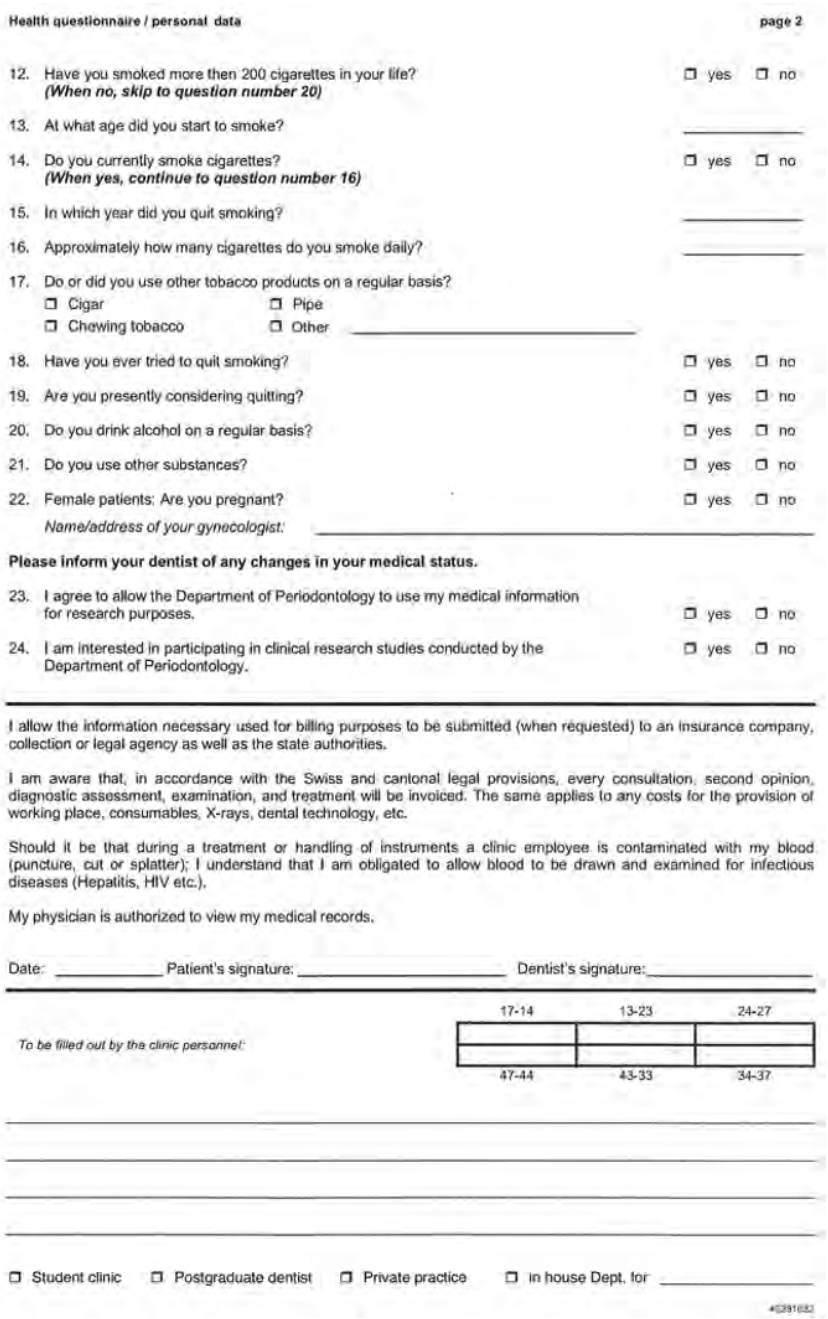
Fig. 24-1 Standard form used to collect health history data from the patient.



Health questionnaire / personal data page 2

12. Have you smoked more then 200 cigarettes in your life? ☐ yes ☐ no
(When no, skip to question number 20)
13. At what age did you start to smoke? _____
14. Do you currently smoke cigarettes? ☐ yes ☐ no
(When yes, continue to question number 16)
15. In which year did you quit smoking? _____
16. Approximately how many cigarettes do you smoke daily? _____
17. Do or did you use other tobacco products on a regular basis?
☐ Cigar ☐ Pipe
☐ Chewing tobacco ☐ Other _____
18. Have you ever tried to quit smoking? ☐ yes ☐ no
19. Are you presently considering quitting? ☐ yes ☐ no
20. Do you drink alcohol on a regular basis? ☐ yes ☐ no
21. Do you use other substances? ☐ yes ☐ no
22. Female patients: Are you pregnant? ☐ yes ☐ no
Name/address of your gynecologist: _____

Please inform your dentist of any changes in your medical status.

23. I agree to allow the Department of Periodontology to use my medical information for research purposes. ☐ yes ☐ no
24. I am interested in participating in clinical research studies conducted by the Department of Periodontology. ☐ yes ☐ no

I allow the information necessary used for billing purposes to be submitted (when requested) to an insurance company, collection or legal agency as well as the state authorities.

I am aware that, in accordance with the Swiss and cantonal legal provisions, every consultation, second opinion, diagnostic assessment, examination, and treatment will be invoiced. The same applies to any costs for the provision of working place, consumables, X-rays, dental technology, etc.

Should it be that during a treatment or handling of instruments a clinic employee is contaminated with my blood (puncture, cut or splatter); I understand that I am obligated to allow blood to be drawn and examined for infectious diseases (Hepatitis, HIV etc.).

My physician is authorized to view my medical records.

Date: _____ Patient's signature: _____ Dentist's signature: _____

To be filled out by the clinic personnel:

17-14	13-23	24-27
47-44	43-33	34-37

☐ Student clinic ☐ Postgraduate dentist ☐ Private practice ☐ in house Dept. for _____

Fig. 24-1 (Continued)

mellitus, corticosteroid medications). Therefore, in the patient-specific risk assessment the presence of osteoporosis should alert the clinician to the possible presence of osteoporosis-associated circumstances that are known to increase the risk of implant failures.

Diabetes mellitus

Although there is a slight tendency for increased implant loss in a patient with diabetes compared with a patient without diabetes, the increased risk is not substantial in patients who are under good metabolic control (Shernoff *et al*. 1994; Kapur *et al*. 1998; Balshi & Wolfinger 1999; Fiorellini *et al*. 2000; Morris *et al*. 2000; Olson *et al*. 2000).

Patients with diabetes under suboptimal metabolic control often experience wound-healing difficulties and have an increased susceptibility to infections due to a variety of problems associated with immune dysfunctions. Solid clinical evidence, however, for the association of glycemic control with implant loss is lacking (Oates *et al*. 2013). In the risk evaluation of patients with diabetes it is important to establish the level of metabolic control of the disease. A useful test to determine the level of control over the last 90 days is a blood test for glycosylated hemoglobin (HbA_{1c}). This is a test for the percentage of hemoglobin to which glucose is bound. Normal values for a healthy individual or a patient with diabetes under good metabolic control are HbA_{1c} <6–6.5% and fasting blood

glucose <6.1 mmol/L (110 mg/dL). Patients with diabetes with HbA_{1c} values >8% are considered poorly controlled and have an elevated risk of encountering wound healing problems and infections.

Immunosuppression

In the early years of the AIDS epidemic, placement of dental implants was ill advised since affected patients developed major life-threatening oral infections. With the advent of effective HAART (i.e. highly active anti-retroviral therapy) regimens, most HIV-positive patients who take their medications live for many years without developing severe opportunistic infections. There have been no controlled studies dealing with the risk of dental implant failures in HIV-positive individuals. However, several publications suggest that placement of dental implants in HIV-positive patients is not associated with elevated failure rates (Rajnay & Hochstetter 1998; Baron et al. 2004; Shetty & Achong 2005; Achong *et al*. 2006; Oliveira *et al*. 2011). Low T-helper (CD4) cell counts (i.e. <200/μL) do not appear to predict increased susceptibility to intraoral wound infections or elevated failure rates of dental implants (Achong *et al*. 2006). Although more studies are needed, it appears that it is safe to place dental implants if the patient's HIV disease is under medical control.

History of radiation therapy to the jaws

Patients who have received radiation (i.e. absorbed dose of ≥60 Gy) to the head and neck as part of the treatment for malignancies are at an increased risk of developing osteoradionecrosis (ORN). Most cases of this complication of cancer treatment are triggered by the extraction of teeth or other oral surgery procedures such as insertion of implants. Implant failure rates of up to 40% have been reported in patients who have had a history of radiation therapy (Granström *et al*. 1993, 1999; Beumer *et al*. 1995; Lindquist *et al*. 1988). At one time it was believed that ORN was due to vascular derangement and hypoxia of bone cells caused by the tissue-damaging effects of radiation (Teng & Futran 2005). Based on this hypothesis, it has been recommended that oral surgical procedures in patients at risk of ORN be performed in conjunction with hyperbaric oxygen (HBO) therapy. Indeed, Granström *et al*. (1999) reported that use of HBO therapy improved implant survival rates. However, the value of HBO therapy for the management of ORN has been called into question partly based on a placebo-controlled, randomized clinical trial (Annane *et al*. 2004) and other reports indicating no advantage to HBO interventions (Maier *et al*. 2000; Gal *et al*. 2003). In addition, a systematic review by Coulthard *et al*. (2008) indicated that there is no evidence that HBO therapy improves implant survival in irradiated patients.

It is now believed that the pathogenesis of ORN is much more complex than a simple hypoxia-related phenomenon related to poor vascularity of irradiated tissues. Current evidence supports the view that ORN is a fibroatrophic process (Teng & Futran 2005). From the perspective of risk-assessment procedures for implant placement, patients who have a history of irradiation to the jaws should be considered at high risk for implant loss and HBO interventions will probably not lower that risk.

Hematologic and lymphoreticular disorders

A number of hematologic and lymphoreticular disorders carry an increased susceptibility to periodontitis and other infections (Kinane 1999). Among these disorders are: agranulocytosis, acquired neutropenia, cyclic neutropenia, leukocyte adherence deficiency, and aplastic anemia (e.g. Fanconi's syndrome). Since patients with these diseases frequently lose teeth early in life they often have extensive prosthetic needs that can be met by the placement of dental implants. In the risk-assessment process prior to implant placement the major concern to be considered is the increased susceptibility to infections that could occur around any implants that might be placed. There are no well-controlled studies of the success rates of implants placed in patients with these disorders. However, implants can be placed if the patient's disease is under control or in remission and a rigorous supportive therapy program must be an integral part of the overall treatment plan.

Medications

Bisphosphonates

Bisphosphonates are a widely prescribed class of drugs used for the treatment of osteoporosis and to reduce the bone-lytic effects of malignancies such as multiple myeloma and metastatic breast cancer (Woo *et al*. 2006). These pyrophosphate drugs are potent inhibitors of osteoclast activity that also have antiangiogenic effects by inhibiting the production of vascular endothelial growth factor (VEGF). The drugs have a high affinity for hydroxyapatite, are rapidly incorporated into all parts of the skeleton and have a very long half-life (i.e. decades). Relative potencies of the agents depend on their formulation. A complication associated with the use of bisphosphonates is the increased risk of developing osteonecrosis of the jaws (i.e. bisphopsphonates-related osteonecrosis of the jaws, BRONJ) (Ruggiero *et al*. 2004; Marx *et al*. 2005; Braun & Iacono 2006). The vast majority of cases of BRONJ occur in cancer patients who have received high-potency aminobisphosphonates (e.g. zoledronate, pamidronate) delivered intravenously to decrease the osteolytic effects of multiple myeloma or malignancies that have metastasized to bone (e.g. breast or prostate cancer).

Of major concern to the prospective implant patient who has been taking an oral bisphosphonate for osteoporosis is the possible risk of developing BRONJ after implant placement. Oral bisphosphonates have been reported to be associated with implant failure (Starck & Epker 1995; Chappuis *et al*. 2018) and BRONJ (Ruggiero *et al*. 2004; Marx *et al*. 2005; Kwon *et al*. 2012). Since bisphosphonates tightly bind to hydroxyapatite and have a very long half-life, it is likely that the length of time a patient has been taking oral bisphosphonates is important in determining the level of risk. Since oral bisphosphonates slowly accumulate in bone with time, an osteoporosis patient who has been taking the drug for 1 year is at a lower risk of developing BRONJ or implant failure than someone who has been on the drug for many years. It should be kept in mind that bone-remodeling processes are inhibited in patients who have been chronically taking oral bisphosphonates for osteoporosis. Collectively, the duration, the route (i.e. oral or intravenous), the type of bisphosphonate, and the dosage of the medication play an important role in the development of BRONJ (Bornstein *et al*. 2009; Madrid & Sanz 2009a; Otomo-Corgel 2012).

Anticoagulants

Patients who have blood-coagulation disorders or are taking anticoagulants are at an elevated risk of experiencing postoperative bleeding problems after implant surgery. Some patients with coagulation disorders may be at an elevated risk of implant loss (van Steenberghe *et al*. 2003), whereas other patients who chronically take oral anticoagulants can safely receive dental implants (Weischer *et al*. 2005). Patients who are on continuous oral anticoagulant therapy (e.g. coumarin derivatives, rivaroxaban) to reduce the risk of thromboembolic events and require dental implants for optimal restorative care should be evaluated on a case-by-case basis. Most of these patients can safely continue their anticoagulant therapy when they receive standard implant surgery (Madrid & Sanz 2009b). In such patients, local bleeding after the placement of dental implants can usually be well controlled by conventional hemostatic methods. The risk of developing life-threatening bleeding or bleeding that cannot be controlled using local measures following placement of dental implants is so low that there is no need to stop oral anticoagulant therapy (Beirne 2005). In addition, the risk of discontinuing anticoagulant medication prior to implant surgery thereby increasing the probability of thromboembolic events must be accounted for (Madrid & Sanz 2009b).

Therapeutic levels of an anticoagulant drug are measured by the international normalized ratio (INR) which is the patient's prothrombin time (PT) divided by the mean normal PT for the laboratory (i.e. PTR). The PTR is then adjusted for the reagents used to arrive at a standardized INR value that will be comparable anywhere in the world. A higher INR reflects a higher level of anticoagulation with an expected increased risk of hemorrhage (Herman *et al*. 1997). Although there are insufficient data to draw any evidence-based conclusions, placement of single implants is regarded as safe when the INR target values are 2.0–2.4 (Herman *et al*. 1997).

Cancer chemotherapy

Oral cancer patients are frequently candidates for the placement of dental implants since prostheses designed to replace missing portions of the jaws need to be anchored to implants. Since antimitotic drugs used as chemotherapy for cancer might affect wound healing and suppress components of the immune system, it is important to know if these drugs interfere with osseointegration and success of dental implants. In a retrospective study, implant success was compared in 16 oral cancer patients who had no chemotherapy with that in 20 patients who received postsurgical adjuvant chemotherapy with either cis- or carboplatin and 5-fluorouracil (Kovács 2001). It was found that these drugs did not have any detrimental effects on the survival and success of implants placed in the mandible. It has also been reported that some cancer patients who received cytotoxic antineoplastic drugs experienced infections around existing dental implants (Karr *et al*. 1992). Therefore, it is important to recognize that many anticancer drugs suppress or kill cells necessary for optimal innate and adaptive immunity. Patients who are receiving cancer chemotherapy should have thorough periodontal and supportive therapy in order to minimize the development of biologic complications.

Immunosuppressive agents

Any medication that interferes with wound healing or suppresses components of innate and adaptive immunity (e.g. corticosteroids) can theoretically increase the risk of implant loss. These drugs are potent anti-inflammatory agents that are commonly used for the management of a wide variety of medical conditions such as after liver transplants (Gu & Yu 2011). They can interfere with wound healing by blocking key inflammatory events needed for satisfactory repair. In addition, through their immunosuppressive effects on lymphocytes, they can increase the rate of postoperative infections. In general, these undesirable effects are greatest in patients who take high doses of the drugs for long periods of time.

Other medications

Recently, outcomes of a systematic review (Chappuis *et al*. 2018) indicated that proton pump inhibitors and serotonin reuptake inhibitors are significantly associated with implant loss. Hence, clinicians should consider the increased risk for implant loss in candidates for implant therapy and under the medication of such drugs.

Age

In adult patients, age is usually not considered a risk factor for implant loss. Indeed, most longitudinal studies of survival rates of implants include some patients who are well over 75 years of age (Dao *et al*. 1993; Hutton *et al*. 1995; Nevins & Langer 1995; Davarpanah *et al*. 2002; Becktor *et al*. 2004; Fugazzotto *et al*. 2004; Karoussis *et al*. 2004; Fransson *et al*. 2005; Herrmann *et al*. 2005; Quirynen *et al*. 2005; Mundt *et al*. 2006; Wagenberg & Froum 2006). An upper age limit is usually not listed as an exclusion criterion in such studies. Several reports indicate that there is not a statistically significant relationship between age of the patient and implant loss (Dao *et al*. 1993; Hutton *et al*. 1995; Bryant & Zarb 1998; Fransson *et al*. 2005; Herrmann *et al*. 2005; Mundt *et al*. 2006; Wagenberg & Froum 2006). It cannot be excluded that there may have been some selection bias in the above studies since older patients might have been excluded for medical reasons. On the other hand, older individuals included in the above studies may be atypical in that they were healthy enough to be good candidates for implant placement.

Outcomes of a longitudinal retrospective study indicated that patients aged 65 and older presented a similarly low rate of early implant loss compared with patients aged 35 to <55 years, while patients aged 80 years and older displayed a slight tendency for a higher rate of early implant loss suggesting that ageing does not seem to substantially compromise early wound healing of dental implants (Bertl *et al*. 2019).

Growth considerations

At the other end of the spectrum, a potential problem associated with the placement of dental implants in still-growing children and adolescents is the possibility of interfering with growth patterns of the jaws (Op Heij *et al*. 2003). Osseointegrated implants in growing jaws behave like ankylosed teeth in that they do not erupt and the surrounding alveolar housing remains underdeveloped. Dental implants may be of great help to young people who have lost teeth due to trauma or have congenitally missing permanent teeth. However, because of the potential deleterious effects of implants on growing jaws it is highly recommended that implants are not placed until craniofacial growth has ceased or is almost complete (Thilander *et al*. 2001). As a rule of thumb, implants should not be placed in young adults of less than 20 years of age.

Untreated periodontitis and oral hygiene habits

The association between self-performed oral hygiene levels and peri-implantitis has been shown to be dose-dependent (Ferreira *et al*. 2006). Partially edentulous patients with very poor and poor oral hygiene are at statistically significantly higher risks of developing peri-implant mucositis and peri-implantitis compared with patients with proper biofilm control (Ferreira *et al*. 2006). A direct cause–effect relationship between a 3-week period of abolished oral hygiene practices with experimental biofilm accumulation and the development of experimental peri-implant mucositis has been shown in humans (Pontoriero *et al*. 1994; Zitzmann *et al*. 2001; Salvi *et al*. 2012). A period of 3 weeks of resumed oral hygiene practices followed the experimental biofilm accumulation period (Salvi *et al*. 2012). Despite resumed optimal biofilm control, however, 3 weeks of wound healing were insufficient to re-establish pre-experimental levels of peri-implant mucosal health (Salvi *et al*. 2012). Furthermore, it has been shown that partially edentulous patients with high biofilm scores before implant placement experience more implant losses than those with lower biofilm levels (van Steenberghe *et al*. 1993).

Based on this evidence, it may be postulated that, if left untreated, peri-implant mucositis may lead to progressive destruction of peri-implant marginal bone (i.e. peri-implantitis) and, eventually, implant loss.

Moreover, high percentages of implants diagnosed with peri-implantitis are associated with the presence of iatrogenic factors such as cement remnants (Wilson 2009; Linkevicius *et al*. 2013; Kordbacheh Changi *et al*. 2019) and with an inadequate access for self-performed oral hygiene (Serino & Ström 2009). These findings indicate that, in addition to insufficient oral hygiene habits, retentive factors are related to the presence of peri-implantitis

Based on this evidence any patient-specific risk assessment should include an evaluation of the patient's ability to maintain high levels of self-performed biofilm control (Salvi & Lang 2004).

History of treated periodontitis

Periodontitis-susceptible patients treated for their periodontal conditions may experience more biologic complications and implant losses compared with non-periodontitis patients (Hardt *et al*. 2002; Karoussis *et al*. 2003; Ong *et al*. 2008; De Boever *et al*. 2009; Matarasso *et al*. 2010; Aglietta *et al*. 2011; Kordbacheh Changi *et al*. 2019). This observation is of special interest in patients treated for Stage III–IV periodontitis and rehabilitated with dental implants (De Boever *et al*. 2009; Swierkot *et al*. 2012; Sgolastra *et al*. 2015). One implication of these findings is that patients who have lost their teeth because of periodontitis might also be more susceptible to peri-implant infections.

Outcomes from long-term clinical studies of patients with treated periodontal conditions indicated that residual pocket probing depths (PPD) ≥6 mm, full-mouth bleeding on probing (BoP^+) ≥30% and heavy smoking (i.e. ≥20 cigarettes/day) represented risk factors for periodontal disease progression and tooth

loss over a mean period of 11 years of SPT (Matuliene *et al*. 2008). Moreover, findings from two clinical studies indicated that residual PPD ≥5 mm and BoP+ after completion of periodontal therapy represented risk factors for the survival and success rates of implants placed in periodontally compromised patients (Lee *et al*. 2012; Pjetursson *et al*. 2012). In a retrospective case-control study, the effects of periodontal conditions on the outcomes of implant therapy were evaluated in periodontally compromised patients stratified according to the presence of ≥1 residual PPD ≥6 mm after a mean follow-up period of 8.2 years (Lee *et al*. 2012). Patients with ≥1 residual PPD ≥6 mm displayed a significantly greater mean peri-implant PPD and radiographic bone loss compared with both periodontally healthy and periodontally compromised patients without residual PPD, respectively (Lee *et al*. 2012). Moreover, patients with ≥1 residual PPD ≥6 mm had significantly more implants with PPD ≥5 mm with BoP+ and radiographic bone loss compared with either of the other two groups of patients (Lee *et al*. 2012). Residual PPD ≥5 mm at the end of active periodontal therapy represented a significant risk for the onset of peri-implantitis and implant loss over a mean follow-up period of 7.9 years (Pjetursson *et al*. 2012). In addition, patients enrolled in regular SPT and developing periodontal re-infections were at greater risk for peri-implantitis and implant loss compared with periodontally stable patients (Pjetursson *et al*. 2012).

From a microbiological point of view, a similar composition of the subgingival microbiota was found in pockets around teeth and implants with similar probing depths (Papaioannou *et al*. 1996; Sbordone *et al*. 1999; Hultin *et al*. 2000; Agerbaek *et al*. 2006). Moreover, evidence exists that periodontal pockets might serve as reservoirs of bacterial pathogens (Apse *et al*. 1989; Quirynen & Listgarten 1990; Mombelli *et al*. 1995; Papaioannou *et al*. 1996; van Winkelhoff et al. 2000; Fürst *et al*. 2007; Salvi *et al*. 2008) that may be transmitted from teeth to implants (Quirynen *et al*. 1996; Sumida *et al*. 2002). Therefore, the risk assessment of patients with a history of treated periodontitis should emphasize the increased risk of developing peri-implantitis and should highlight the importance of successful periodontal therapy and regular maintenance care.

Compliance with supportive therapy

Based on the fact that biological implant complications are characterized by similar etiologic factors as those involved in the development of periodontal diseases (Heitz-Mayfield & Lang 2010), it may be assumed that long-term survival and success rates of dental implants can be achieved by applying the same principles used during supportive therapy (ST) of teeth. Outcomes from long-term clinical studies indicated that compliance with ST is an essential component for the prevention of disease recurrence (e.g. caries and periodontitis) and tooth loss (Lindhe & Nyman 1984; Ramfjord 1987; Kaldahl *et al*. 1996; Rosling *et al*. 2001; Axelsson *et al*. 2004). Patients treated for stage III–IV periodontitis and subsequently enrolled in a regular ST program experienced a mean incidence of tooth loss ranging between 2% and 5% over an observation period of 10 years (Lindhe & Nyman 1984; Yi *et al*. 1995; Rosling *et al*. 2001; König *et al*. 2002; Karoussis *et al*. 2004). On the other hand, lack of compliance with ST was associated with disease progression and higher rates of tooth loss (Axelsson *et al*. 2004; Ng *et al*. 2011; Costa *et al*. 2012a). In the majority of patients complying with ST, periodontal disease progression and tooth loss occurred rarely (Ng *et al*. 2011). In non-compliant patients, however, a seven-fold increase in tooth loss due to periodontitis was reported compared with compliant patients (Ng *et al*. 2011). Despite the evident benefits of ST, however, only a minority of patients complied with the recommended recall intervals (Mendoza *et al*. 1991; Checchi *et al*. 1994; Demetriou *et al*. 1995).

Peri-implant mucositis represents a common finding among patients not enrolled in a regular ST program including anti-infective preventive measures (Roos-Jansåker *et al*. 2006). Lack of adherence of partially edentulous patients with dental implants to a regular ST program was associated with a higher incidence of peri-implantitis and implant loss compared with those of compliant patients (Costa *et al*. 2012b; Roccuzzo *et al*. 2010, 2012; Monje *et al*. 2017). In partially edentulous patients, pre-existing peri-implant mucositis in conjunction with lack of ST was associated with a higher incidence of peri-implantitis over a 5-year follow-up period (Costa *et al*. 2012b). The outcomes of that study (Costa *et al*. 2012b) yielded a 5-year incidence of peri-implantitis of 18.0% in the group of patients with ST and of 43.9% in the group without ST, respectively. The logistic regression analysis revealed that lack of ST within the overall patient sample was significantly associated with peri-implantitis with an odds ratio (OR) of 5.92. Moreover, a diagnosis of periodontitis was significantly associated with the occurrence of peri-implantitis in the overall patient sample (OR = 9.20) and particularly in patients without ST (OR = 11.43) (Costa *et al*. 2012b). Patients with a history of stage III periodontitis and erratic compliance with ST yielded a significantly higher incidence of implant losses and peri-implant bone loss ≥3 mm compared with compliant patients after a follow-up period of 10 years (Roccuzzo *et al*. 2010, 2012). On the other hand, low incidences of peri-implant bone loss and high implant survival rates were reported in patients treated for periodontal disease and enrolled in regular ST (Wennström *et al*. 2004; Rodrigo *et al*. 2012). Patients attending a ST program two to three times a year over the 5 years after implant placement experienced a high implant survival rate (i.e. 97.3%), low amounts of bone level changes during the final 4 years (i.e. 0.02 mm/year), and a low percentage (i.e. 11%) of implants with >2 mm bone loss (Wennström *et al*. 2004).

Outcomes of a prospective cohort study with a 5-year follow-up indicated that implants placed in patients with treated periodontal conditions and enrolled in ST yielded a 20% prevalence of mucositis (Rodrigo *et al*. 2012). In that study (Rodrigo *et al*. 2012), upon diagnosis of mucositis or peri-implantitis, all implants with the exception of one were successfully treated according to a cumulative interceptive anti-infective protocol (Lang *et al*. 1997). In addition, data indicated that patients susceptible to periodontitis who received dental implants as part of their oral rehabilitation displayed a higher rate of compliance with scheduled ST appointments compared with patients who underwent periodontal surgery without receiving dental implants (Cardaropoli & Gaveglio 2012). Hence, in order to achieve high long-term survival and success rates of dental implants, enrolment in regular ST including anti-infective preventive measures should be implemented (Salvi & Zitzmann 2014). Therapy of peri-implant mucositis should be considered as a preventive measure for the onset of peri-implantitis.

Tobacco use history

Tobacco use is generally accepted as an important modifiable risk factor for the development and progression of periodontitis (Johnson & Hill 2004) and peri-implantitis (Javed *et al*. 2019). The reasons that smokers are more susceptible to both periodontitis and peri-implantitis are complex, but usually involve impairment in innate and adaptive immune responses (Kinane & Chestnutt 2000; Johnson & Hill 2004) and interference with wound healing (Johnson & Hill 2004; Labriola *et al*. 2005). Based on data from several longitudinal studies on implant survival, cigarette smoking has been identified as a statistically significant risk factor for implant loss (Bain & Moy 1993; Strietzel *et al*. 2007). In addition, smoking has been associated with increased risk for peri-implant marginal bone loss (Lindquist *et al*. 1997; Galindo-Moreno *et al*. 2005; Nitzan *et al*. 2005; Aglietta *et al*. 2011) and postoperative complications after sinus floor elevation and placement of onlay bone grafts (Levin *et al*. 2004). Tobacco consumption is such a strong risk factor for implant failure that smoking-cessation protocols are implemented as part of the treatment plan for implant patients (Bain 1996; Johnson & Hill 2004).

Although cigarette smoking does not represent an absolute contraindication for implant placement, smokers should be informed that they are at increased risk of implant loss and development of peri-implantitis with odds ratios ranging from 3.6 to 4.6 (Heitz-Mayfield & Huynh-Ba 2009).

Genetic susceptibility traits

Genetic polymorphisms are small variations in base-pair components of DNA that occur with a frequency of approximately 1–2% in the general population (Kornman & Newman 2000). These small variations in genes are biologically normal and do not cause major disease. However, gene polymorphisms can affect in subtle ways how different people respond to environmental challenges. Within the context of risk assessment for implant therapy, they affect how people respond to a microbial challenge and how efficiently their wounds heal.

Polymorphisms in the interleukin-1 (*IL-1*) gene cluster on chromosome 2q13 have been associated with a hyper-responsive inflammatory reaction to a microbial challenge. A specific composite genotype of *IL-1A* and *IL-1B* polymorphisms, consisting of allele 2 of both *IL-1A* –889 (or the concordant +4845) and *IL-1B* +3954 was associated with an increased risk of severe periodontitis in non-smokers (Kornman *et al*. 1997). Several investigators have attempted to determine whether this composite IL-1 genotype can serve as a risk marker for biologic complications such as marginal bone loss or even implant loss (Wilson & Nunn 1999; Rogers *et al*. 2002; Feloutzis *et al*. 2003; Gruica *et al*. 2004; Jansson *et al*. 2005). All of these reports found that being positive for the composite *IL-1* genotype was not associated with an increased risk of marginal bone loss or other implant-related problems. Hence, based on available evidence, it may be considered irrational to recommend a systematic genetic screening of patients who are candidates for implant therapy (Huynh-Ba *et al*. 2008; Dereka *et al*. 2012).

Conclusion

Patient-based risk-assessment represents a process in which an attempt is made to identify factors or indicators increasing the risk of complications that eventually lead to implant loss. Risk assessment of the implant patient is a critically important preamble to treatment planning and if properly done can minimize the complications associated with dental implants. In many cases, early identification of these factors or indicators makes it possible to avoid or eliminate them, thereby increasing the chances of long-term implant survival and success. Most of the systemic risk factors for implant complications are those that increase the patient's susceptibility to infections or those that interfere with wound healing. Important risk factors that can interfere with wound healing around dental implants are long-term use of bisphosphonates, history of radiation therapy of the jaws, and poor metabolic control of diabetes mellitus. Additional factors such as parafunctional habits (e.g. bruxism) and relationships of the jaws (e.g. vertical and sagittal dimensions) should be included in a comprehensive patient-based risk assessment.

Based on the fact that untreated oral infections can lead to implant complications, it is highly recommended that any endodontic, periodontal, or other oral infections be treated prior to implant placement.

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Part 10: Treatment Planning Protocols

Chapter 25

Treatment Planning of Patients with Periodontal Diseases

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Introduction

Caries, periodontal disease, and peri-implant disease represent opportunistic infections caused by biofilm development on the surfaces of teeth and implants. Factors such as bacterial specificity and pathogenicity as well as the susceptibility of the individual for disease, for example local and general resistance, may influence the onset, the rate of progression, and clinical characteristics of the biofilm-associated oral disorders. Findings from animal experiments and longitudinal studies in humans, however, have demonstrated that treatment, including the elimination or the control of the biofilm infection and the introduction of careful biofilm control measures, in most, if not all, cases results in dental, periodontal, and peri-implant health. Even if health cannot always be achieved and maintained, the arrest of disease progression following treatment must be the goal of modern dental care.

The treatment of patients affected by caries, periodontal disease, and peri-implant disease, including symptoms of associated pathologic conditions such as pulpitis, periapical periodontitis, marginal abscesses, tooth migration, etc., may be divided into four different phases:

1. Systemic phase of therapy including smoking counseling
2. Initial (or hygienic) phase of periodontal therapy, that is, cause-related therapy
3. Corrective phase of therapy, that is, additional measures such as periodontal surgery, and/or endodontic therapy, implant surgery, restorative, orthodontic and/or prosthetic treatment
4. Maintenance phase (care), that is, supportive periodontal therapy (SPT).

Treatment goals

In every patient diagnosed with periodontitis, a treatment strategy including the elimination of the opportunistic infection must be defined and

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followed. This treatment strategy must also define the clinical outcome parameters to be reached through therapy. Such clinical parameters include:

- Reduction or resolution of gingivitis (bleeding on probing [BoP]): a full-mouth mean BoP ≤20% should be reached
- Reduction in pocket probing depth (PPD): no residual pockets with PPD >5 mm should be present
- Elimination of open furcations in multirooted teeth: beginning furcation involvement should not exceed 2–3 mm in horizontal direction
- Absence of pain
- Individually satisfactory esthetics and function.

It must be emphasized that risk factors for periodontal and peri-implant diseases that can be controlled must also be addressed. The three main risk factors for periodontal and peri-implant diseases are: (1) improper biofilm control, (2) tobacco consumption, and (3) uncontrolled diabetes mellitus (Kinane *et al*. 2006; Monje *et al*. 2017).

Systemic phase (including smoking counseling)

The goal of this phase is to eliminate or decrease the influence of systemic conditions on the outcomes of therapy and to protect the patient and the dental care providers against infectious hazards.

Consultation with a physician or specialist should enable appropriate preventive measures to be taken, if necessary. Efforts must be made to stimulate a smoker to enroll in a tobacco cessation program. Additional aspects are discussed in Chapter 27.

Initial phase (hygienic phase, infection control)

This phase represents the major cause-related therapy. Hence, the objective of this phase is the achievement of clean and infection-free conditions in the oral cavity through complete removal of all soft and hard deposits and their retentive factors. Furthermore, this phase should aim at motivating the patient to perform optimal biofilm control. Moreover, the initial phase of periodontal therapy may include caries excavation and provisional root canal medication. This phase is concluded by a re-evaluation and a planning of both additional and supportive therapies.

Corrective phase (additional therapeutic measures)

This phase addresses the sequelae of the opportunistic infections and includes therapeutic measures such as periodontal and implant surgery, root canal filling, and restorative and/or prosthetic treatment. The volume of corrective therapy required and the selection of means for the restorative and prosthetic therapy can be determined only when the level of success of the cause-related therapy can be properly evaluated. The patient's willingness and ability to cooperate in the overall therapy must determine the content of the corrective treatment. If this cooperation is unsatisfactory, it may not be worth initiating treatment procedures and there will no permanent improvement in oral health, function, and esthetics. The validity of this statement can be exemplified by the results of studies aimed at assessing the relative value of different types of surgical methods in the treatment of periodontal disease. Thus, a number of clinical trials (Lindhe & Nyman 1975; Nyman *et al*. 1975, 1977; Rosling *et al*. 1976a, b; Nyman & Lindhe 1979) have demonstrated that gingivectomy and flap procedures performed in patients with proper biofilm control levels often result in gain of alveolar bone and clinical attachment, while surgery in biofilm-contaminated dentitions may cause additional destruction of the periodontium.

Maintenance phase (supportive periodontal and peri-implant therapy)

The aim of this treatment is the prevention of reinfection and disease recurrence. For each individual patient a recall system must be designed that includes: (1) assessment of deepened sites with bleeding on probing, (2) instrumentation of such sites and (3) fluoride application for the prevention of dental caries (see Chapter 48). In addition, this treatment involves the regular control of prosthetic restorations incorporated during the corrective phase of therapy. Tooth sensitivity testing is applied to abutment teeth owing to the fact that loss of vitality represents a frequently encountered complication (Bergenholtz & Nyman 1984; Lang *et al*. 2004; Lulic *et al*. 2007). Based on the individual caries activity, bitewing radiographs should be incorporated in SPT at regular intervals.

Screening for periodontal disease

A patient seeking dental care is usually screened for the presence of carious lesions by means of clinical and radiographic examination. Likewise, it is imperative that such a patient is screened for the presence of periodontitis as well using a procedure termed the *basic periodontal examination* (BPE) or periodontal screening record (PSR).

Basic periodontal examination

The goal of the BPE is to screen the periodontal conditions of a new patient and to facilitate treatment planning. BPE scoring will allow the therapist to identify:

- Healthy or marginally inflamed (i.e. gingivitis) periodontal conditions in need of long-term preventive measures
- Periodontitis in need of periodontal therapy.

In the BPE the screening of each tooth or implant is evaluated. For this purpose, the use of a thin

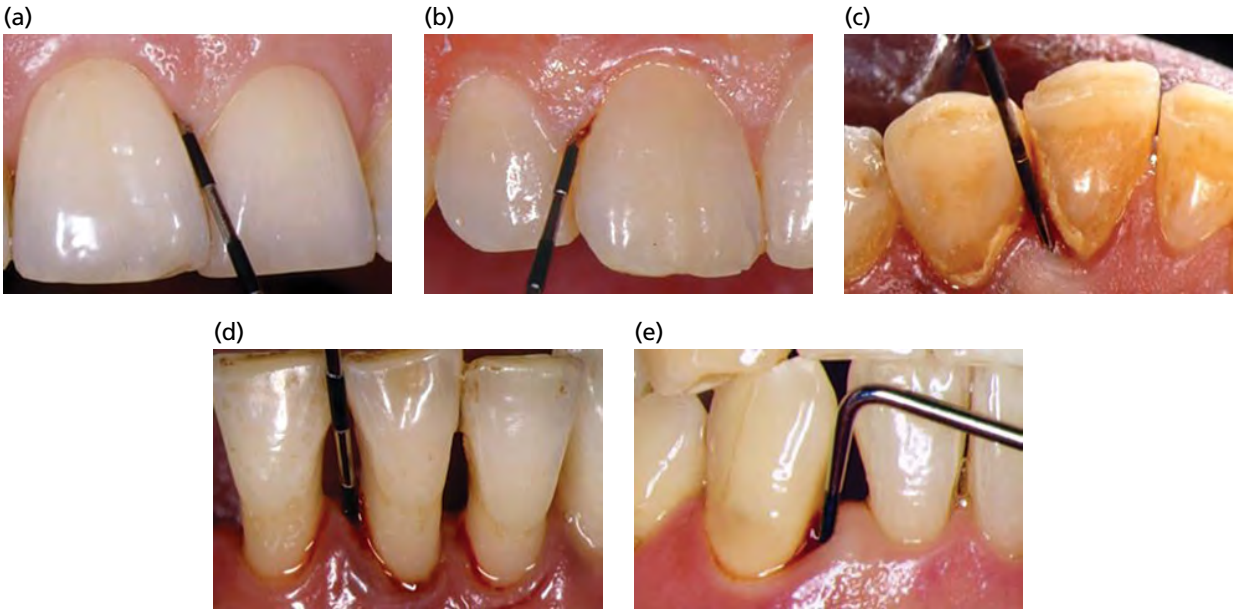


Fig. 25-1 Basic periodontal examination system code. (a) Code 0. (b) Code 1. (c) Code 2. (d) Code3. (e) Code 4. See text for details.

graduated periodontal probe is recommended. At least two sites per tooth/implant (i.e. mesiobuccal and distobuccal) should be probed using a light force (i.e 0.2 N). Each dentate sextant within the dentition is given a BPE code or score, whereby the *highest* individual site score is used.

BPE system code

- *Code 0*: PPD ≤3 mm, BoP negative, no calculus or overhanging fillings (Fig. 25-1a).
- *Code 1*: PPD ≤3 mm, BoP positive, no calculus or overhanging fillings (Fig. 25-1b).
- *Code 2*: PPD ≤3 mm, BoP positive, presence of supra- and/or subgingival calculus and/or overhanging fillings (Fig. 25-1c).
- *Code 3*: PPD >3 mm but ≤5 mm, BoP positive (Fig. 25-1d).
- *Code 4*: PPD >5 mm (Fig. 25-1e).

If an examiner identifies one single site with PPD >5 mm within a sextant, the sextant will receive a code of 4, and no further assessments are needed in this particular sextant. Patients with sextants given codes of 0, 1, or 2 belong to the relatively periodontally healthy category. A patient exhibiting a sextant with codes of 3 or 4 must undergo a more comprehensive periodontal examination (for details see Chapter 22).

The aim of the following text is to explain the overall objectives of the treatment planning of patients with BPE codes of 3 and 4 undergoing a comprehensive diagnostic process.

Diagnosis

The basis for the treatment planning described in this chapter is established by the clinical data collected from the patient's examination (see Chapter 22). As an example, a 27-year-old systemically healthy and non-smoking female patient (S.B.) was examined with respect to her periodontal conditions: gingival sites displaying signs of *BoP* were identified, *PPD* were measured, the *periodontal attachment level* was calculated, *furcation involvements* were graded, *tooth mobility* was assessed, and the radiographs were analyzed to determine the *height* and *outline* of the *alveolar bone crest*.

The clinical characteristics of the dentition of this patient are shown in Fig. 25-2. The periodontal chart and the radiographs are presented in Fig. 25-3 and Fig. 25-4, respectively. Based on these findings, each tooth in the dentition was given a diagnosis of either gingivitis or periodontitis and a pretherapeutic prognosis (Fig. 25-5). In addition to the examination of the periodontal conditions, detailed assessments of primary and recurrent caries were made for all tooth surfaces in the dentition. Furthermore, the patient was examined with respect to endodontic and occlusal problems as well as temporomandibular joint dysfunctions.

Treatment planning

Initial treatment plan

Provided that the patient's examination has been completed (see Chapter 22) and a diagnosis of all pathologic conditions has been made, an initial treatment plan can be established. At this early stage in the management of a patient, it is, in most instances, impossible to make definite decisions regarding all aspects of the treatment sequence, because:

1. *The degree of success of initial therapy is unknown.* The re-evaluation after initial, cause-related therapy forms the basis for the selection of the type of additional therapy. The degree of disease elimina-

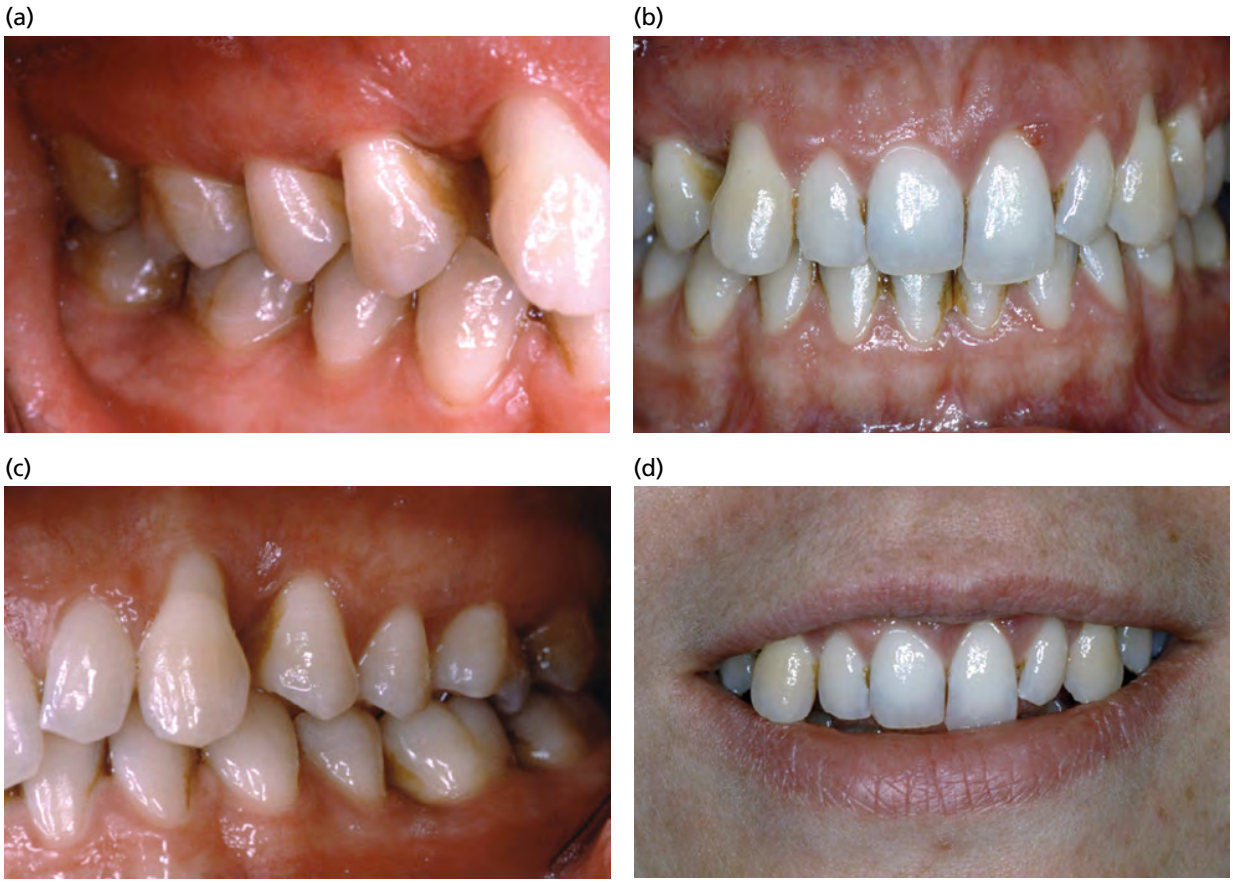


Fig. 25-2 (a–d) Clinical extra- and intraoral photographs of a 27-year-old female patient (S.B.) diagnosed with periodontitis stage III grade C with furcation involvement.

tion that can be reached depends on the outcome of subgingival instrumentation, but also on the patient's ability and willingness to exercise proper biofilm control and to adopt adequate dietary habits.

2. *The patient's "subjective" need for additional (periodontal and/or restorative) therapy is unknown*. When the dentist has completed the examination of the patient and an inventory has been made regarding periodontal and/or peri-implant diseases, caries, pulpal disease, and temporomandibular joint disorders, the observations are presented to the patient (i.e. "the case presentation"). During the session of case presentation it is important to find out if the patient's subjective need for dental therapy coincides with the dentist's professional appreciation of the kind and volume of therapy that is required. It is important that the dentist understands that the main objective of dental therapy, besides *elimination of pain, is to satisfy the patient's claims regarding chewing function (comfort) and esthetics*, demands that certainly vary considerably from one individual to another.
3. *The result of some treatment steps cannot be predicted*. In patients exhibiting advanced forms of caries and periodontal or peri-implant diseases it is often impossible to anticipate whether or not all teeth that are present at the initial examination can be successfully treated, or to predict the result of certain parts of the intended therapy. In other words, critical and difficult parts of the treatment must be performed first, and the outcome of this treatment must be evaluated before all aspects of the definitive corrective phase can be properly anticipated and described.

Pretherapeutic single tooth prognosis (Fig. 25-5)

Based on the results of the comprehensive examination including assessments of periodontitis, peri-implantitis, caries, tooth sensitivity, and the resulting diagnosis, as well as considering the patient's needs regarding esthetics and function, a pre-therapeutic prognosis for each individual tooth (root) is made.

Three major questions are addressed:

1. Which tooth/root has a "*good" (secure)* prognosis?
2. Which tooth/root is "*irrational-to-treat*"?
3. Which tooth/root has a *"doubtful"(insecure)* prognosis?

Teeth with a *good* prognosis will require relatively simple therapy and may be regarded as secure abutments for function.

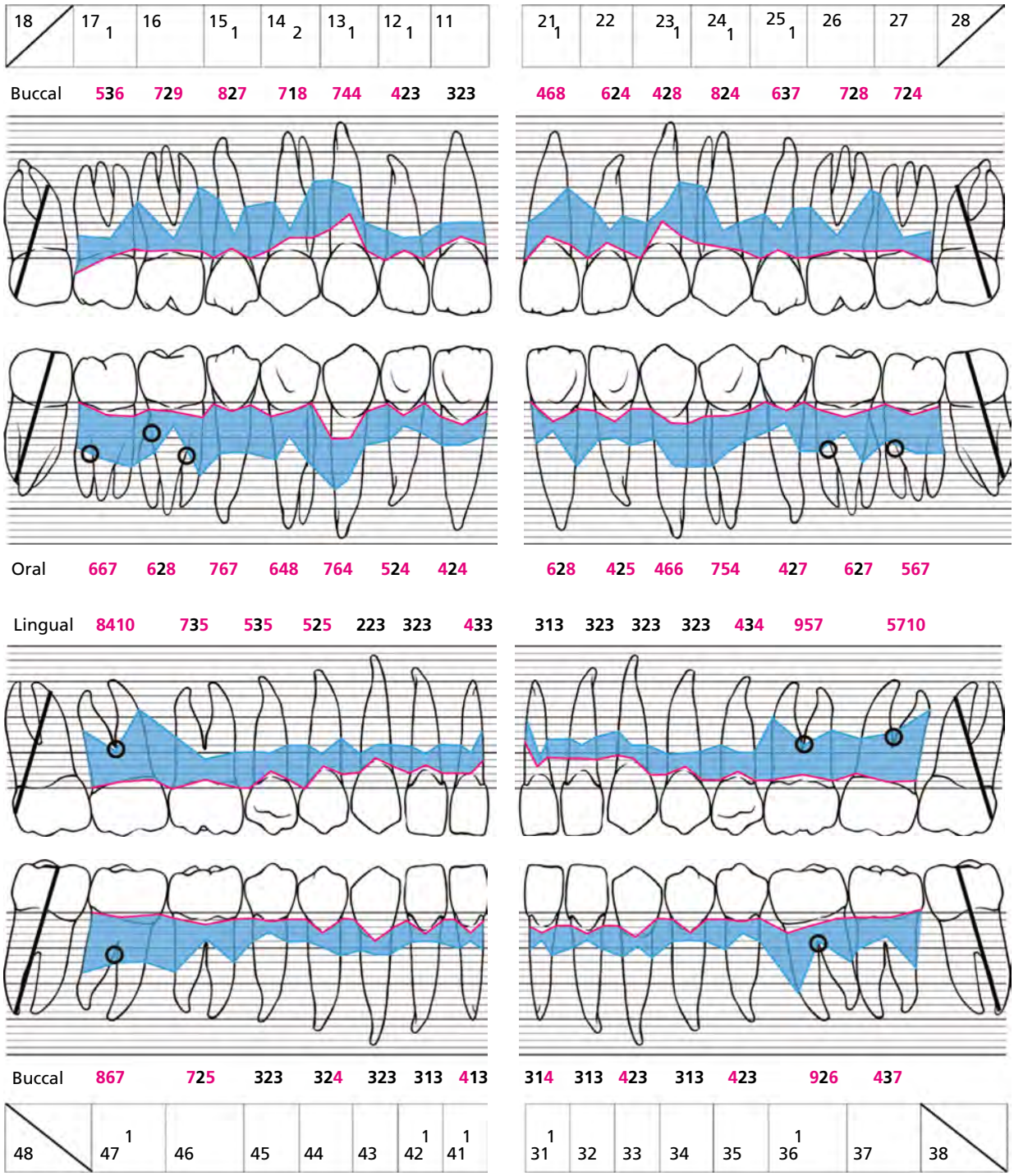


Fig. 25-3 Periodontal chart of the patient presented in Fig. 25-2.

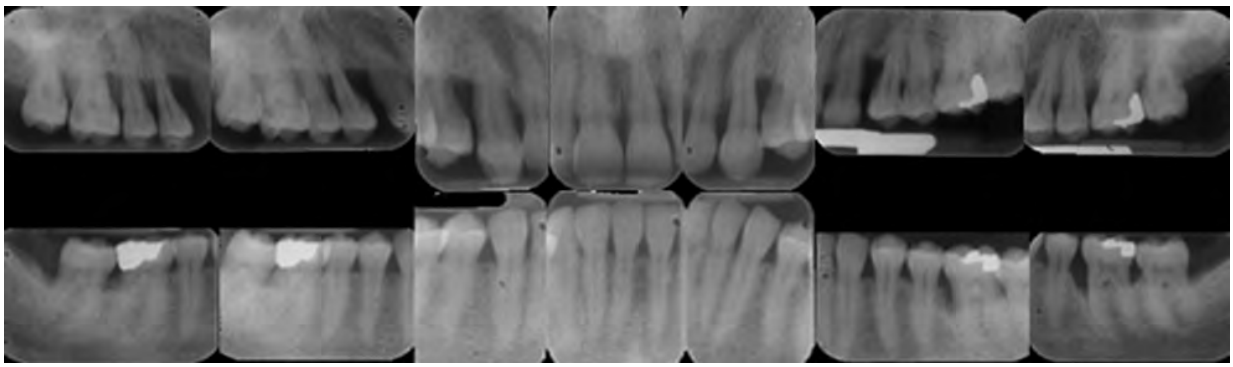


Fig. 25-4 Radiographs of the patient presented in Fig. 25-2.

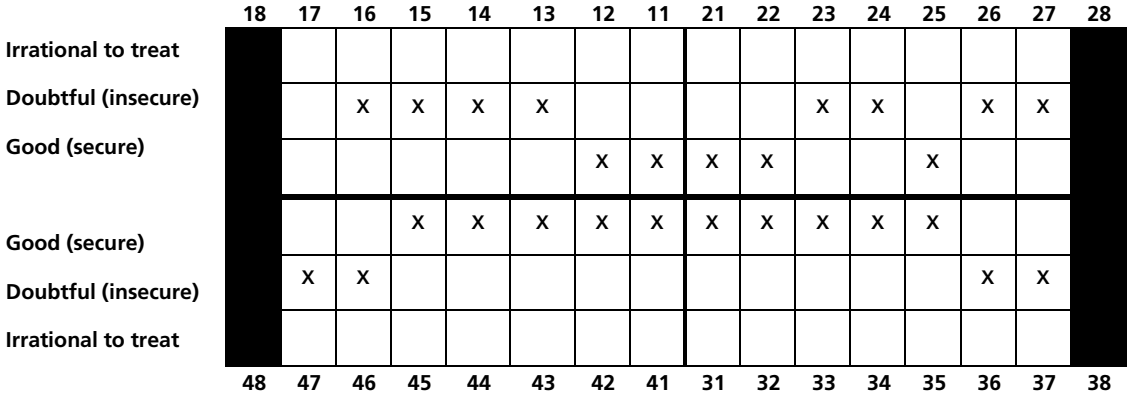


Fig. 25-5 Pretherapeutic single tooth prognosis of the patient presented in Fig. 25-2.

Teeth that are considered "irrational-to-treat" should be extracted during initial, cause-related therapy. Such teeth may be identified on the basis of the following criteria:

- *Periodontal:*
  - Recurrent periodontal abscesses
  - Combined periodontal-endodontic lesions
  - Attachment loss to the apical region.
- *Endodontic:*
  - Root perforation in the apical half of the root
  - Extensive periapical lesions (i.e. diameter >6 mm).
- *Dental:*
  - Vertical fracture of the root (hairline fracture)
  - Oblique fracture in the middle third of the root
  - Caries lesions extending into the root canal.
- *Functional:*
  - Third molars without antagonists and with periodontitis/caries.

Teeth with a *doubtful (insecure)* prognosis are usually in need of comprehensive therapy and must be brought into the category of teeth with a *good (secure)* prognosis by means of additional therapy. Such teeth may be identified on the basis of the following criteria:

- *Periodontal:*
  - Furcation involvement (class II or III)
  - Angular (i.e. vertical) bony defects
  - "Horizontal" bone loss involving more than two-thirds of the root
- *Endodontic:*
  - Incomplete root canal therapy
  - Periapical pathology
  - Presence of voluminous posts/screws.
- *Dental:*
  - Extensive root caries.

Case presentations

Case presentation 1

The "case presentation" is an essential component of the initial treatment plan and must include a description for the patient of different therapeutic goals and the modalities by which these may be reached. At the case presentation for patient S.B. the following treatment plan was described:

- The teeth in the dentition from 12 to 22 and from 45 to 35 will probably not confront the dentist with any major therapeutic challenges. For the remaining teeth in the dentition, however, the treatment plan may involve several additional measures.

Expected benefits inherent to a certain treatment plan versus obvious disadvantages should always be explained to and discussed with the patient. His/her attitude to the alternatives presented must guide the dentist in the design of the overall treatment plan.

Based on the pretherapeutic single tooth prognosis (Fig. 25-5), the following detailed treatment plan was presented to the patient.

Systemic phase

Owing to the fact that the patient was systemically healthy and a non-smoker, no medical examination and tobacco cessation counseling were required.

Initial phase (cause-related therapy, infection control)

The treatment was initiated and included the following measures to eliminate or control the bacterial infection:

1. *Motivation* of the patient and *instruction* in oral hygiene practices with subsequent check-ups and reinstruction.
2. *Scaling and root planing* under local anesthesia in combination with removal of biofilm retentive factors and teeth irrational to treat, if any.
3. *Excavation and restoration* of carious lesions of teeth 16 and 26.
4. *Endodontic treatment* of tooth 46.

Re-evaluation after initial phase

The initial phase of therapy is completed with a thorough analysis of the results obtained with respect to the elimination or degree of control of

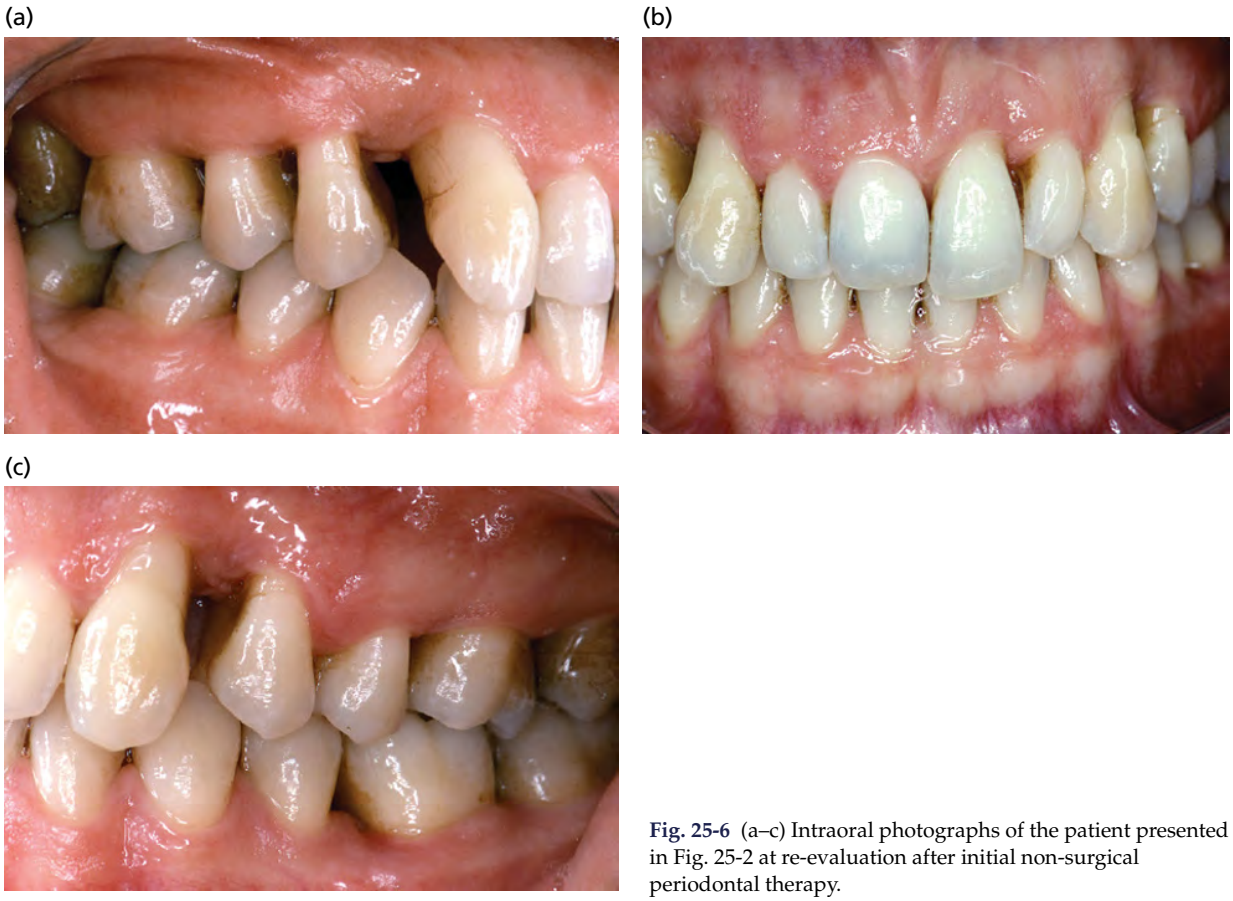


Fig. 25-6 (a–c) Intraoral photographs of the patient presented in Fig. 25-2 at re-evaluation after initial non-surgical periodontal therapy.

the oral infections. This implies that a re-evaluation of the patient's periodontal conditions and caries activity must be performed. The results of this re-evaluation (Figs. 25-6, 25-7) form the basis for the selection, if necessary, of additional corrective measures to be performed in the phase of definitive treatment (i.e. corrective phase). In order to provide time for the tissues to heal, the re-evaluation should be performed not earlier than 6–12 weeks following the last session of subgingival mechanical instrumentation.

Planning of the corrective phase (i.e. additional therapy)

If the results of the re-evaluation, performed 6–12 weeks after completion of the initial treatment phase, show that periodontal disease and caries have been brought under control and the treatment goals (see previously) have either been reached completely or have been approached substantially, the additional treatment may be carried out. The main goal of this phase is to correct the sequelae caused by oral infections (i.e. periodontal and peri-implant diseases and caries). The following procedures may be performed:

- *Additional endodontic treatment with/without post-and-core build-ups*.
- *Periodontal surgery*: type (i.e. open flap debridement, regenerative or resective surgery) and extent of surgical treatment should be based on PPD measurements, degree of furcation involvement and BoP scores assessed at re-evaluation. Periodontal surgery is often confined to those areas of the dentition where the inflammatory lesions were not resolved by root instrumentation alone, in areas with angular bony defects or in furcation-involved multirooted teeth.
- *Installation of oral implants*: in regions of the dentition where tooth abutments are missing, implant therapy for esthetic and functional reasons may be considered. *It is essential to realize that implant therapy must be initiated when all dental infections are under control, i.e. after successful periodontal therapy.*
- *Definitive restorative and prosthetic treatment* including fixed or removable dental prostheses.

Corrective phase (additional therapy)

Patient S.B. exhibited, after initial therapy, low plaque and gingivitis scores (i.e. 5–10%) and no active carious lesions. The corrective phase, therefore, included the following components:

1. *Periodontal surgery (i.e. open flap debridement)* in the maxillary left and right quadrants as well as in the mandibular molar regions (Fig. 25-8)

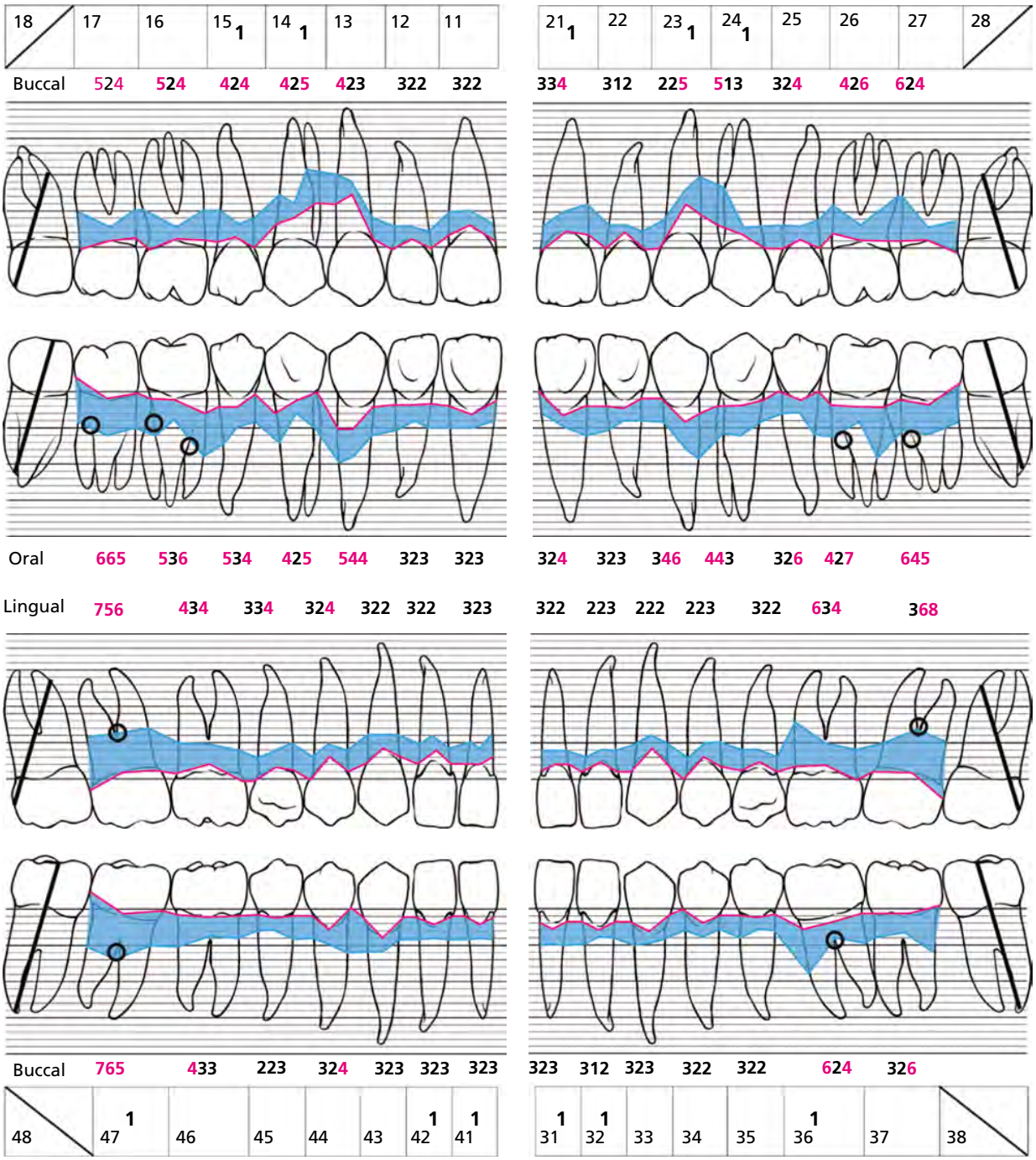


Fig. 25-7 Periodontal chart of the patient presented in Fig. 25-2 at re-evaluation after initial non-surgical periodontal therapy.

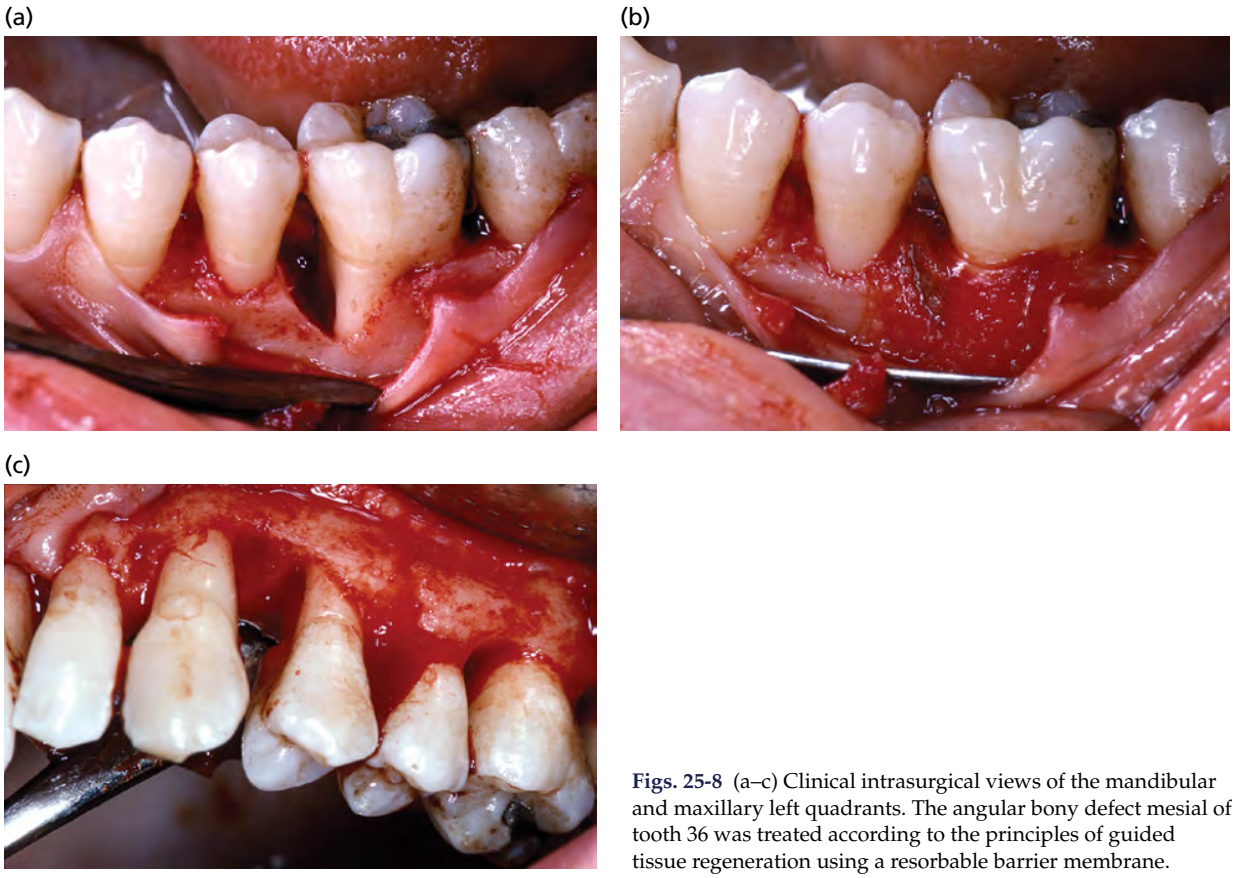
2. *Guided tissue regeneration (GTR)* for tooth 36 (Cortellini *et al*. 1995, 1999)
3. *Re-evaluation* after periodontal surgery (Figs. 25-9, 25-10)
4. *Orthodontic therapy* in the maxillary front area (Fig. 25-11)
5. *Restorative therapy* in the maxillary front area for esthetic reasons (Fig. 25-12).

Re-evaluation after corrective phase

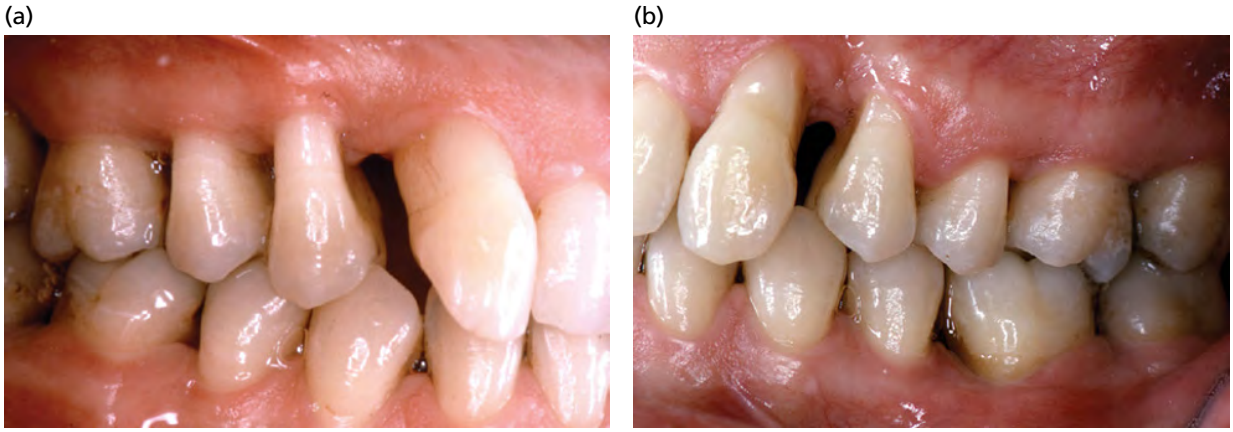
The corrective phase of therapy is completed with a thorough analysis of the results obtained with respect to the elimination of the sequelae of periodontal tissue destruction (Figs. 25-13, 25-14, 25-15). This implies that a re-evaluation of the patient's periodontal and peri-implant conditions must be performed. The results of this re-evaluation form the basis for the assessment of the residual periodontal risk. The outcomes of the periodontal risk assessment (PRA) (Lang & Tonetti 2003), in turn, will determine the recall frequency of the patient during the maintenance phase.

Maintenance phase (supportive periodontal and peri-implant therapy)

Following completion of cause-related therapy, the patient must be enrolled in a recall system aiming at preventing the recurrence of oral infections



Figs. 25-8 (a–c) Clinical intrasurgical views of the mandibular and maxillary left quadrants. The angular bony defect mesial of tooth 36 was treated according to the principles of guided tissue regeneration using a resorbable barrier membrane.



Figs. 25-9 (a, b) Clinical lateral views of the patient presented in Fig. 25-2 at re-evaluation after periodontal surgery.

(i.e. periodontitis, caries, and peri-implantitis). *SPT* should be scheduled at the re-evaluation after initial therapy and independently of the need for additional therapy. The time interval between the recall appointments should be based on a PRA (see Chapter 48) established at the re-evaluation after the corrective phase. It has been well established that self-performed biofilm control combined with regular attendance of maintenance care visits following active periodontal treatment represented effective means of controlling gingivitis and periodontitis and limiting tooth mortality over a 30-year period (Axelsson *et al*. 2004). It is important to emphasize, however, that the recall program must be designed to meet the individual needs of the patient. According to a PRA performed after completion of active therapy, some patients should be recalled every 3 months, while others may have to be checked once or twice a year (Lang & Tonetti 2003).

At the recall visits the following procedures should be carried out:

1. Update of the medical and tobacco use history
2. Soft tissue examination as a cancer screening
3. Recording of the full-mouth PPD ≥5 mm with concomitant BoP

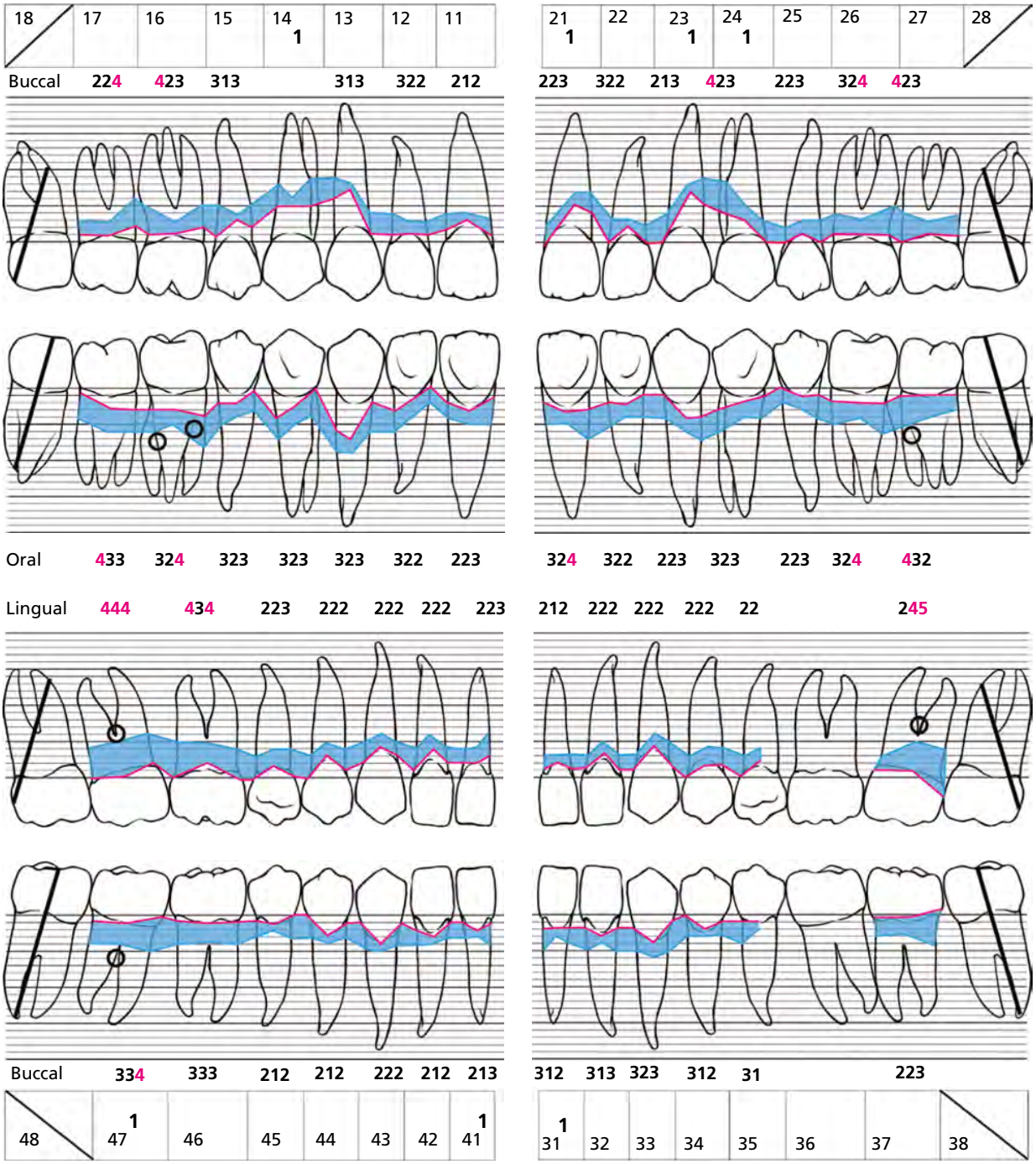


Fig. 25-10 Periodontal chart of the patient presented in Fig. 25-2 at re-evaluation after periodontal surgery. Tooth 36 has not been charted due to a 6-month healing period following guided tissue regeneration.

4. Re-instrumentation of bleeding sites with PPD ≥5 mm
5. Polishing and fluoridation for the prevention of dental caries.

Patient S.B., who is presented to describe the guiding principles of treatment planning was, during the first 6 months following active therapy, recalled twice (i.e. every 3 months) and subsequently once every 6 months based on the individual PRA.

Re-evaluation 20 years following active periodontal therapy

The SPT rendered according to the individual PRA has been successful in maintaining the dentition of this initially challenging case for at least 20 years (Figs. 25-16, 25-17, 25-18).

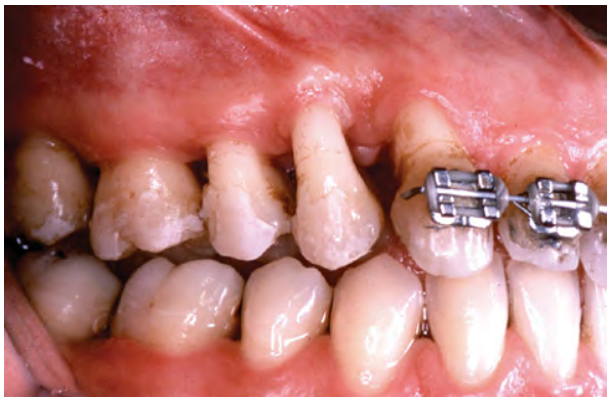
Case presentation 2

The treatment plan and treatment procedures of a 48-year-old male patient (M.A.) are presented. Patient M.A. was referred by his family dentist after spontaneous loss of tooth 17.

Dental history

The patient reported abscesses, especially in the posterior area and more frequently in the upper left molar area. In addition, he complained about gingival

(a)



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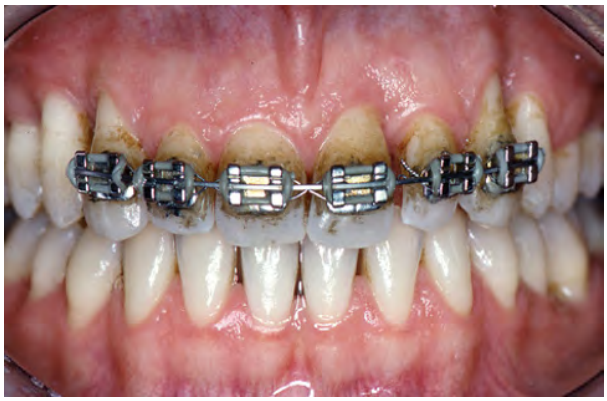

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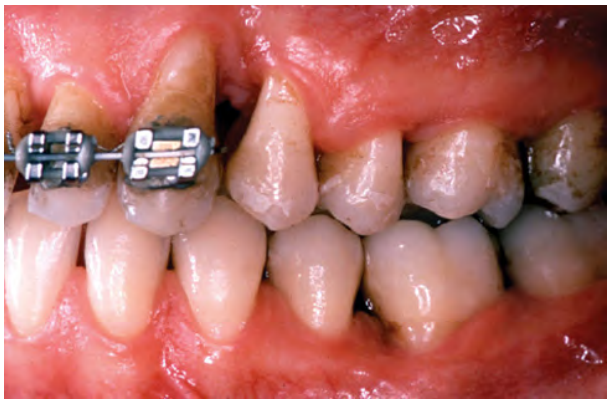
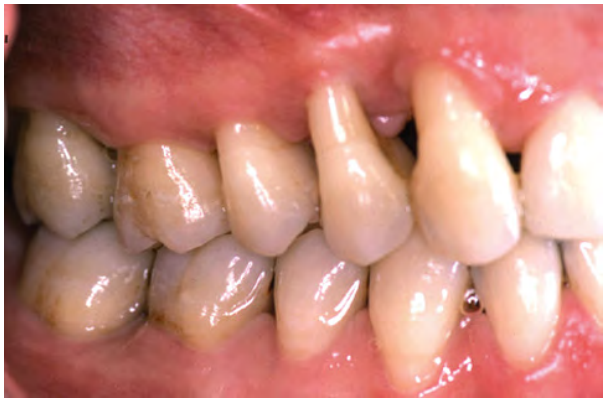


Figs. 25-11 (a–c) Intraoral photographs of the patient presented in Fig. 25-2 during orthodontic therapy of the maxillary front teeth.

(a)



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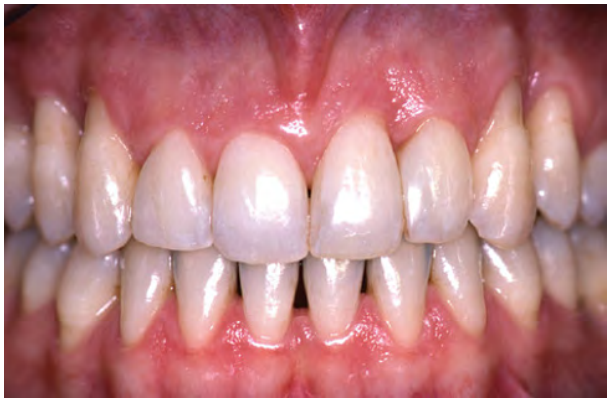

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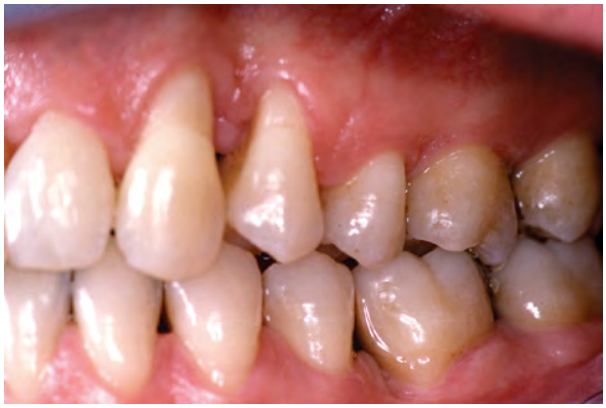


Figs. 25-12 (a–c) Intraoral photographs of the patient presented in Fig. 25-2 at the re-evaluation following active therapy. To improve the esthetic outcome, the maxillary front teeth were restored with composite fillings.

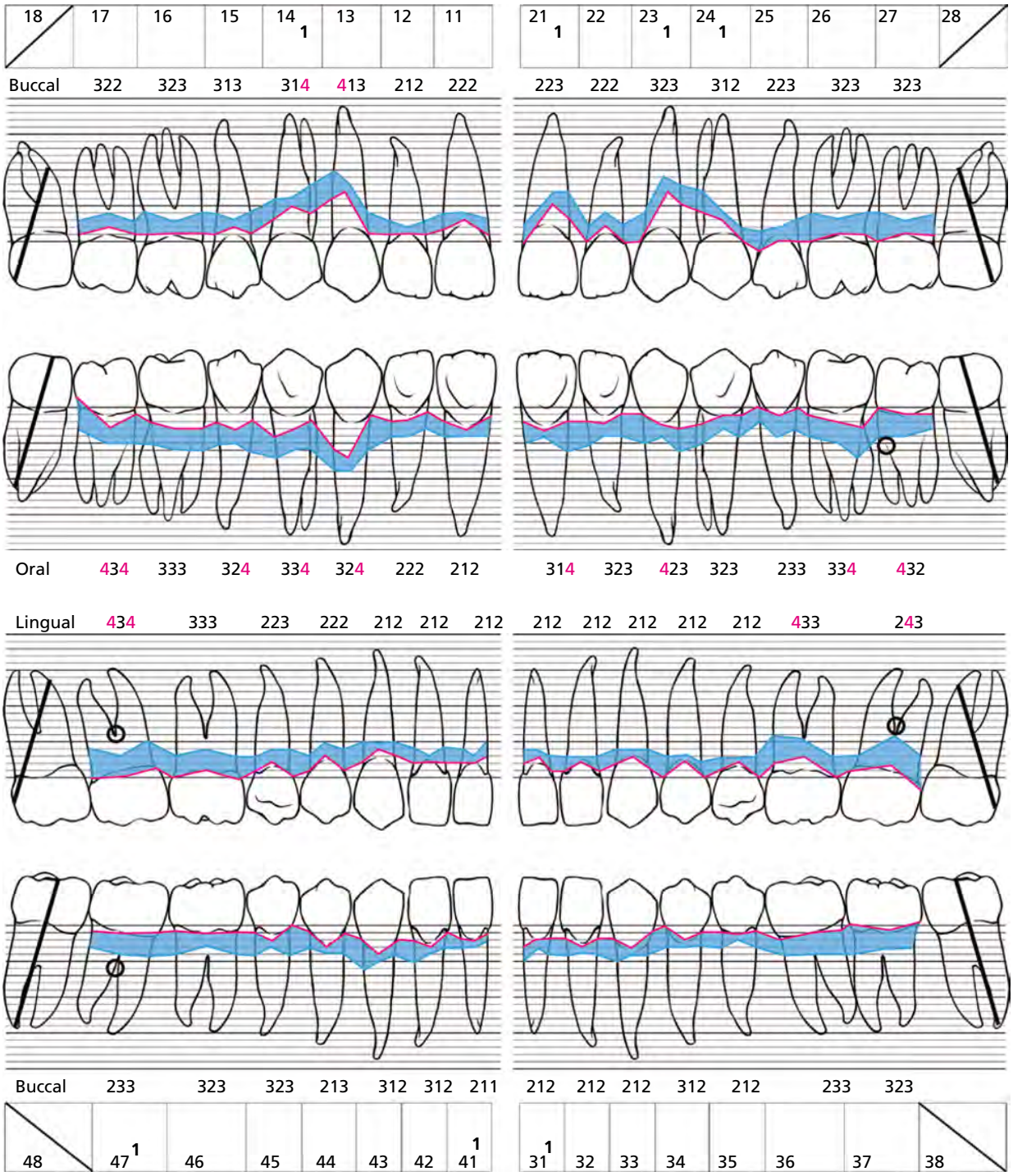


Fig. 25-13 Periodontal chart of the patient presented in Fig. 25-2 at the re-evaluation following active therapy.

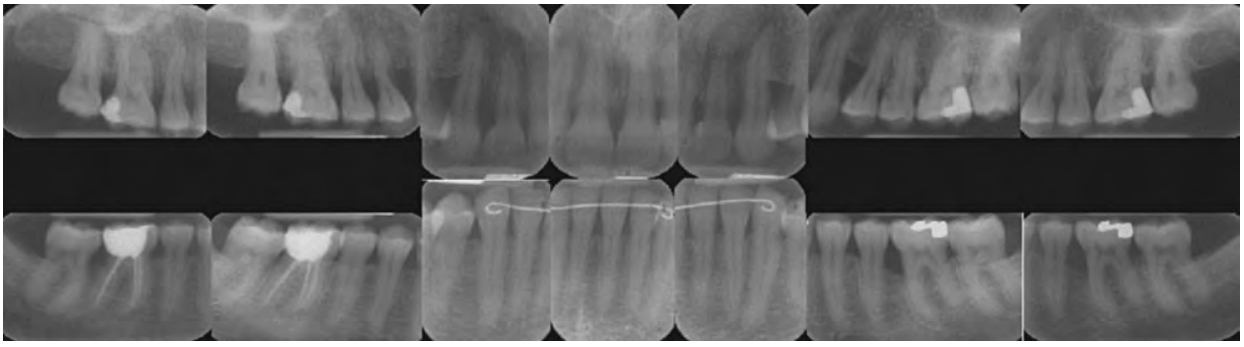
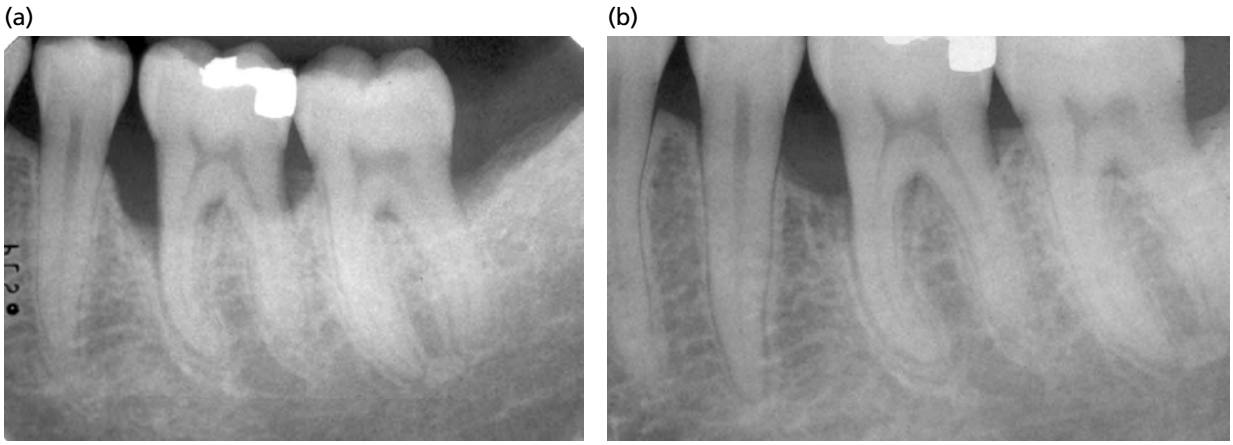


Fig. 25-14 Periapical radiographs of the patient presented in Fig. 25-2 at the re-evaluation following active therapy.



Figs. 25-15 (a, b) Periapical radiographs of tooth 36 of the patient presented in Fig. 25-2 before and after regenerative periodontal therapy according to the principles of guided tissue regeneration.

Fig. 25-16 Intraoral photographs of patient S.B. 20 years following completion of active therapy.

bleeding while brushing and even spontaneous bleeding, bad breath and bad taste, increased tooth mobility, and impaired mastication on the left side. He had received a dental examination 2 years before, when he also received professional oral hygiene treatment. Home care was based on tooth brushing once per day with a manual toothbrush in the evening, without the use of any interdental cleansing devices.

The patient was concerned about the spontaneous loss of tooth 17 and reported that his father had lost many teeth in the same way. He also felt an increasing negative impact of his oral conditions on the

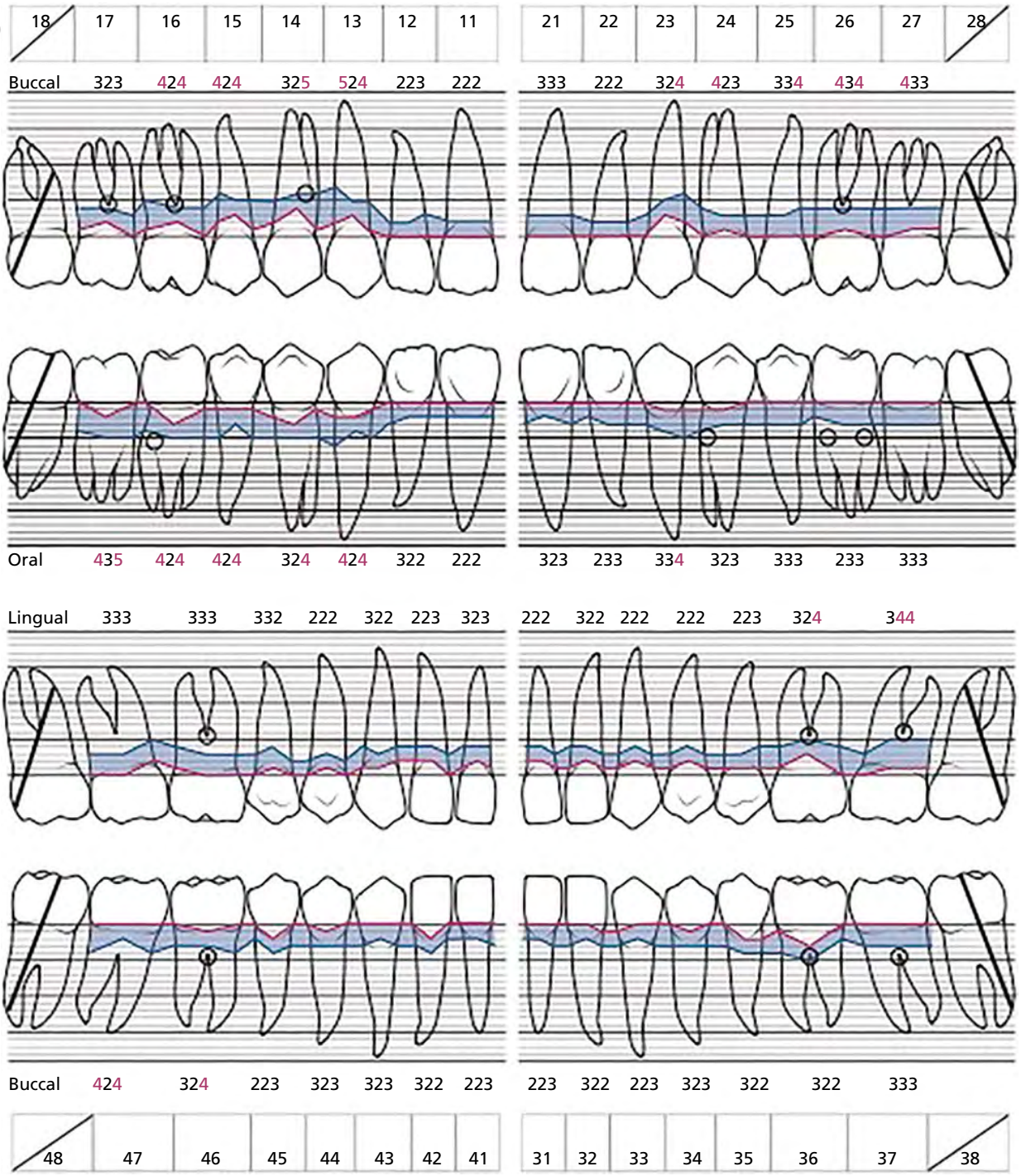


Fig. 25-17 Periodontal chart of patient S.B. 20 years following completion of active therapy.

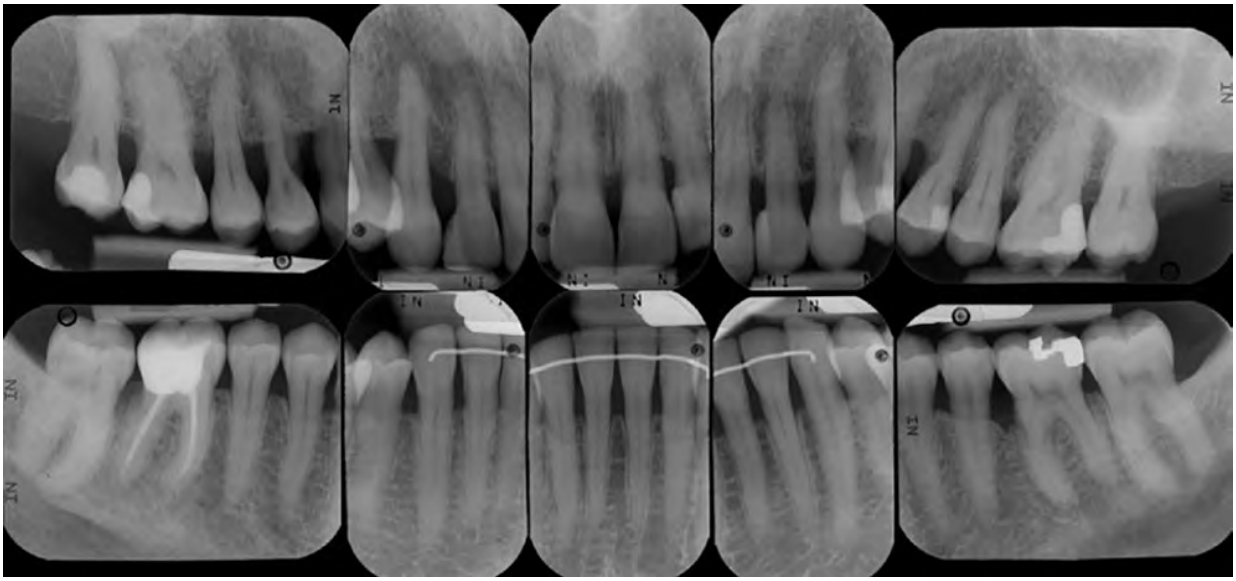


Fig. 25-18 Periapical radiographs of patient S.B. 20 years following completion of active therapy.

quality of his daily life especially in terms of chewing comfort and social relationships. The patient's main requests were to save as many teeth as possible and regain oral health and chewing comfort.

Medical history

At time of intake, patient M.A. was systemically healthy and reported a normal body weight and absence of stress. He was a non-smoker and in good physical shape, regularly partaking in physical activity. He was a full-time employee of the Italian state train company and married with two children.

Extra- and intraoral examinations

The extraoral examination, including the functional analysis of the temporomandibular joints, were within normal limits.

The intraoral examination revealed large amounts of bacterial biofilm and calculus in every sextant with the concomitant presence of severe gingival inflammation. In some sites, the gingiva was bleeding upon air blow. Tooth 17 was missing. In the upper left area, severe swelling was evident and purulence could be observed upon light finger pressure. The upper left molars were highly mobile and increased tooth mobility could be detected on several additional teeth. Multiple carious lesions were also detected. The BPE yielded a score of 4 in all sextants indicating the presence of severe periodontitis and thereby requiring a more comprehensive oral and periodontal examination.

Diagnosis

An appointment for a more comprehensive oral examination was scheduled during which intraoral photographs, full periapical radiographs, and a periodontal chart were taken (Fig. 25-19). Pulp sensitivity revealed that tooth 16 was vital whereas tooth 27 displayed questionable vitality and tooth 28 was non-vital. Primary and recurrent caries were diagnosed on teeth 14, 15, 16, 24, 26, 27, 28, 46, 45, 35, and 36.

The periodontal chart (Fig. 25-19) revealed a full-mouth plaque score (FMPS) of 78%, a full-mouth bleeding score (FMBS) of 85%, deep PPDs around most teeth in association with severe attachment loss, deep furcation involvement (FI) on tooth 16 and 26 and increased tooth mobility (TM) particularly in the upper left molar area.

Based on these findings, the patient was given a diagnosis of generalized periodontitis type III and grade B. In addition to caries, a diagnosis of endodontic-periodontal lesions was given to teeth 27 and 28.

Single tooth pretherapeutic prognosis

The single tooth pretherapeutic prognosis is shown in Fig. 25-20. Teeth 28, 48, and 38 were considered irrational to treat. Keeping in mind the expectation of the patient to save as many teeth as possible, teeth 18 and 27 were placed into the "doubtful" category. The rationale about keeping tooth 27 was to observe its potential for improvement after cause-related therapy, while tooth 18 did not present severe treats to justify its immediate extraction.

Systemic phase

Based on the fact that the patient was systemically healthy and a non-smoker, no medical or behavioral interventions were indicated.

Cause-related therapy

Non-surgical therapy consisted of motivation and instructions in oral hygiene practices followed by supragingival scaling and root planing under local anaesthesia. All bacterial biofilms, supra- and subgingival calculus deposits as well as their retentive factors were carefully eliminated. Controls of self-performed oral hygiene and re-instructions were scheduled during this phase. Moreover, teeth irrational to treat (i.e. 28, 38, 48) were extracted. The carious lesions were eliminated and teeth 46, 45, 14, 25, 35, 36, 21, 22, 23, 24, and 26 were restored with composite fillings.

Re-evaluation after cause-related therapy

The periodontal conditions were re-evaluated 3 months following completion of non-surgical therapy (Fig. 25-21). The periodontal chart shows the high-quality performance of the patient in terms of plaque control (FMPS: 5%) and very low levels of residual inflammation (FMBS: 8%). Most of the deep PPDs present at intake were resolved with an obvious increase in gingival recessions. Residual PPDs were still present at teeth 18, 16, 15, and 14 and FI degree 2 was diagnosed on the distal aspect of tooth 16. Furthermore, residual PPDs up to 13 mm were still present on the distal aspect of tooth 27 also revealing an open FI of this tooth. A residual PPD of 6 mm associated with an intrabony defect was detected on tooth 36 distally while on teeth 46 and 47 residual PPDs up to 8 mm were associated with osseous craters.

Most of the symptoms described by the patient at intake were resolved although an increase in root sensitivity was reported and treated with proper dietary instructions and topical fluoride application. The patient was enrolled into SPT with a 3-month recall frequency.

Corrective phase

At this time, tooth 27 was considered hopeless and extracted while periodontal surgery was planned in areas with residual PPDs.

In the first sextant, resective surgery was planned and performed on teeth 18, 16, 15, and 14 including

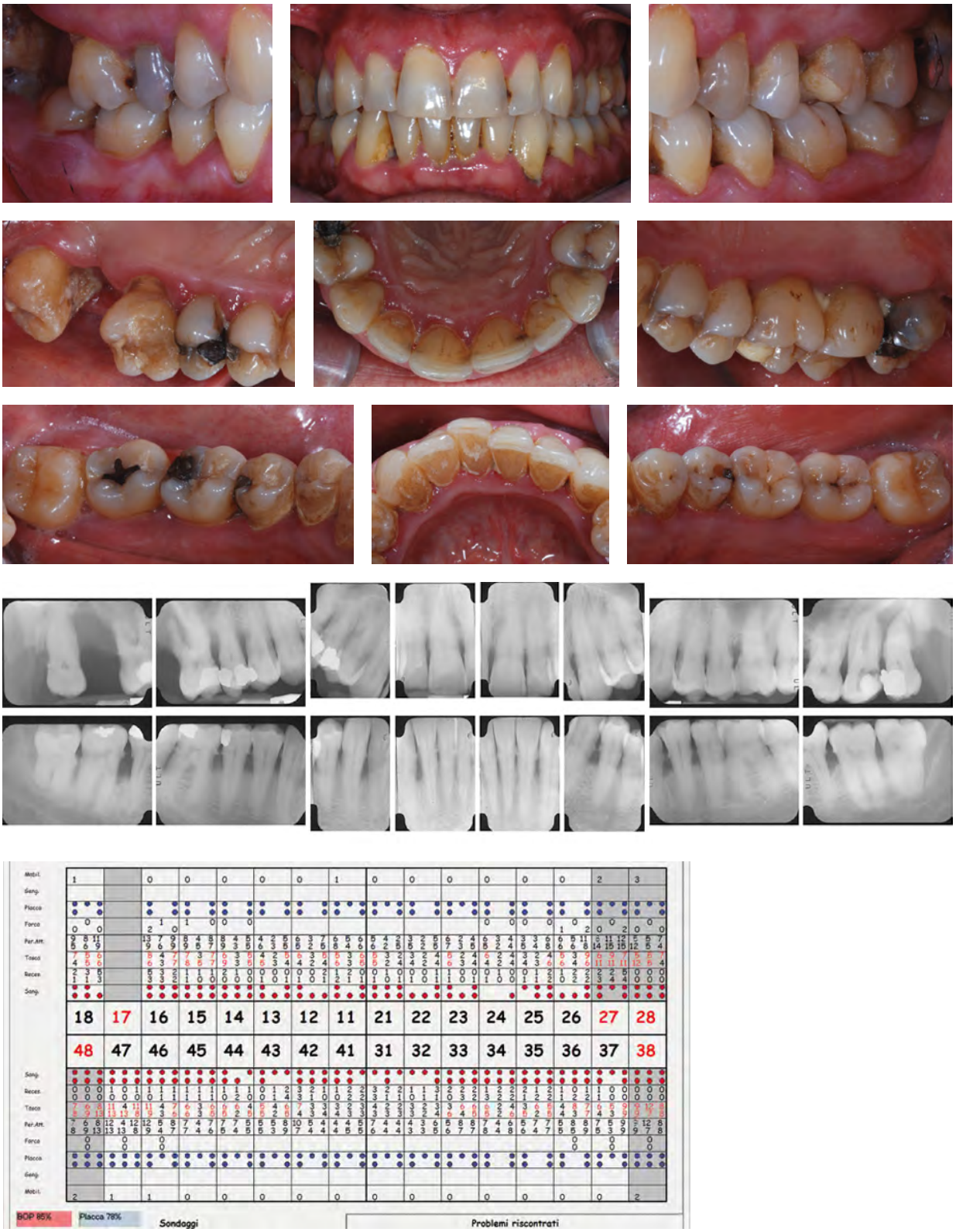


Fig. 25-19 Intraoral photographs, periapical radiographs, and periodontal chart of patient M.A. at intake.

root separation and extraction of the distobuccal root of 16 (Fig. 25-22a–f). Before surgery tooth 15 was treated with a temporary composite build-up and tooth 16 endodontically treated and restored with composite. Four months after surgery, tooth 16 was restored with a single-unit crown and tooth 15 with an onlay (Fig. 25-22g–l). Resective surgery was performed on teeth 47 and 46 (Fig. 25-23) and regenerative surgery was applied on tooth 36 (Fig. 25-24).

Patient M.A. was maintained in SPT with a 3-month recall frequency during the entire corrective phase.

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Irrational to treat																X
Doubtful (insecure)	X		X	X	X									X	X	
Good (secure)						X	X	X	X	X	X	X	X			
Good (secure)				X	X	X	X	X	X	X	X	X	X			
Doubtful (insecure)		X	X											X	X	
Irrational to treat	X															X
	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

Fig. 25-20 Pretherapeutic single tooth prognosis of patient M.A.

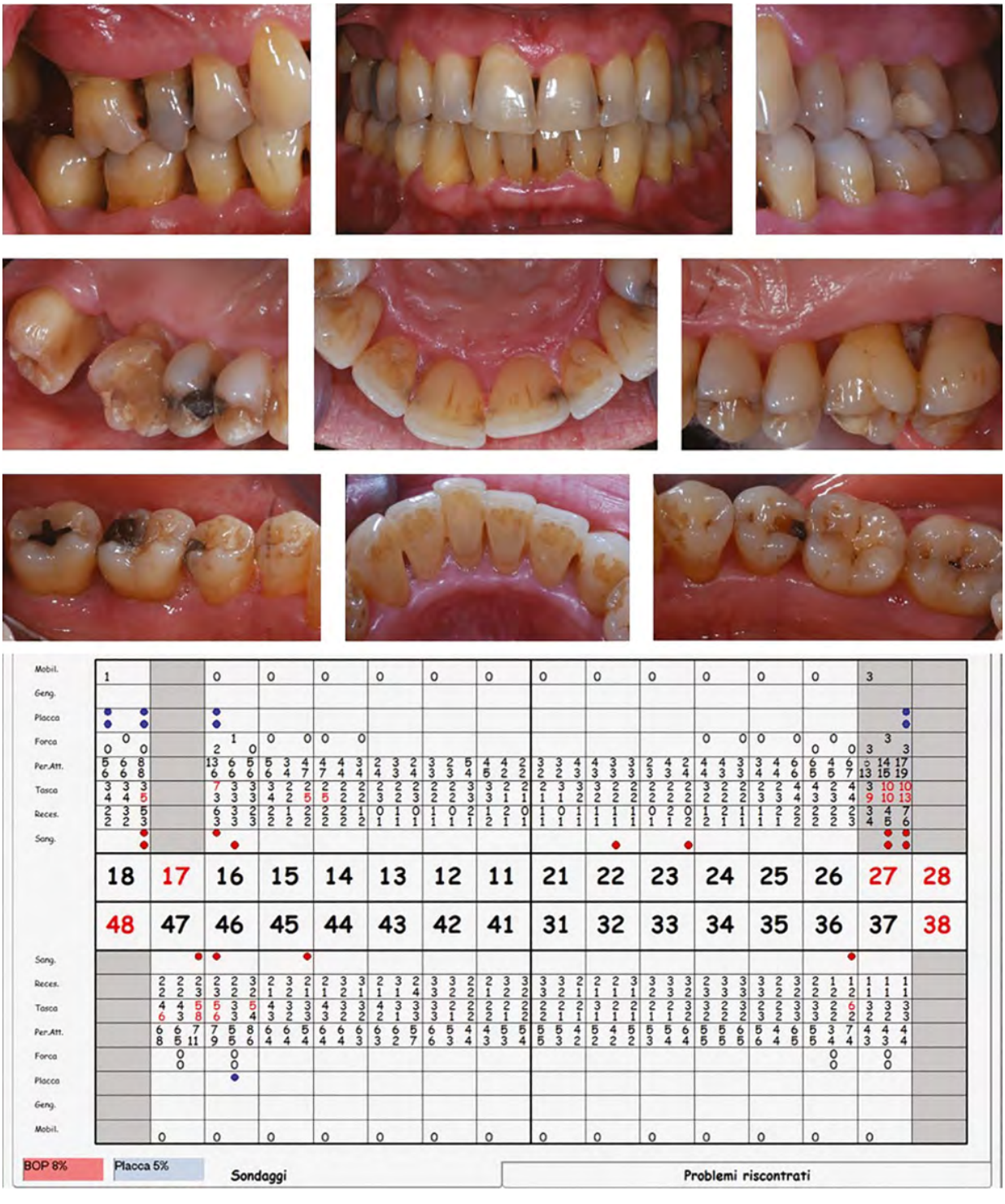


Fig. 25-21 Intraoral photographs and periodontal chart of patient M.A. 3 months following completion of cause-related therapy.

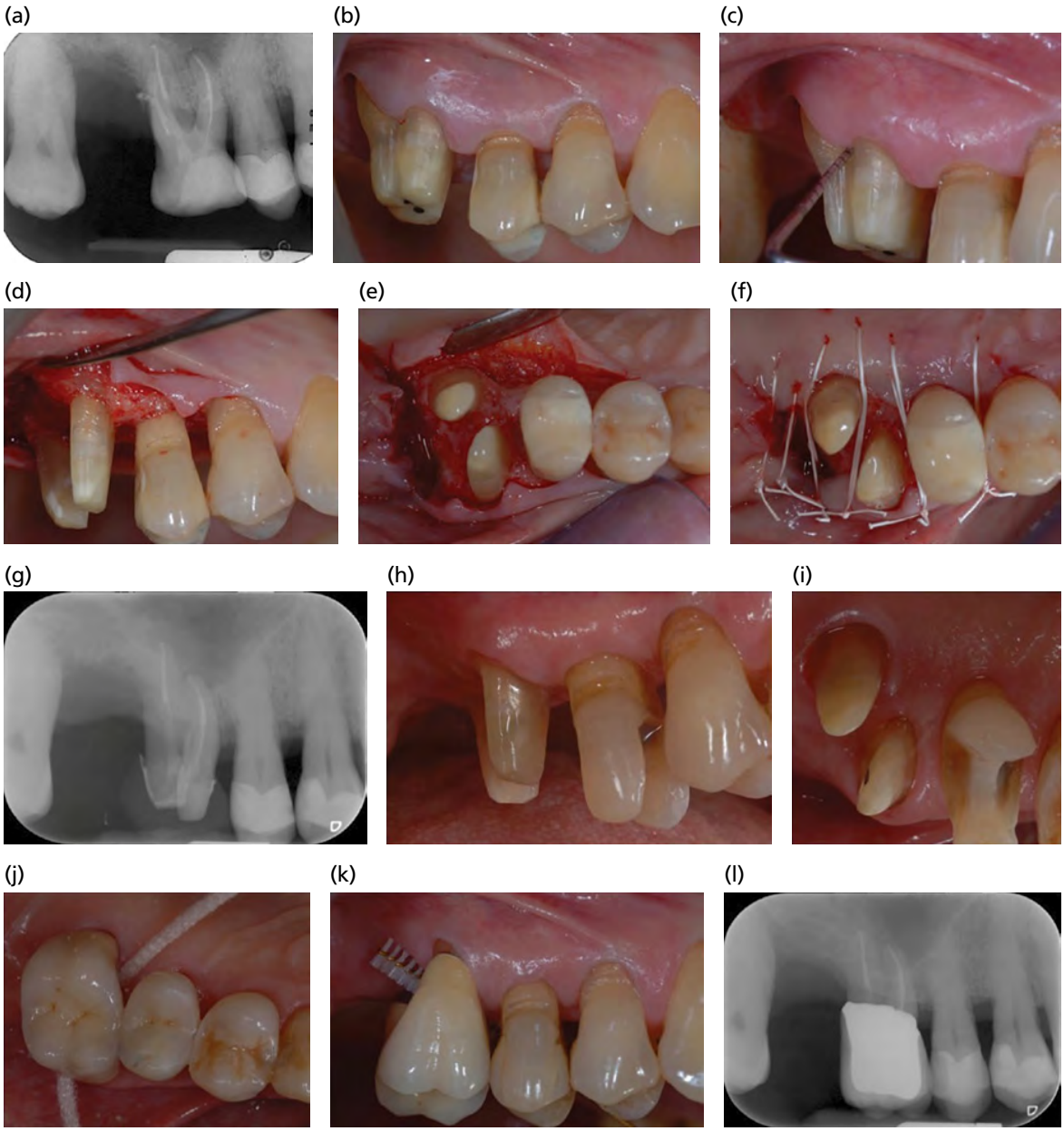


Fig. 25-22 (a–l) Resective surgery and reconstructions in the first sextant of patient M.A.

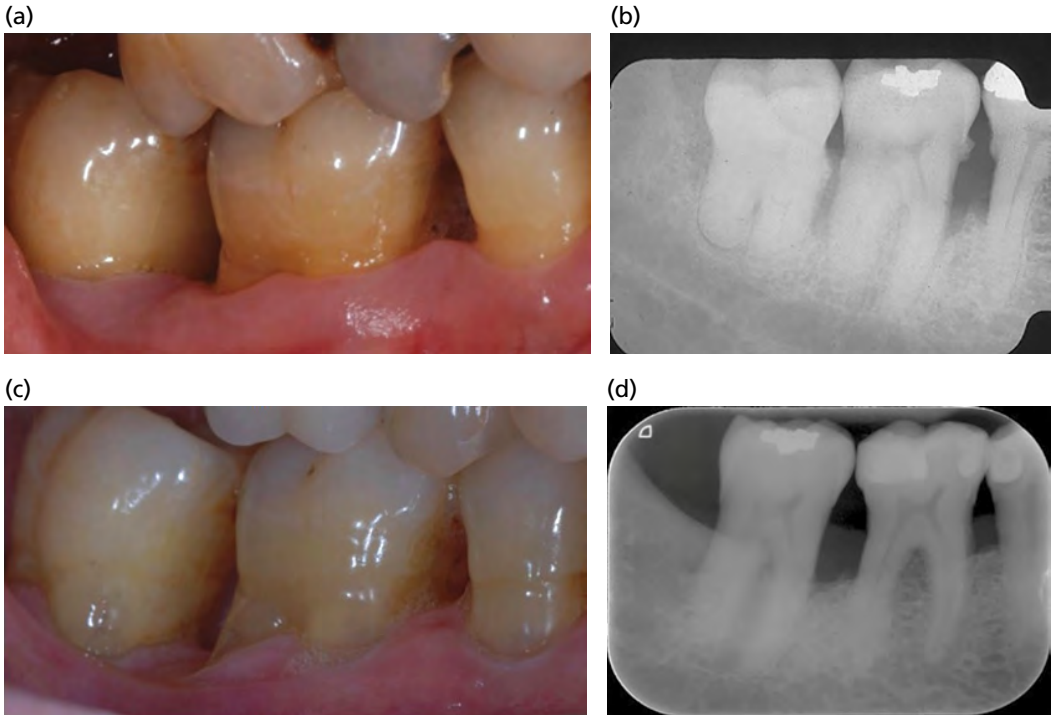


Fig. 25-23 Clinical and radiographic aspects (a, b) before and (c, d) after (resective surgery at teeth 46 and 47 of patient M.A. Tooth 48 was extracted during cause-related therapy.

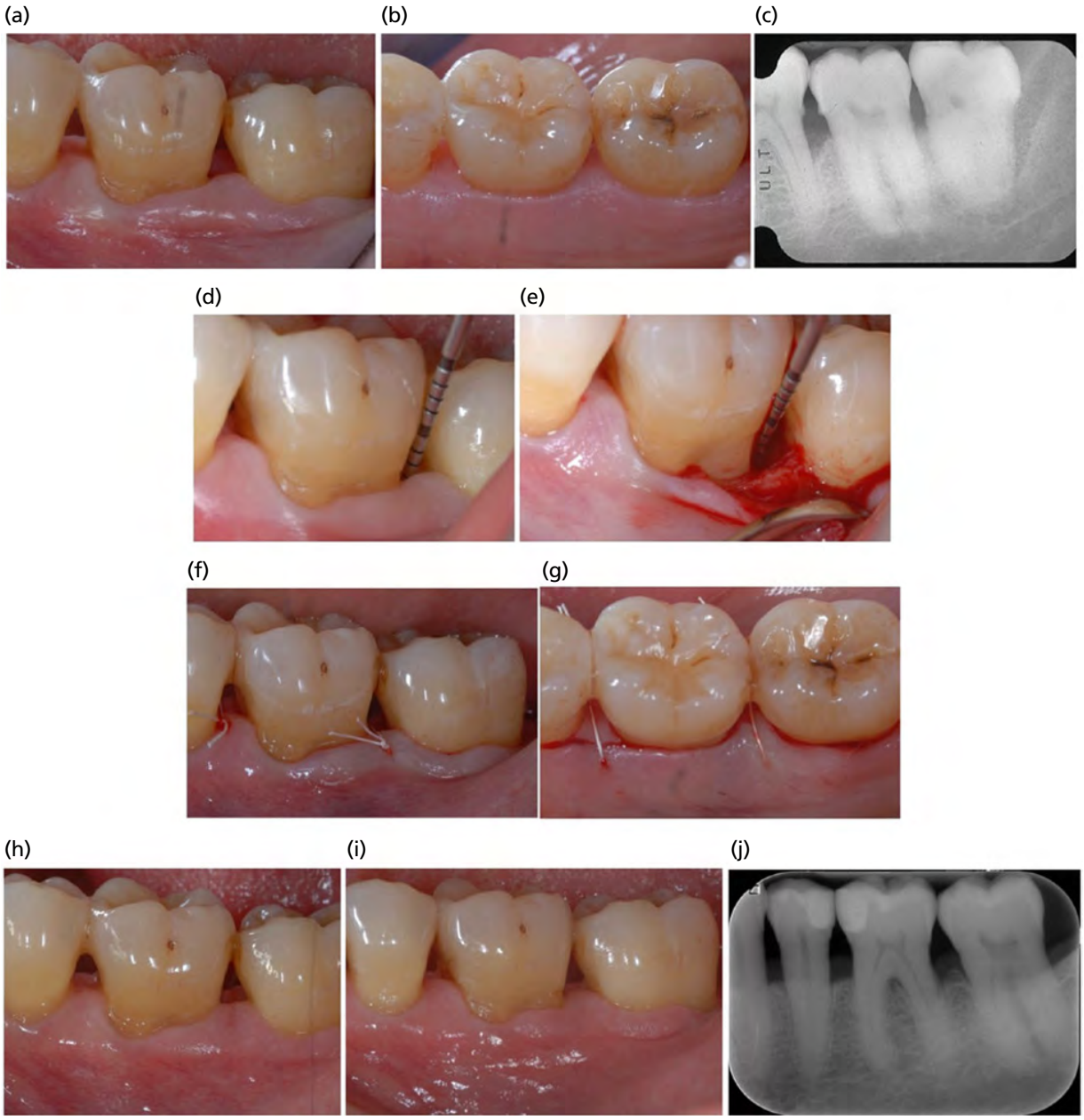


Fig. 25-24 (a–j) Clinical and radiographic views of periodontal regeneration at the distal aspect of tooth 36 by means of minimally invasive surgery in combination with enamel matrix derivative. Tooth 38 was extracted during cause-related therapy.

Re-evaluation after corrective phase

After completion of the corrective phase including periodontal surgery and restorative therapy, a re-evaluation was performed 18 months after intake of the patient. Photographs and periapical radiographs were taken, and a periodontal chart made at this timepoint (Fig. 25-25). A FMPS of 14% and a FMBS of 4% were assessed with absence of residual PPDs >4 mm. No increased TM was detected. Except for minimal root sensitivity, the patient reported full chewing comfort and resolution of the symptoms described at intake.

The PRA indicated a residual low risk profile (Lang & Tonetti 2003) (Fig. 25-26). Despite this low residual risk, it was decided, with the agreement of the patient, to maintain a stringent SPT based on a 3-month recall frequency.

Re-evaluation 10 years following active periodontal therapy

Fig. 25-27 illustrates the photographs, periapical radiographs, and periodontal chart of patient M.A. 10 years after completion of active therapy. A FMPS of 11% combined with a FMBS of 14%, absence of residual PPDs >4 mm, stable radiographic marginal bone levels, and absence of recurrent caries indicated that patient's compliance and SPT were successful in maintaining long-term oral health following active periodontal therapy.

Conclusion

The overall treatment plan and the sequence of the different treatment procedures used in both case presentations were selected in order to illustrate the

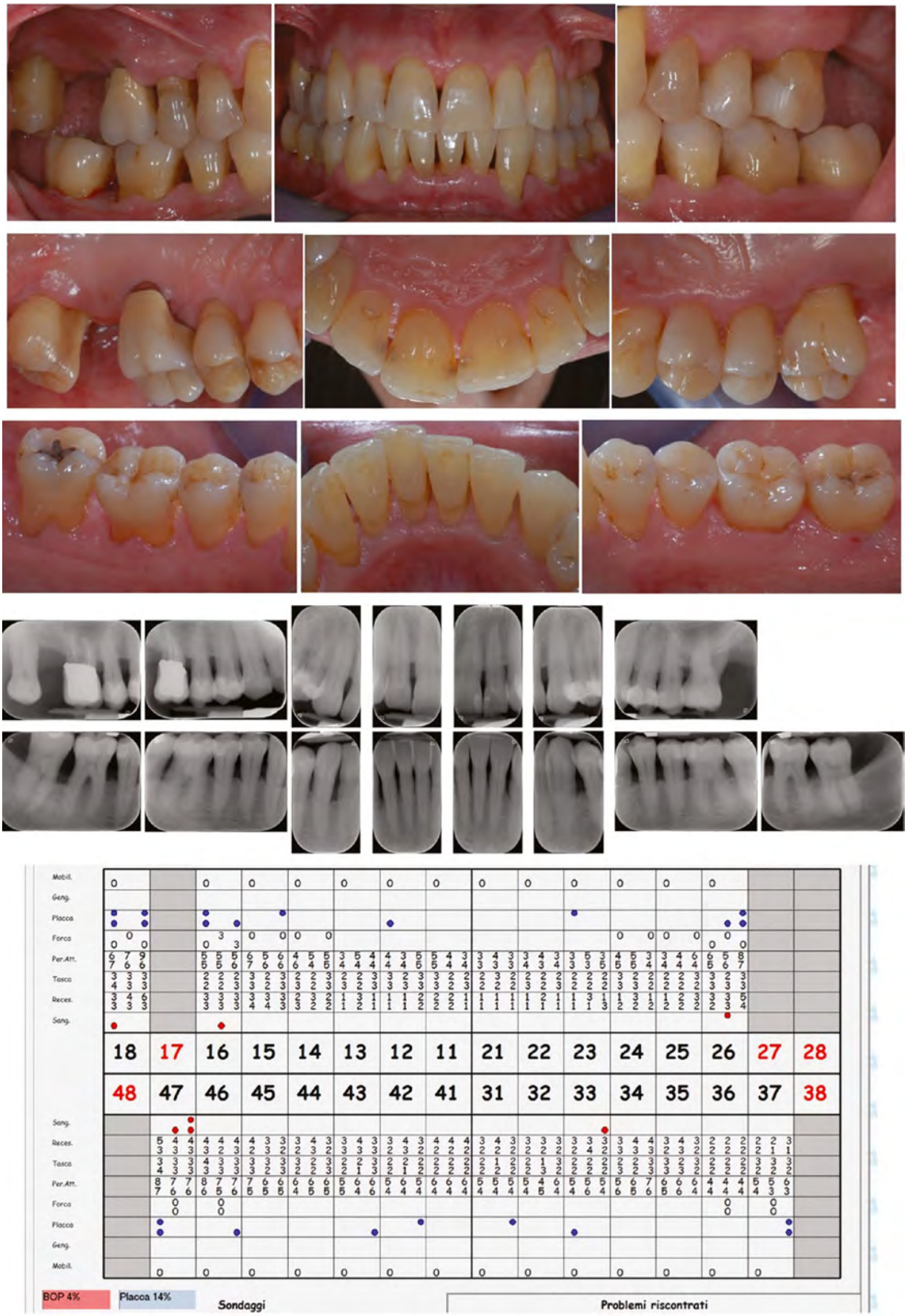


Fig. 25-25 Intraoral photographs, periapical radiographs, and periodontal chart of patient M.A. at completion of active therapy 18 months following intake.

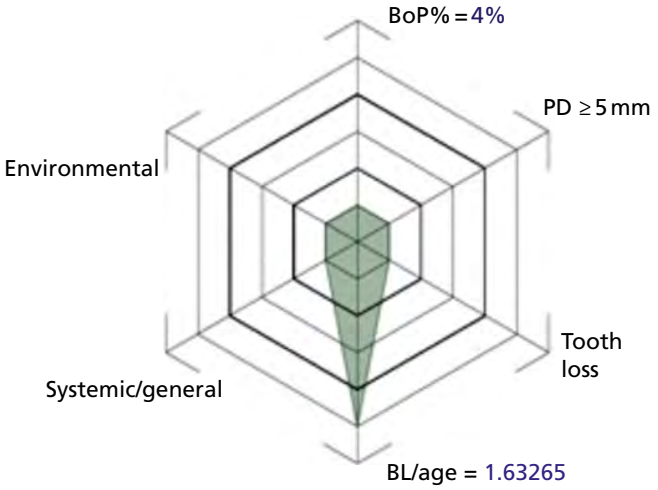


Fig. 25-26 Periodontal risk assessment of patient M.A. at completion of active therapy.

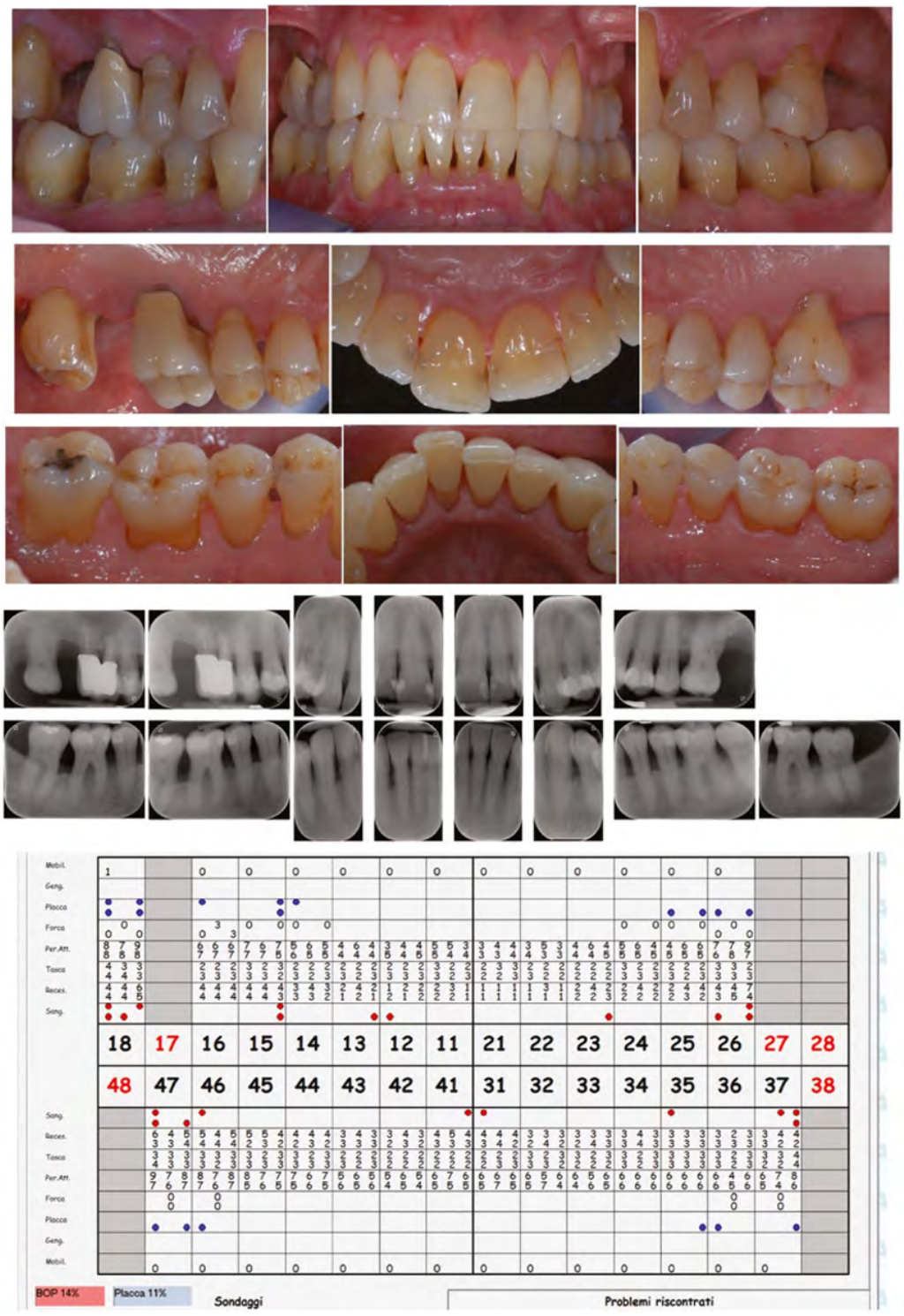


Fig. 25-27 Intraoral photographs, periapical radiographs, and periodontal chart of patient M.A. 10 years following completion of active therapy.

following principle: *in patients exhibiting a generalized advanced breakdown of the periodontal tissues, considerable efforts should be made to maintain a functional dentition*. Extraction of one single tooth in such a dentition will frequently call for the extraction of several additional teeth for "prosthetic reasons". The end result of such an approach thus includes a prosthetic rehabilitation that, if the treatment planning had been properly done, could have been avoided.

The large variety of treatment problems that different patients present may obviously require deviations from the sequence of treatment phases (i.e. systemic phase, initial cause-related therapy, corrective phase, and supportive care) discussed in this chapter. Such deviations may be accepted as long as the fundamental principles characterizing the treatment phases are understood.

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Chapter 26

Systemic Phase of Therapy

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Introduction

The systemic phase of periodontal therapy should be concerned with general health implications of periodontal diseases and periodontal treatment. While the former aspects are described in Chapters 11, 12, and 14, the latter aspects are presented in this chapter.

The systemic phase of periodontal therapy is designed to protect the patient against unforeseen systemic reactions, to prevent complications affecting the general health of the patient and to protect the health care providers from (predominantly infectious) hazards in conjunction with the treatment of patients at risk.

In order to plan the systemic phase adequately, results from a health questionnaire filled in by the patient in the waiting area, the family and social history, the general medical and, in particular, the tobacco use history have to be evaluated. Also, any extra- and intraoral findings pertinent to the patient's systemic health have to be considered.

The systemic phase of periodontal therapy encompasses:

- Precautions for protecting the general health of the dental team and other patients against infectious and contagious diseases
- Protection against potentially harmful systemic effects of routine therapy
- Making allowances for systemic diseases or disorders that may influence the etiology, the healing potential, and the systemic response to therapy
- Controlling anxiety and low pain threshold
- Risk assessment and considerations of systematic supportive periodontal and peri-implant therapy
- Smoking counseling and instituting tobacco use cessation programs.

Protection of the dental team and their patients against infectious diseases

As a general principle, routine periodontal therapy should be postponed in a patient with an active contagious state of a disease until he/she has received adequate medical treatment. Given the fact that patients may not always be aware of such a state or

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

that all manifestations of disease may have abated, but the patient may still be a carrier of infectious agents, routine dental treatment should be carried out using specific precautions against transmission of the most serious diseases being transmitted orally. These include hepatitis A, B, and C (Levin *et al*. 1974), human immunodeficiency virus (HIV) infection, and venereal diseases (Chue 1975). Hygiene in the dental office, therefore, has to address the most contagious level of infective agents, the hepatitis viruses, and cope with the prevention of the transmission of these infections. As a minimal precaution, the wearing of rubber gloves and a fluid-resistant surgical mouth mask (Type IIR) is highly recommended for all dental therapy in all patients. Also, protective glasses for both the therapist and the patient should be worn during procedures generating aerosols, and FFP3 masks, visors, gowns, and head covers may be required for patients with SARS-COV-2.

Herpes simplex virus (Nahmias & Roizman 1973) and tuberculosis are further infectious diseases with a high transmission potential. Special precautions should be observed in patients with a recent history (2–3 years) of hepatitis, although the dental team may be vaccinated against hepatitis. If the medical history and the oral examination reveal that the patient may have overt or hidden systemic disease, he/she should be referred for medical examination prior to enrolling the patient into comprehensive periodontal care.

Protection of the patient's health

A number of systemic conditions may affect treatment planning, although they may have no direct relevance upon the pathogenesis and healing potential of periodontal lesions. Because over 50% of patients over 40 years of age may have systemic conditions or take medications affecting periodontal therapy, these aspects have to be carefully appraised prior to instituting further therapeutic measures.

For patients with life-threatening systemic conditions, such as coronary insufficiency or hypertensive heart disease, their physician should be consulted about appropriate patient management and whether treatment should be performed in a hospital or specialist clinic rather than a private practice setting. If the dental office is considered to be an adequate environment for treating these patients, shorter appointments should be scheduled. The treatment should be performed with complete pain control using local anesthesia with appropriate vasoconstrictors.

Prevention of complications

The complications most commonly encountered in the dental office are:

- Infective endocarditis
- Bleeding
- Cardiovascular incidents
- Allergic reactions and drug interactions
- Specific medications: bisphosphonates.

These may be prevented if appropriate precautions are taken. Hence, gaining awareness of possible complications from a medical history is an important step in treatment planning and comprehensive patient care.

Infective endocarditis and its prevention

Infective endocarditis (IE) is an uncommon, but life-threatening endocardial infection that arises due to bacteremia in patients who have congenital or acquired cardiac abnormalities. The incidence of IE is 1 per 100 000 individuals per year (DeSimone 2015). It causes significant morbidity, such as the need for remedial cardiac surgery (Murdoch *et al*. 2009), and the estimated absolute risk of mortality arising following dental interventions is illustrated in Table 26-1.

Invasive dental procedures are traditionally regarded as the most common risk factor for IE and consequently antibiotic prophylaxis (ABP) prior to such interventions has been the standard of care for over 50 years in most parts of the world (Wilson *et al*. 2007; Habib *et al*. 2015).

Interestingly, the risk of fatal anaphylaxis due to penicillin is estimated as 1 in 100 000 when administered orally and higher when administered parenterally (Kaufman 2003). Such adverse event statistics have historically created a dilemma when deciding on the balance of mortality risk for using ABP in IE prevention versus mortality risk when not using ABP in specific groups at risk of IE (Table 26-1). Moreover,

Table 26-1 Absolute risk following dental interventions. (Source: Adapted from Lalani *et al*. 2013.).

Condition	Mortality (per procedure)	Increasing risk of IE
Mitral valve prolapse	1 per 1 100 000 procedures	
Congenital heart disease	1 per 475 000	
Rheumatic heart disease	1 per 142 000	
Prosthetic heart valve	1 per 114 000	
History of previous IE	1 per 95 000	

IE, infective endocarditis.

there is a longstanding lack of evidence from randomized controlled trials (RCT) for any efficacy of ABP in preventing IE, due to ethical concerns over conducting such studies. In 2008, this led to a landmark decision in the UK by the National Institute for Health and Care Excellence (NICE) to conclude that ABP prior to invasive dental procedures was not cost-effective and should stop (NICE 2008). In contrast, the 2007 American Heart Association (AHA) guidelines (Wilson *et al*. 2007) retained the recommendation for ABP in high-risk patients only, as did the 2009 guidelines from the European Society of Cardiology (ESC) (Habib *et al*. 2009). However, the ESC amended their guidance in 2015 by expert consensus, in order to provide "clear and simple recommendations" (Habib *et al*. 2015). The latter include the use of a single oral dose of amoxicillin (2 g) administered 1 hour prior to high-risk procedures, and a single dose of oral clindamycin 600 mg 1 hour preoperatively in penicillin-allergic patients. The ESC update was published just prior to new data demonstrating a higher risk of fatal adverse reactions to clindamycin than to amoxicillin (Thornhill *et al*. 2015), further complicating the clinical decision-making algorithms.

This section, therefore, aims to discuss the background and controversy of the last 10–15 years surrounding the use, or non-use, of ABP for IE prevention in dental surgery and to document the current consensus guidance, derived from the AHA, ESC, and NICE recommendations, recently summarized in a pragmatic and balanced implementation document produced by the Scottish Dental Clinical Effectiveness Program (SDCEP 2018).

Pathogenesis of infective endocarditis

IE develops as an outcome of a complex series of interactions between the blood coagulation system (platelets and fibrin), matrix molecules, and blood-borne bacteria entering the vasculature at distant sites, such as the periodontium or tooth socket. Thus, the term "infective" is used and the manifestations of the endocarditis emanate from the hosts' immune-inflammatory response. There are four stages to the process.

Stage 1: development of non-infectious thrombotic endocarditis

The endothelium becomes traumatized by long-standing turbulent blood flow across a congenitally deformed cardiac structure (e.g. valve), normally through a narrow orifice or where blood travels from a high pressure to a low-pressure system (e.g. septal defect). The turbulence activates platelets and causes fibrin formation, resulting in endocardial deposits.

Stage 2a: a transient bacteremia

Bacteremia arising due to organisms passing through an exposed wound during periodontal therapy or tooth extraction can introduce *Streptococcal* species such as *S. viridans*, *Staphylococci* or *Enterococci* capable of adhering to the damaged endocardium. For example, FimA proteins from streptococci or adhesins from staphylococci can bind the fibrin-platelet complex and form small vegetations (Burnette-Curley *et al*. 1995).

Periodontal probing, ultrasonic scaling, and toothbrushing all produce bacteremia, but there is a lack of evidence from adequately powered studies that this is larger the more severe the periodontitis (Kinane *et al*. 2005).

Stage 2b: chronic low-grade bacteremia

Alternatively to Stage 2a, vascular entry of oral bacteria during normal daily function, such as chewing, tooth brushing, and interdental cleaning has been demonstrated to create an exposure equivalent to 5730 minutes per month of bacteremia (Guntheroth *et al*. 1984). Indeed, it has been proposed that twice daily tooth brushing creates a 154 000 times greater risk of bacteremia than a single tooth extraction, and that the sum of all routine daily activities over a year may create a 5.6 million times greater cumulative exposure to bacteremia than a tooth extraction (Roberts 1999). A systematic review and meta- analysis of the impact of oral daily activities and bacteremia reported that plaque accumulation and gingival inflammation significantly increased the prevalence of bacteremia following tooth brushing (Tomás *et al*. 2012).

Stage 3: bacterial adherence

Various aforementioned mediators of bacterial adhesion (e.g. FimA or adhesins) facilitate bacterial colonization of the platelet/fibrin/endothelium complex and an infected vegetation forms.

Stage 4: vegetation formation due to bacterial proliferation

The initial colonizers provide a substrate for adhesion of additional bacteria and vegetation density can reach 108–1011 bacteria per gram of vegetation, particularly on the left side of the heart (Wilson *et al*. 2007).

Signs, symptoms, and clinical investigations for IE

Symptoms of IE can develop in an "acute" manner over just a few days, or more insidiously over several weeks (Thornhill *et al*. 2016). Early identification is critically important to survival statistics, and at-risk patients should be educated in their identification. They include:

- Night sweats
- Dyspnea on exertion (shortness of breath)
- Spiking temperatures of 38°C or higher (90% of cases)
- Fatigue

- Joint pains
- Muscle pains
- Weight loss (unexplained)
- Skin rash (petechial-like red spots)
- New or worsening heart murmur (85% of cases)
- Red and sore lesions under skin of toes and fingers called Osler's nodes
- Confusion
- Stroke.

Diagnosis of IE is challenging. C-reactive protein (CRP) levels are elevated but are a non-specific finding, and blood cultures are essential in order to try and isolate causative organisms by polymerase chain reaction (PCR) or traditional selective culture (Habib *et al*. 2015). Imaging techniques such as echocardiography and transesophageal echocardiography are extremely important investigations. In addition, MRI (magnetic resonance imaging), PET (positron emission tomography) or CT (computerized tomography) scans may also be necessary.

Evidence for efficacy of antibacterial prophylaxis and risks

Remarkably, there is no evidence to support the effectiveness of ABP in the prevention of IE (Lockhart *et al*. 2007), due to a lack of RCTs (Durack 1995). Therefore, the decision by NICE in 2008 to cease recommending ABP in the UK provided an opportunity to explore the impact of dramatically reduced rates of prescribing ABP upon changes to the prevalence of IE and associated mortality in the UK. Thornhill and coworkers (2016) employed "change point analysis" to analyze a large dataset on ABP prescribing between January 2004 and March 2013 from the English Health Service Business Services Authority against IE incidence data and associated mortality between January 2000 and March 2013, obtained from UK hospital episode statistics (Thornhill *et al*. 2016). They employed a segmented regression analysis of an interrupted time series, with the interruption point set at 2008, and also analyzed secondary codes to identify patients at high risk of IE and also the causative bacteria. They reported that the reduction in ABP prescribing post-2008 was strongly and significantly associated with an increase in IE incidence in England in that period (Dayer *et al*. 2015), accounting for a further 35 cases per month. However, there was an overall gradual trend towards increased IE incidence pre-withdrawal of ABP prescribing, and the increase was in both high risk and lower risk individuals. There was a trend towards an associated "in-hospital mortality" increase, but this did not reach statistical significance. This study, although controversial, provides some new evidence for the use of ABP in high-risk groups, due to the demonstration of a temporal relationship between new IE cases in England following dramatic attenuation in ABP prescribing. It does not, however, establish a causal relationship and randomized trials are needed to achieve this, although they would be ethically challenging.

A further important advance in knowledge was new data demonstrating the adverse event rates from using ABP for IE were lower than previously thought. The American Heart Association (AHA) report on the need for ABP in IE prevention did not identify any proven cases of mortality arising from anaphylaxis associated with ABP in the preceding 50 years (Wilson *et al*. 2007). Indeed, there was only one fatal case reported for the use of 2 g oral amoxicillin, the mainstay of ABP provision in almost 50 years (Lee & Shanson 2007). Thornhill and co-workers (2016) examined ABP prescribing data between January 2004 and March 2014 in England, and data reported routinely in England using a long-established adverse event reporting system. The UK recommended dose for oral amoxicillin is 3 g and in penicillin-allergic patients, clindamycin is used at a single 600 mg oral dose, 1-hour presurgically. They found no reported fatalities from over 3 million prescriptions of amoxicillin and 22.6 non-fatal reactions per million prescriptions (Thornhill *et al*. 2015). For clindamycin there were 13 fatal and 149 non-fatal reactions per 1 million prescriptions. The authors concluded that amoxicillin used for ABP against IE was relatively safe but raised the small number of fatal and non-fatal reactions to clindamycin as worthy of note. The 2015 ESC guidelines recommend 600 mg oral clindamycin in penicillin-allergic patients for ABP, which was questioned by Thornhill and colleagues (2016). However, it is important to recognize that, by definition, clindamycin is employed only in patients with a history of atopy (to penicillin), and therefore the comparison between the relative safety of the two regimes needs careful interpretation.

High risk groups for IE and high-risk dental procedures

There is substantial consensus between the AHA, ESC, and NICE guidelines regarding high-risk groups for IE, albeit based largely on expert opinion (Table 26-2). In addition, the AHA and ESC guidelines identify three sub-groups (in italic in Table 26-2) that require special consideration due to their elevated risk of life-threatening complications and dental practitioners should consult with a cardiologist for such cases.

The use of ABP in high-risk cases should be limited to high-risk (invasive) procedures and is not necessary for routine care (Table 26-3).

The ESC, AHA, NICE, and SDCEP guidelines all highlight the critical importance of attaining and maintaining good oral health and hygiene as a primary preventive strategy for IE. This advice includes hygiene around oral piercings and recognizes the

chronic entry of oral bacteria during normal daily function as being a far greater risk than isolated invasive dental procedures (Tomás *et al*. 2012).

Table 26-2 Consensus of The American Heart Association, the European Society of Cardiology, and the National Institute for Health and Care Excellence guidelines regarding high-risk groups for infective endocarditis (IE). Italic typeface cases require "special consideration".

High risk for IE	Moderate risk for IE
Previous episode of IE	History of rheumatic fever
Structural congenital heart disease, including surgically corrected or palliated structural conditions (NOT isolated ASD, fully repaired VSD, or fully repaired DA, and closure devices that have fully endothelialized)	Unrepaired congenital anomalies of heart valves
Prosthetic cardiac valve replacement or repair with prosthetic material	Native valve disease not classified as high risk, e.g. bicuspid aortic valve, mitral valve prolapse, calcification within aortic stenosis
Acquired valvular heart disease with stenosis or regurgitation, or shunts	
Any type of cyanotic heart disease	

ASD, atrial-septal defect; DA, ductus arteriosus; VSD, ventricular-septal defect.

Consensus regime for ABP in IE

The recommended regimes for ABP in situations where it is deemed wise and requested by the patient are largely consistent in recommending oral amoxicillin 2 g (3 g in the UK) and oral clindamycin, 600 mg in penicillin-allergic patients, 1 hour presurgically. Parenteral administration is associated with a higher risk of adverse events and should ideally be limited to procedures performed under general anesthesia. Here, patients are starved presurgically and *Staphylococcal* bacteremia of nasal origin following nasal intubation is believed to pose a particular risk. The SDCEP guidance advocates the use of azithromycin oral suspension (200 mg/5 mL) in penicillin-allergic patients who cannot swallow clindamycin capsules and provides recommended protocols for intravenous administration and for children/adolescents.

Consent – who makes the decision?

"Informed consent" is the core, underpinning principal for any medical treatment and essentially involves a patient agreeing to do something or to allow something to happen only after all relevant facts have been disclosed. Patients must be mentally and linguistically competent to understand all the material risks and consequences of the proposed procedure, as well as alternatives, and should have been allowed time

Table 26-3 The use of antibacterial prophylaxis in high-risk cases should be limited to high-risk procedures. (Source: Adapted from SDCEP guidance.)

High-risk (invasive) procedures	Low-risk procedures
Root surface debridement/subgingival scaling	Basic periodontal examination/community periodontal index of treatment needs (CPITN) screening
Full periodontal examination (pocket charting in inflamed tissues)	Supragingival scaling
Surgical procedures with mucoperiosteal elevation	Supragingival prophylaxis
Periodontal plastic surgery procedures	Suture removal
Incision and drainage of abscesses	Administration of block or infiltration anesthetic in non-infected tissues
Placement of dental implants and uncovering of implants (second stage surgery)	Radiographs
Subgingival restorations including fixed prosthodontics	Placement or adjustment of orthodontic or removable prostheses
Treatment of peri-implantitis using submucosal access	Supragingival orthodontic band placement
Tooth extractions	
Endodontic treatment before apical stop has been established	
Placement of matrix bands	
Placement of subgingival rubber dam clamps	
Placement of preformed metal crowns	

to ask questions and clarify any concerns. Ultimately, the treatment decision, based on presentation of risks and benefits by the clinician, is made by the patient.

Summary

There is a European and North American consensus on the provision of ABP for the prevention of IE following dental procedures. Recent new evidence has informed the debate on this controversial area, and whilst the evidence base for efficacy of ABP is poor, recent UK data has demonstrated that ABP should be considered for high-risk patients undergoing invasive (high-risk) procedures. The decision lies with the patient, but clinicians should provide data on the risks and benefits, as well as alternatives, in a manner understood by the patient, thus enabling the patient to decide on their preferred course of action.

Bleeding

Due consideration must be given to patient on anticoagulant medication or patients on preventive anticoagulant drugs. For the first group of patients, a consultation with the patient's physician is indispensable. Especially prior to periodontal or implant surgical procedures, temporary adjustment of the intake of anticoagulant medication should be undertaken in cooperation with the physician. Careful planning and timing of these procedures is mandatory.

Salicylate therapy does not generally create issues for routine dental therapy, including surgical procedures, although consultation with the patient's physician is still advisable.

Individuals with known liver cirrhosis, or even patients with high alcohol consumption over many years without diagnosed cirrhosis, are at a potential risk for bleeding complications during periodontal and/or implant surgery, as their clotting mechanisms may be affected (Nichols *et al*. 1974). Again, medical consultation is recommended prior to periodontal treatment of such patients.

Extra precautions against bleeding should be taken when treating patients with any kind of blood dyscrasia or hemophilia. Following mandatory consultation with the patient's physician, it is recommended to render treatment in small segments (only a few teeth being instrumented at each visit) and to apply periodontal dressings over the treated area, even if the treatment only consisted of root instrumentation. With systematic periodontal treatment and institution of efficacious oral hygiene measures, the challenging symptom of oral bleeding can often be controlled irrespective of the patient's bleeding disorder.

Cardiovascular incidents

Cardiac patients are often treated with anticoagulants and, hence, may develop bleeding problems (as indicated previously), especially if their prescribed drugs (e.g. aspirin, indomethacin, sulfonamide, tetracycline) interact with coagulation. Other cardiovascular drugs (e.g. antihypertensive, anti-arrhythmic, diuretic) are often used in these patients and may increase the danger of hypotensive episodes during dental treatment.

Stress associated with dental procedures may precipitate anginal pain or congestive heart failure in patients with cardiovascular disease. Therefore, every effort should be taken in this patient population to keep dental appointments brief and to control anxiety and pain.

Allergic reactions and drug interactions

Full awareness of the patient's known allergies and the medications he/she is taking is essential before any drug is prescribed, administered, or used during treatment. The most common allergic reactions encountered in the dental office are those to some local anesthetics (Novocain®), penicillins, sulfonamide derivatives, and disinfectants, such as iodine. In case of known allergies, such drugs must be avoided. A consultation with the patient's physician is advisable to discuss the possible administration of replacement drugs.

Many patients – over 90% of those over the age of 60 years – regularly take medications for various systemic conditions. Special attention has to be devoted to possible drug interactions, especially in the elderly. Drugs prescribed as part of periodontal therapy or used during treatment may interfere with the effectiveness of drugs the patient is already taking, possibly creating a hazardous interaction. Hence, no new drugs should be prescribed without fully understanding their possible interaction with drugs already in use. Dentists should never change an existing drug therapy without prior discussion and preferably written consent from the physician.

Many patients regularly take tranquilizers and antidepressant drugs that have the potential for summation and synergistic effects with drugs that may be used during periodontal therapy. Moreover, the interaction and potentiation of these drugs with alcohol should be discussed with the patient.

Systemic diseases, disorders, or conditions influencing pathogenesis and healing potential

All possible attempts should be made to alleviate the effects of systemic diseases, such as blood disorders and diabetes mellitus, before any periodontal treatment is initiated. However, cause-related therapy may easily be carried out and generally results in remarkable success even during active stages of these systemic conditions. How far the treatment plan should progress with respect to pocket reduction and/or regenerative surgical procedures depends on

the seriousness of the patient's systemic involvement and likewise, to a great extent, on the potential threat to the patient's health from incomplete periodontal therapy.

Diabetes control, as an example, may be facilitated by successful control of the periodontal infection (Grossi *et al*. 1997; Genco *et al*. 2005). Thus, periodontal treatment may have a beneficial effect on the systemic health of the patient. Palliative treatment of advanced periodontitis with furcation involvement and residual deep pockets that cannot be reduced should not be undertaken for such patients. Rather, the involved teeth with repeated abscesses and pus formation should be extracted if necessary to accomplish infection control.

Clinical experience indicates that the healing response of the periodontal tissues is as good in patients with diabetes as in healthy individuals provided that the diabetes is well controlled. However, patients with juvenile diabetes may have angiopathic changes associated with a lowered resistance to infection that may require the use of antibiotics following periodontal or implant surgery. With controlled diabetes, premedication with antibiotics is not indicated. Hypoglycemia may be aggravated by the stress of periodontal surgery and, hence, precautions have to be taken to avoid hypoglycemic reactions in such patients.

Therapeutic doses of cortisone over a long period of time may cause considerable metabolic effects with systemic manifestations of a reduced rate of fibroblastic activity and hence, a lowered resistance to infection during wound healing. Nevertheless, such patients can be treated successfully by regular cause-related therapy with no significant delay in healing. The use of antibiotics is not recommended for these patients, unless there is a serious infectious condition in the mouth associated with the development of fever or swelling that is compromising the airway.

Specific medications: bisphosphonates as a threat to implant therapy

More than 10 years ago it was discovered that nitrogen-containing bisphosphonates inhibit an enzyme that controls osteoclastic function. The inhibition of this enzyme also inhibits the migration of the cells responsible for osseous healing. Hence, it is most likely that osteonecrosis may result from the inhibition of cell migration in cases of surgically exposed bone such as in implant installation. Bisphosphonate-related osteonecrosis of the jaws (BRONJ), therefore, represents a risk that should not be underestimated even in patients who are taking *oral* bisphosphonates. It should be a warning to all implant dentists that as early as 1 year after *oral administration* of biphosphonates, BRONJ has been reported (Sedghizadeh *et al*. 2009). Following the discovery of these results, a new pharmacokinetic model was developed to assess drug accumulation at 1 year. In this model the accumulated concentration of bisphosphonates in bone appears to predict toxic levels that lead to poor healing, when the jaw bone is exposed as a result of surgical therapy. This new mechanism for BRONJ was discovered by Landsberg *et al*. (2008). In this model the relevant toxicity level does not necessarily affect osteoclasts as hitherto believed, but it affects keratinocytes, endothelial cells, fibroblasts, macrophages, osteoblasts, osteoclast precursor bone marrow cells, and T-cells. All these cells are heavily involved in the healing of surgically denuded bone. Hence, it is most likely that by impaired osseous wound healing nitrogen-containing bisphosphonates may lead to BRONJ. Non-nitrogen bisphosphonates do not cause BRONJ.

The *in vitro* threshold for inhibition of keratinocyte migration (0.1 µM) was used as the toxic bisphosphonate level for wound healing inhibition in cases of surgically denuded bone. By administering an equivalent of 70 mg Fosamax® weekly, the number of doses resulting in toxic threshold levels could be calculated for various bone masses. The size of the individual's skeleton may therefore be the determining factor for the risk of BRONJ. Since the total quantity of bone mineral into which nitrogen containing bisphosphonates are stored affects the toxic threshold of a patient, it is obvious that the skeleton of smaller patients will reach toxic levels sooner than in larger patients. Once the toxic threshold for nitrogen-containing bisphosphonates in bone is surpassed, osteoclastic resorption will release enough drug to inhibit the ingrowth of the cell's indispensable for healing of denuded bone.

In patients on bisphosphonate medication, it is of utmost importance to evaluate carefully the history of the medication and relate it to the habitus of the patient before making decisions on possible implant or other surgical therapy. Consulting with the patient's physician is highly recommended.

Control of anxiety and pain

Many patients interested in maintaining a healthy dentition do not regularly seek dental care because of anxiety and apprehension related to such treatment. A recent study conducted in Australia revealed a prevalence of dental fear in adults ranging from 7.8% to 18.8% and of dental phobia ranging from 0.9% to 5.4%, respectively (Armfield 2010). Modern dentistry offers a variety of effective means for controlling pain and apprehension. This, in turn, means that dental treatments should no longer be feared by these patients. During history taking and the oral examination, the patient's profile regarding anxiety and pain thresholds should be considered.

Prior to therapy, an apprehensive patient may be premedicated using diazepam (benzodiazepine, Valium®, 2–5 mg) taken the night before, in the morning, and half an hour before an extensive

and/or surgical procedure. Painless dental care can be achieved by carefully and slowly applying local anesthetics.

Postoperative analgesic medication, such as non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and antipyretic properties are recommended. Diclofenac potassium, the active ingredient of Voltaren® (Voltarol) Rapid, inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. Following any kind of periodontal and implant surgery, 50 mg twice daily of Voltaren® Rapid is administered for 3 days (note: patients with gastric ulcers should not receive Voltaren® Rapid and care should be taken in patients with asthma). In addition, further adjunctive pain killers (mefenaminic acid, e.g. Ponstan® or Mephadolor® 500 mg not more than every 6–8 hours) may be prescribed depending on the individual patient's need and pain threshold.

Favorable personality interactions between the patient, the therapist, and the entire office staff may contribute to the overall control of anxiety but may require more time and consideration than that allocated to the routine patient.

Tobacco use cessation counseling

Second to poor oral hygiene habits, cigarette smoking constitutes the most important modifiable risk factor in the etiology and pathogenesis of periodontal diseases (Ramseier 2005; Ramseier *et al*. 2020). A careful assessment of the patient's smoking history has therefore become indispensable for comprehensive periodontal care.

In order to support periodontal patients to quit tobacco use, it is helpful for the clinician to have a proper understanding of the genesis of tobacco dependence. The term *tobacco dependence* refers to the condition of tobacco users suffering from both psychological tobacco use dependence and physical addiction to nicotine. Therefore, in order to predictably help people who smoke to quit, any approach to support tobacco use cessation should include both behavioural support to address the psychological component of the dependence and pharmacotherapy to treat the physical symptoms of withdrawal.

Today, professional evidence-based methods for tobacco use cessation predominantly consist of professional behavioural change counselling applying the so called "5A Method" (Ask, Advise, Assess, Assist and Arrange) in combination with pharmacotherapy. It has been shown that the success rates achieved by smoking cessation counselling are generally dependent on (1) the amount of time spent counseling, and (2) the prescribed drug. The success rates achieved by counseling lasting for 1–3 minutes, 4–30 minutes, 31–90 minutes, and >90 minutes are 14.0 %, 18.8 %, 26.5% and 28.4%, respectively (Fiore *et al*. 2008).

For practical reasons, periodontal care of people who smoke includes tobacco use brief interventions lasting 3–5 minutes at each appointment while focusing on the "AAR Method" (Ask, Advise, Refer) (Ramseier *et al*. 2010, Tonetti *et al*. 2015):

1. *Ask*: It is well recognized that the general medical history form plays a critical role in asking all patients about their tobacco use history. Asking all patients on a regular basis, allows a non-threatening introduction to the ensuing conversation between oral health professional and patient.
2. *Advise*: When advised and further asked about their readiness to quit, tobacco users often reply that they want to quit smoking "sometime" but that the time is not yet right. There are certain things they need to do first, which are seen as more important than giving up smoking. Even if the patient feels that they are ready to quit smoking, there may still be some uncertainty about the next steps. They may experience a lack of confidence to achieve this goal and feel under prepared to make a quit attempt. Behind this attitude is often the fear of failure, potential change to social habits, or worry about unwanted weight gain.
3. *Refer*: Making the arrangements for on-going support either via the dental office or other health agencies may provide the patients with valuable resources as they undertake a quit attempt. When available, referring to professional tobacco use cessation counseling services, whether in-house (including suitably trained dental personnel) or external (e.g. www.quitline.com) should be pursued.

Tobacco use brief intervention

A brief intervention for tobacco use cessation using motivational interviewing is presented in a clinical case example dialogue between a periodontist (Dr) and a patient (P) at the beginning of periodontal therapy (for more detailed information on motivational interviewing see Chapter 27).

Dr	"According to your tobacco use history, you are currently smoking cigarettes. May I ask you a few questions about your smoking?"	*Raising the topic Asking permission*
P	"Yes."	
Dr	"Could you tell me how you feel about your smoking?"	*Asking open questions (eliciting what the patient already knows)*
P	"Well I know I should quit. I know it's not good for my health. But I don't want to quit right now."	
Dr.	"So you don't feel that you want to quit right now, but you do have some concern about the health effects."	*Rolling with resistance*

P	"Yes."	
Dr	"Well, tell me more about what concerns you?"	
P	"Well, mainly that I would get lung cancer or something."	
Dr	"So you worry a bit about getting cancer because of smoking. Is there anything else that you don't like about smoking?"	
P	"Well if I quit my clothes would stop smelling."	
Dr	"So the smell of tobacco smoke is something you would like to be rid of?"	
P	"Yes, but I've smoked for many years, you know, and I tried to quit once before."	
Dr	"So even though you would like to be a non-smoker for health and other reasons you haven't had much success quitting."	*Reflecting on ambivalence*
P	"Yes, and right now I'm enjoying smoking so there's not much motivation to do try."	
Dr	"Well it sounds like even though you have some important reasons to quit, you're not very confident you could succeed and you don't feel ready to take on this challenge right now. I wonder if it would be OK for us to talk about this again next time to see where you are with it and whether I could help?"	*Summarizing*
P	"Yes that sounds fine."	

Conclusion

The goals of the systemic phase of periodontal therapy are to appraise those aspects that both the dental team and the systemic health of the patient may need to be protected against. Infection control in the dental office plays a central role. Protecting the patient against presumptive complications, such as infection, especially bacterial endocarditis, bleeding, cardiovascular episodes, and allergies, requires in-depth knowledge of the patient's medical history and oral examination.

Infective endocarditis prophylaxis is nowadays reserved for those patients with a history of a previous infective endocarditis, prosthetic heart valves, or surgically constructed conduits, and the use of antibiotics before dental treatment is unnecessary for patients with other cardiac abnormalities. Patients with systemic diseases such as diabetes mellitus or cardiovascular diseases are usually treated with a number of medications that may interact with drugs prescribed during periodontal therapy. Precautions should be taken, and consultation with the patient's physician prior to systematic periodontal therapy is recommended.

It has to be realized that periodontal treatment may also have a beneficial effect on the systemic health of the patient. Glycemic control may be facilitated in patients with diabetes if proper periodontal therapy is rendered.

Finally, tobacco use cessation counseling is part of modern periodontal treatment owing to the fact that, after inadequate oral hygiene standards, cigarette smoking constitutes the second most important risk factor for periodontitis.

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Part 11: Initial Periodontal Therapy (Infection Control)

Chapter 27

Oral Hygiene Motivation

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Health behavior change counseling in periodontal care

Periodontal health is supported by healthy behaviors such as regular self-performed plaque control, avoidance of tobacco, and glycemic control in type 2 diabetes mellitus. Inadequate oral hygiene, tobacco use, and uncontrolled glucose levels, on the other hand, are shown to have a destructive impact on periodontal tissues. The dental community involved with oral health care should strive to enhance their understanding of the beneficial effects of healthy behaviors to target prevention and disease control successfully. With increasing evidence to support the potential benefits of health behavior change interventions, services aimed at the improvement of prevention on the individual level oriented toward encouragement of beneficial lifestyle behaviors have become a professional responsibility for all oral health care providers.

Data from epidemiological studies consistently reveal the prevalence of periodontal diseases in 20–50% of the adult population (Eke *et al*. 2012; Ide & Papapanou 2013). Gingivitis and periodontitis are initiated by oral pathogens that colonize to form a plaque biofilm (referred to as a polymicrobial community), then further modulated by local or systemic host factors (Hajishengallis & Lamont 2014). Based upon current models of periodontal pathogenesis, it is well accepted that disease occurs as a result of the interplay between the commensal microbiota, host, and environmental factors (Lang & Bartold 2018). Therefore, removal of the plaque biofilm remains as one of the key factors in attaining and maintaining periodontal health and therefore a prime focus for clinicians in facilitating adequate patient self-care.

In addition to the causal relationship of dental biofilms, a positive association between periodontal disease and tobacco use has been documented (Bergström 1989; Haber *et al*. 1993; Tomar & Asma 2000). Tobacco use contributes to the global burden of public health with almost one-third of the adult population using various forms of tobacco and an increasing number of annual deaths from tobacco-related diseases. Moreover, dietary factors have been shown

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to significantly impact chronic diseases including obesity, cardiovascular diseases, type 2 diabetes, cancer, osteoporosis, and oral diseases (Petersen 2003; Suvan *et al*. 2018).

In summary, there is sufficient evidence to suggest that the patient's individual lifestyle behaviors are seen to be critical for the success of periodontal therapy with the benefits of therapy diminished in patients lacking in appropriate behaviors. In recent systematic reviews, it has been shown that in addition to self-performed plaque control, smoking cessation and the promotion of healthy lifestyles were the most important measures for the management of periodontitis (Carra *et al*. 2020; Ramseier *et al*. 2020). Therefore, it appears to be reasonable in clinical concepts for periodontal care to:

1. Incorporate behavior change techniques or tools to enhance patient motivation and capability toward oral hygiene self-care
2. Include holistic assessments of patient behaviors
3. Provide effective risk factor control interventions and behavior change counseling methods (where applicable).

The challenge

Since the 1960s, following the confirmation of plaque as an etiologic agent in gingival and periodontal inflammation by Löe and co-workers, periodontal care has traditionally included the instruction of effective oral hygiene procedures (Löe *et al*. 1965). In practice, as an example, a demonstration of a suitable toothbrushing method would be given to the patient, followed by recommendations of both the frequency and length of time per brushing. Earlier studies on the effectiveness of oral hygiene instructions consistently revealed that patient adherence to a proper daily oral hygiene regime fluctuates or generally remains poor (Johansson *et al*. 1984; Schüz *et al*. 2006). The reinforcement of oral hygiene habits through additional recall appointments may sometimes compensate for the ineffectiveness of one-time or repeated oral hygiene instructions. However, due to inconsistent patient adherence to clinician recommendations, supportive periodontal care visits are often cancelled resulting in a lack of professional maintenance care, in addition to wavering self-care, thus resulting in the further potential for recurrence of periodontal inflammation (Wilson *et al*. 1984; Demetriou *et al*. 1995; Schüz *et al*. 2006).

Unfortunately, many health education approaches seem to be inefficient in accomplishing long-term behavior change, potentially leading to frustration for both the patient and the clinician. The following hypothetical dialogue between a clinician (C) and a patient (P) illustrates how using a directive advice-oriented method for behavior change counseling may lead to an unproductive conversation and little likelihood of change by the patient:

C "Are you using the interdental brushes regularly?"
P "Yes, but not as often as I should."
C "I would strongly recommend that you try to use them daily. As you probably know there may be serious consequences if you don't clean between the teeth frequently enough."
P "I know I should use them more often, but…"
C "It's not something that is optional but rather very important!"
P "I know … …but I don't have the time!"

Since the clinician fails to offer the patient a chance to discuss the reasons to clean interdentally on a regular basis or the patient's perceived barriers to using interdental cleaning aids, the conversation reaches an impasse and behavior change becomes unlikely. In certain cases, the patient may even be blamed for poor compliance and further oral health education may be seen as pointless.

In order to reliably achieve beneficial outcomes in periodontal care, effective oral hygiene self-care (and risk factor control) is critical, and therefore it may be necessary to apply different tools or techniques as part of behavior change interventions for each individual and behavior. This can appear complicated and discouraging for clinicians. However, a focus on approaches based upon health behavior change principles common across a multitude of psychological theories can serve to simplify learning and application of health behavior change methods for clinicians. Motivational interviewing is an example of an approach that encompasses aspects fundamental to facilitating choice of healthy lifestyle habits and health behavior evidenced in the field of behavioral sciences. The preferred aim is to apply approaches to clinical practice that are shown to be effective in both primary and secondary prevention of oral diseases and are:

- based on the best available evidence
- applicable to oral hygiene behavior, tobacco use prevention and cessation, and dietary counseling, and
- suitable for implementation by the dental practice team in a cost-effective way.

Clinician–patient communication

At the center point of achieving meaningful clinician–patient interactions, regardless of the topic, lies the importance of effective communication. There are several different communication styles used, largely unconsciously, when interacting with people in everyday life. In providing patient care, evidence from psychological models suggest it is preferable to adapt to each patient's individual behavioral needs and to their own perceived interests or concerns using styles of communication as an advantage. As a framework for communication, Rollnick and colleagues have

proposed a three-style model for health care clinicians to communicate with their patients in daily practice, consisting of a directing, guiding, or following style (Rollnick *et al*. 2008):

- A *directing* style includes the delivery of expert advice and support. This has traditionally been a standard approach within dental care settings. Directing is appropriately used where there is a good rapport between the clinician and the patient. The advice should be well-timed, personally relevant, and delivered in such a way as to engage the patient. A directing style can be used after the patient poses a question or expresses interest in a topic. For example, "What can I do to stop the need for scaling every time I come back here?".
- A *following* style relies upon attentive listening skills and occurs in situations where understanding or sensitivity is required (such as when a patient has a particular concern or is perhaps upset). The goal of a clinician using a following style is not to immediately solve the patient's problem, but to provide support and encouragement. The *following* style is a valuable tool in enhancing rapport as it is a tangible demonstration of respect for the patient and their concern. As an example, the following style can be used after the patient has said something like: "There's so much going on in my life and now I am discouraged about my teeth too."
- In *guiding*, the clinician is collaborating with the patients to help them identify the patient's own goals, and how they might best achieve them. This style is most appropriate in clinician–patient discussions about health behavior changes, especially with individuals who may be ambivalent about changing a habit. An example of a statement of ambivalence might be: "I know that smoking isn't good for me, but it's the only pleasure I have in life". A *guiding* style would explore both sides of the statement further to allow the patient to identify for themself how to move from this ambivalent position.

During health behavior change conversations, some patients may benefit from *direction*, particularly those who have expressed interest in further information or advice. Others may have more pressing concerns and therefore need to be *followed*. However, those patients who appear to know what they need to do, but have not managed to do it yet, will be most receptive to a *guiding* (Rollnick *et al*. 2008).

During patient communication, it is important to be sensitive to the patient's response to the various styles of communication and to flow seamlessly between the styles as appropriate. If the rapport between the clinician and the patient seems to be interrupted this may be an alert that the style is too directive and not sufficiently engaging for the patient. The primary aim is for the interaction to be shared collaborative communication. Throughout all communication interactions with the patient, it is valuable to remember that asking questions should only occur when the patient is able to respond comfortably (i.e. without being interrupted by the clinician). Without this consideration, communication success will be challenged as the patient may feel a loss of control. A guiding interaction with the optimal opportunity to facilitate behavior change is based upon rapport and respect. It is focused on enhancing patient perception of autonomy, self-control or self-efficacy.

To keep a good balance of both rapport and progress being made toward establishing healthy habits during patient communication, four primary communication techniques may be considered and are summarized with the acronym OARS: *O*pen-ended questions, *A*ffirm the patient, *R*eflect, and *S*ummarize:

- *Ask open-ended questions*: Approaching the patient with multiple closed-ended questions (question that will be answered with "yes" or "no" or one-word responses) sets the patient's role to be passive rather than active. Open-ended questions invite thought, collaboration, and effort on the part of the patient. Example: "How do you feel about your oral hygiene regime?"
- *Affirm the patient*: It is human nature to presume a negative attitude, particularly when one's own behavior is coming under scrutiny. Acknowledging the patient's strengths and appreciation of his or her honesty will decrease defensiveness, increase openness, and the likelihood of change. Example: "You're clearly telling me just why you're not very concerned about your toothbrushing and I appreciate that honesty".
- *Reflect on what the patient is communicating*: Reflection is the primary way to demonstrate empathy (ability to understand another person's perspective). Appropriate reflection includes the genuine effort to understand the patient's perspective. It (1) captures the underlying meaning of the patient's words, (2) is concise, (3) is spoken as an observation or a comment, and (4) conveys understanding rather than judgment. Example: "You really seem to have lost hope that you will ever manage to clean between your teeth on a daily basis."
- *Summarize*: Summarizing the patient's statements demonstrates interest, organizes the conversation, and can be utilized to redirect a conversation that may have diverged, if necessary. It involves the compilation of the patient's thoughts on making a change in habit or behavior mentioned during the interactions. For example, "So there's a big part of you that doesn't feel ready to change right now. You really enjoy smoking, but you have been a little worried by the way some people react when they find out that you smoke. Is that about right?"

Evidence for health behavior change counseling

Evidence in general health care

Evidence for the positive impact of health behavior change interventions has generally grown over the past few years. Today, several internationally accepted clinical practice guidelines are available for various health behavior change interventions such as smoking cessation (Fiore *et al*. 2008), diabetes control (WHO 2006; Powers *et al*. 2017; VA/DoD 2017), physical exercise (WHO 2010; Rütten & Pfeifer 2016; Azar 2018), change of diet (WHO 2004; FANTA 2016) including carbohydrate reduction (WHO 2015), and weight loss (NIH 1998; Yumuk *et al*. 2015; Fitzpatrick *et al*. 2016). Most suggested methods include initial brief interventions followed by more extended counseling mostly adopting the basic principles of motivational interviewing (MI). A common recurring theme, across both behavioral scientists and clinicians, is the proposition that a patient's intrinsic motivation is related to patient values, experiences, understanding of risk, feelings of confidence, and self-esteem (Deci & Ryan 2012).

MI was initially developed for the treatment of addictive behaviors, particularly alcohol addiction. Therefore, the bulk of empirical studies pertaining to MI has been conducted in this area. Nevertheless, the explosion in the application of MI to other areas of behavior change has been sufficient to provide evidence for numerous published meta-analyses (Burke *et al*. 2003, 2004; Hettema *et al*. 2005; Rubak *et al*. 2005; Lundahl *et al*. 2010; Magill *et al*. 2018), the more recent of which include nearly 100 clinical trials and more than 3000 participants. The overall majority of meta-analyses indicate that MI-based interventions are at least equivalent to other active treatments and superior to no-treatment or placebo controls for addressing lifestyle choices involving addictive behaviors (drugs, alcohol, smoking, and gambling), health behaviors such as diet and exercise, risk behaviors, and treatment regime engagement, retention, and adherence. Effect sizes, on average in the medium range, are mostly dependent on counseling skills (Hettema *et al*. 2005; Lundahl *et al*. 2010; Magill *et al*. 2018). Of particular relevance to dental settings where only brief counseling is feasible, is that MI-based interventions are similarly efficacious as alternative active interventions despite involving significantly less contact time, suggesting that MI may be a particularly efficient method of counseling (Burke *et al*. 2004; Lundahl *et al*. 2010). Rubak *et al*. (2005) reported that in brief encounters of 15 minutes, 64% of studies showed a beneficial effect. In addition, when the intervention was delivered by physicians, an effect was observed in approximately 80% of studies suggesting that it is feasible for professionals who are not counseling experts to effectively deliver MI in brief encounters (Rubak *et al*. 2005).

Another particularly relevant target behavior for oral health is dietary habits. As indicated, meta-analyses have found significant effects of MI for changing dietary habits. Specifically, these studies have documented changes due to MI in overall dietary intake (Mhurchu 1998), fat intake (Mhurchu 1998; Bowen *et al*. 2002), carbohydrate consumption (Mhurchu 1998), cholesterol intake (Mhurchu 1998), body mass index (BMI) (Mhurchu 1998), weight (Woollard *et al*. 1995), salt intake (Woollard *et al*. 1995), alcohol consumption (Woollard *et al*. 1995), and consumption of fruits and vegetables (Resnicow *et al*. 2001; Richards *et al*. 2006). Particularly noteworthy when considering evidence of MI to facilitate health behavior change interventions in general health care settings are the similarities in effects across disciplines and lifestyle behaviors, suggesting the wide applicability of the methods.

Evidence in periodontal care

Within oral health care, an early study investigating the impact of MI in oral care examined the effect of its use compared with traditional health education for motivating 240 mothers of young children with high risk for developing dental caries to use dietary and non-dietary behaviors for caries prevention (Weinstein *et al*. 2004, 2006). In this study, an MI session and six follow-up phone calls over a year, in addition to an educational pamphlet and a video, was more effective than the pamphlet and video alone in preventing new dental caries among the children after two years. This result has been consistent with the results of the meta-analyses that have found MI to be efficacious on oral health for dietary change (Burke *et al*. 2003; Hettema *et al*. 2005; Lundahl *et al*. 2010).

Related to oral hygiene motivation, both short and long-term studies over the past decade have demonstrated a positive impact on (1) oral hygiene as measured by plaque indices, and (2) gingival inflammation as assessed by gingival indices. Almomani *et al*. (2009) were able to demonstrate a significant positive impact on oral hygiene in a 2-month trial. Subsequently, Jönsson *et al*. (2009a) conducted a case series pilot study with two patients over 2 years to follow the impact of an individually tailored oral hygiene program on the periodontal indices mentioned (Fig. 27-1). Following MI sessions using the techniques described in the present chapter as well as oral hygiene instructions on an individual basis as described in Chapter 28, both patients succeeded to improve their oral hygiene and their gingival health over an observation period of 2 years (Jönsson *et al*. 2009b). The same authors subsequently demonstrated the positive impact of MI in a larger study with 113 patients over a period of 12 months (Jönsson *et al*. 2009a, 2010).

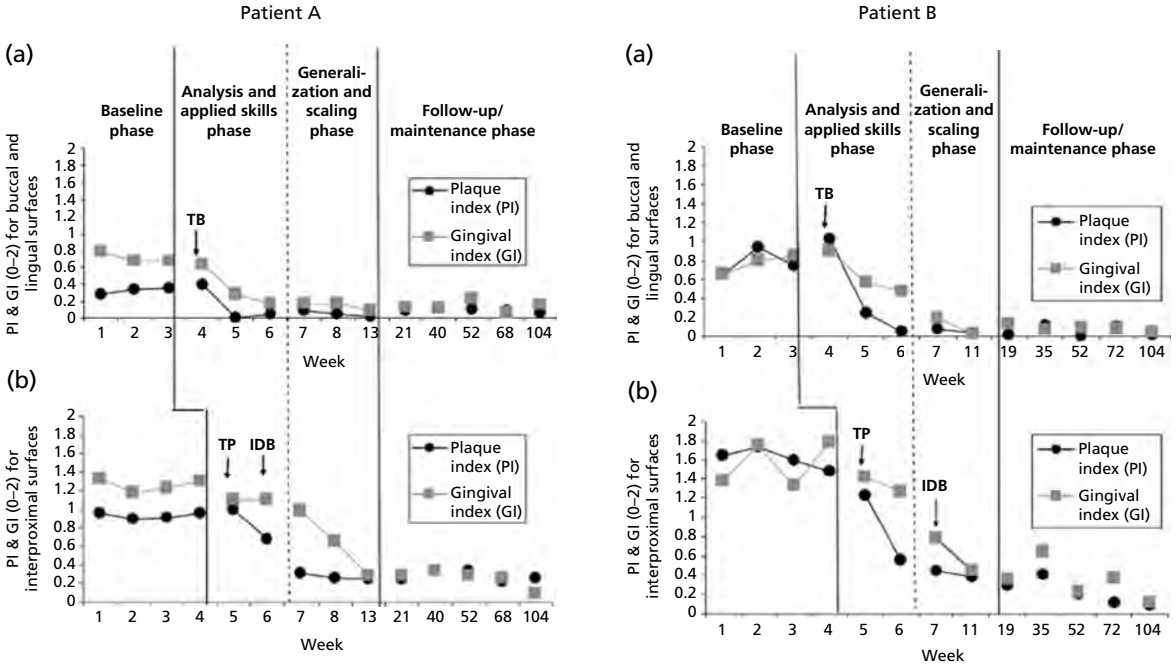

Fig. 27-1 Following an individually tailored treatment program for improved oral hygiene, both full mouth and interproximal plaque index and bleeding index from patient A and patient B dropped significantly over an observation period of 104 weeks. IDB, interdental brush; TB, toothbrush: TP, toothpick. (Source: From Jönsson *et al*. 2010. Reproduced with permission from John Wiley & Sons.)

In summary, evidence-based support for MI as an effective method of counseling for oral hygiene motivation is increasing. Two recent systematic reviews demonstrated improved effectiveness of MI when being implemented in periodontal care (Kopp *et al*. 2017; Carra *et al*. 2020). Moreover, two clinical trials demonstrated their positive impact of MI on communication with patients undergoing periodontal therapy (Woelber *et al*. 2015; Kitzmann *et al*. 2019).

Although second to plaque control, smoking cessation was found to be the next most important measure for the management of periodontitis (Ramseier 2005). Additional evidence suggests that dietary counseling using the principles of MI has an additional positive impact on clinical outcomes following periodontal therapy (Woelber *et al*. 2017, 2019).

Understanding health behavior change counseling

As discussed, focused health *education* efforts provided by clinicians are frequently ineffective in stimulating lasting changes in patient behavior. Considerable behavioral research suggests that the root of this common problem can be traced back to a false assumption inherent in the health education approach. Specifically, that behavior change is simply a function of a patient having the requisite knowledge or understanding, and that the role of the clinician is to provide the relevant information. MI, in contrast, is based on a different assumption of human behavior change. It assumes that the knowledge is insufficient to bring about behavior change and that, instead, sustained behavior change is much more likely when change is connected to something the individual values. In other words, motivation is elicited "from within the patient" rather than externally imposed upon the patient by a clinician. In MI, the assumption is that individuals have "within them" their own reasons for changing and that the role of the clinician is to elicit and reinforce these reasons. Similarly, patients are also the best person to identify attainable goals and the possible steps to reach when guided by a collaborative clinician.

As previously mentioned, MI originated in the field of addictive behavior but has increasingly been applied to a wide variety of other behavior change problems including health behaviors such as tobacco use, and diet and exercise (Burke *et al*. 2004; Hettema *et al*. 2005). The method was originally developed by William Richard Miller in response to his observations of the confrontational approach that was standard treatment for patients with alcohol problems in the 1970s. In contrast, he observed that the research literature suggested that positive outcomes were mostly related to a strong bond or "therapeutic alliance" between the counsellor and the patient. Miller developed an empathy-centered treatment which used the *therapeutic alliance* and *empathy* to engender the client's inherent motivation to change (Miller 1983). Subsequently, Miller met Stephen Rollnick, the co-founder of the MI method, who had been concentrating on *ambivalence*, or the extent to which the client envisioned the pros and cons of changing. Miller and Rollnick together began to explore the use of

language during MI, concentrating on the elicitation of client "change talk" to promote behavior change. In 1991 Miller and Rollnick published the first textbook edition of *Motivational Interviewing: Preparing People to Change Addictive Behaviors* in which they provided a detailed description of the approach. Since then, there has been increasing interest in the research and application of MI, with many researchers addressing the applicability of the method to addressing health behavior change (Resnicow *et al*. 2002). Subsequently, various approaches for the implementation of MI in the dental setting have been published in the textbook *Health Behavior Change in the Dental Practice* by Ramseier and Suvan (2010).

MI was originally defined as "a client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence" (Miller & Rollnick 2002). The client-centered element refers to the emphasis that is placed on understanding and working from the perspective of the patient and their view of what it means to make a behavior change. For example, rather than a clinician simply telling a patient about the benefits of quitting smoking (from the clinician perspective), the clinician invites the patient to describe *his or her own view* of the advantages of quitting and disadvantages of continuing to smoke. Although the patient's perspective is central, because MI is also directive, the clinician takes deliberate steps to facilitate a particular behavioral outcome. For example, in patients undergoing periodontal therapy and without ignoring their concerns about changing, the clinician selectively reinforces and encourages elaboration of any patient statements (i.e. "change talk"), that are oriented toward the possibility or benefits of making a change (e.g. taking more time for oral hygiene self-care) (Kitzmann *et al*. 2019). By eliciting and elaborating upon the patient's own reasons for change the motivation for change that is fostered is intrinsic or internal, rather than externally imposed. This approach rests on the assumption that individuals are almost always ambivalent about changing their behavior (i.e. it is almost always the case that individuals can identify both pros and cons of changing). In applying behavior change approaches, clinicians therefore attempt to enhance intrinsic reasons for change by facilitating an exploration and resolution of the patient's underlying ambivalence.

General principles

Although MI methods and techniques provide a wealth of guidance of what to do and what not to do when counseling patients, Miller and Rollnick (2002) have emphasized that to successfully provoke behavior change, it is more important to embody the underlying philosophy than to be able to apply the collection of techniques. They have identified four general principles that capture the underlying philosophy of the method:

- First, a clinician should *express empathy* for the patient's behavior change dilemma. In other words, the clinician should communicate acceptance of the patient's perspective, providing and *expressing* full acknowledgement of the patient's feelings and concerns.
- The second principle is to *develop discrepancy* between the patient's current behavior and how they would ideally like to behave to be consistent with their broader goals and values. For example, the goal of being strong or responsible, or a good spouse or parent, can often be linked to being healthy and suggest the need for improved health behaviors.
- The third principle is to *roll with resistance*. When patients argue against change there is a strong tendency to fall into the trap of providing counter arguments. As a result, the patient expends all of their energy arguing against change which is precisely the opposite of what is desired, perhaps making them even less likely to change. MI clinicians therefore avoid arguing and instead use MI methods to "roll with resistance".
- The fourth principle is to *support self-efficacy* or the patient's confidence in their ability to make a change. Patients are unlikely to succeed in making a change even if they are motivated when they do not know how or do not believe they can. In periodontal care, clinicians therefore can make efforts to enhance their patients' confidence through such means as expressing their belief in the patient's ability to change or pointing out past successes or steps in the right direction (Woelber *et al*. 2015).

Giving advice

Although we have highlighted the distinction between advice-oriented health education and MI in this chapter, it is important to recognize that at times it is appropriate to provide information to address patients' questions, misapprehensions, or lack of knowledge. The MI skill code, which is used to assess clinician's adherence to principles of MI, distinguishes between giving advice *without* permission, which is prescribed, and giving advice *with* permission which is consistent with MI principles (Moyers *et al*. 2003). In essence, it is consistent with MI to provide information when the patient is willing and interested in receiving it. Clinicians commonly err by providing advice too soon in an encounter with a patient, resulting in patients perceiving the clinician as having an agenda that they are trying to "push". In contrast, it is common in MI practice to find that the process of eliciting the patient's perspective reveals gaps in knowledge, questions and concerns, and misapprehensions for which the patient would appreciate receiving more information. The clinician can then provide particularly relevant information that is much more likely to be well received. Rollnick *et al*. (1999) have outlined a three-step process that serves

as a useful framework for providing advice in an MI consistent style:

- Step 1: *Elicit* the patient's readiness and interest in hearing the information. For example, a clinician might say to a patient "I have some information related to [topic] that you may be interested in. Would you be interested in hearing more about that?"
- Step 2: *Provide* the information in as neutral a fashion as possible. For example, a clinician might say "Research indicates that…" or "Many of my patients tell me that…" This allows oral health-related information to be presented in a manner that supports the patient's autonomy.
- Step 3: *Elicit* the patient's reaction to the information presented. Following up will often facilitate the patient to integrate the new information in a way that brings about a new perspective and increases motivation to change. Alternatively, following up may reveal further gaps in knowledge or misunderstandings that can be addressed. If a patient "rejects" the information, it is important not to get into a debate. It is generally better to simply acknowledge the patient's perspective with statements such as "I can appreciate this information doesn't fit with your experience" or "I understand this information doesn't seem relevant to your situation" and then move on to a more productive area of conversation.

It may take several dental appointments for a patient to make significant and sustained health behavior change. Only relatively small steps towards change are likely to be accomplished following one brief encounter. Dental clinicians, who understand how to limit their expectations for each appointment, may ultimately feel less inclined to push the patient. By taking a long-term perspective (as appropriate for any behavior change process) they may be more aware of what they can accomplish in a relatively short amount of time, and therefore feel less frustration with resistant or highly ambivalent patients.

Agenda setting

Within clinical consultations, it is often the case that there is more than one health behavior affecting the patient's oral health. Achieving small changes can make a patient feel more able and confident to make other changes (Bandura 1995). In these situations, it is important to start where the patient feels most comfortable and encourage them to suggest the aspect they would like to talk about, rather than simply selecting what the dental clinician feels is the most pressing issue. One clinical tool that can help with this task is an 'agenda setting chart' (Rollnick *et al*. 1999). Using this tool, both the clinician and patient are enabled to target and discuss one behavior change goal at a time or at one dental visit, respectively. Moreover, the patient selects the issue that he or she would like to talk about first. Allowing the patient to choose reinforces respect and a sense of equal control.

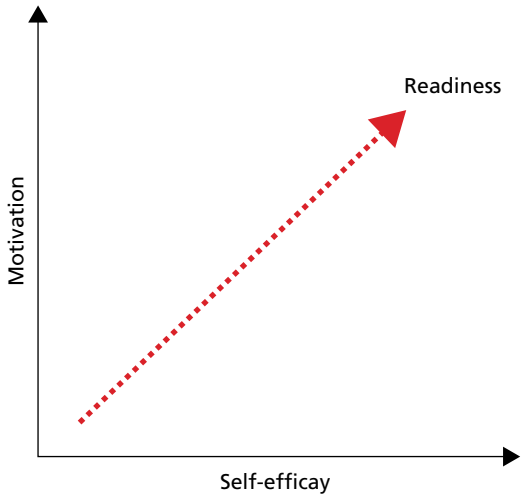

Fig. 27-2 Readiness to change. (Source: Adapted from Rollnick *et al*. 1999. Reproduced with permission from Elsevier.)

Readiness ruler

Clinicians often expect their periodontal patients to be ready to change their oral hygiene habits simply because they would like to have good oral health (Miller & Rollnick 2002). Assessing the periodontal patient's readiness to change involves learning about both the patient's motivation and self-efficacy to change (Rollnick *et al*. 1999; Woelber *et al*. 2015). Using this series of questions about readiness, the clinician can form a rather complete picture of a patient's position regarding change within a short amount of time.

When assessing both motivation and self-efficacy, the clinician seeks to discover the patient's specific motivators and values, in order to link them to the desired behavior change (Fig. 27-2). As described by Koerber (2010), particularly with brief interventions in dental settings, the readiness scale is a useful tool. It consists of (1) the motivation scale, and (2) the self-efficacy scale as described by Rollnick *et al*. (1999).

First, the motivation (importance) scale (Fig. 27-3) consists of three questions. For example:

1. "On a scale of 1 to 10, where 10 is absolutely important and 1 is not at all important, how would you rate the importance of brushing your teeth regularly?"
2. "Why did you rate it as (X) instead of 1?"
3. "Why did you rate it as (X) instead of a 10?"

Note that question 2 reveals the patient's motives, and question 3 reveals the patient's ambivalence.

Second, the self-efficacy (confidence) scale (Fig. 27-3) consists of the following questions:

1. "If you were convinced that brushing your teeth regularly was very important, on a scale of 1 to 10, how confident are you that you could do it? One means not at all confident and 10 means completely confident."
2. "Why did you rate it as (X) instead of 1?"
3. "Why did you rate it as (X) instead of 10?"

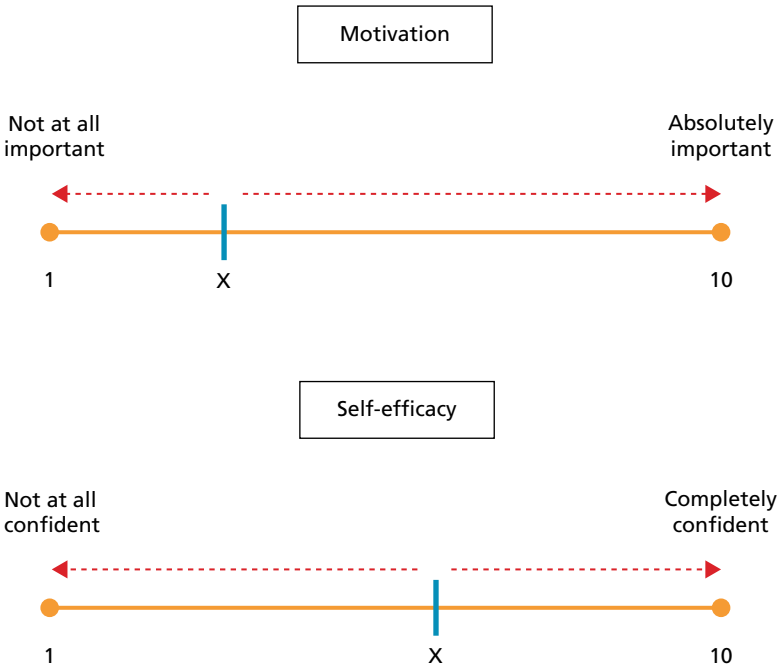

Fig. 27-3 Motivation (importance) and self-efficacy (readiness) scale.

It is to be noted that question 2 reveals a patient's strengths to make the change, and question 3 reveals the barriers.

Goal setting, planning, and self-monitoring

In alignment with the above-mentioned concepts and principles and to further assist the clinician's long-term efforts of patient counseling, a specific approach for oral hygiene motivation was first suggested at the 11th European Workshop of Periodontology in 2015 and summarized with the acronym GPS, for *G*oal setting, *P*lanning, and *S*elf-monitoring (Tonetti *et al*. 2015):

- *Goal setting*: While acknowledging the patient's autonomy and self-determination, the change to be made can be set as a (treatment) goal. In order to facilitate this step, the agenda setting chart can be used in order to address one particular behavior at a time. Alternatively, and often particularly suitable with people who smoke, oral hygiene behavior will be addressed first followed by dietary changes and followed by smoking cessation.
- *Planning*: This step consists of the close collaboration with the patient to decide when, where, and how he or she will undertake which step of (if not a complete) behavior change.
- *Self-monitoring*: Finally, the patients' ability to assess their own behavior in relation to the previously set goals will be encouraged. Clinicians often achieve this by increasing their patients' self-efficacy by giving positive feedback or praise.

Technology to facilitate behavior change

Most recently, technological advances in consumer devices have provided novel ways for clinicians to connect with patients and for patients to self-monitor behaviors ultimately encouraging self-efficacy. One example is the use of text messages to encourage patients in keeping steps toward a goal. In a recent systematic review of studies investigating the effect of mobile applications and text messages compared with standard oral hygiene instructions for improving oral hygiene regimes, 13 of 15 studies demonstrated a benefit associated with the groups that included adjunctive use of mobile applications to reinforce oral hygiene messages (Toniazzo *et al*. 2019). Authors suggest that it is unclear whether the observed benefits were due to increased patient engagement supporting self-efficacy, enhanced clinician patient relationship, increased understanding of their own personal oral health, or the possibility to intervene in breaking former habits. Perhaps the key is a synergy between these multiple aspects. This is a relatively new and emerging area of behavioral research but offers potentially new ways to facilitate healthy behaviors beyond the practice setting.

The patient activation fabric

Implementing motivational interviewing in a dental setting requires consideration of how to ensure the collaborative and empathic spirit of the method (Ramseier & Suvan 2010). A specific patient activation fabric was presented by Suvan *et al*. (2010). This model attempts to capture the interdependent

elements of the dental visit using the concept of interwoven threads (Suvan *et al*. 2010). Communication and information exchange blend together with clinical assessment and treatment (Fig. 27-4).

Band I: establish rapport

The goal of establishing rapport is to engage the patient quickly and establish an environment where both conventional dental treatment and health behavior change counseling can occur. Accomplishing this depends on much more than simply the amount of time taken. A warm, courteous greeting is a critical start in creating an environment of mutual trust and respect. Furthermore, such basic matters as how the patient and clinician are seated can contribute to the patient feeling like they are truly being invited to engage in a dialogue as a partner (Fig. 27-5), rather than feeling they are simply to be the recipient of expert advice (Fig. 27-6). These simple actions create the perception of the patient and clinician having equal control of the situation rather than one being dominant. Beginning with an open question that seeks the patient's chief complaint or reason for attending the visit is another simple and valuable step. These opening moments set the scene for the remainder of the visit and can save valuable time later in the session.

Before proceeding with the clinical assessment, it is important to list briefly the elements of the procedure to the patients then ask them if they would be happy to proceed with it at that time. Asking permission is a simple way to engage the patient while simultaneously encouraging a sense of autonomy. It may be helpful to explain to the patient the relevance of the information that they may hear you give to your assistant. These small actions help to keep your patient engaged in the consultation, rather than allowing them to shift to a passive role of lying helplessly on the dental chair throughout the assessment procedure.

Band II: information exchange

This second stage of the interaction would most often take place following initial clinical assessment of the patient's oral health status. This exchange of information allows both clinician and patient to understand the other's perspective and create a more accurate picture of the clinical problem and approaches to effective management. This discussion can take many different forms.

An alternative approach to providing information is one in which the clinician maintains a focus

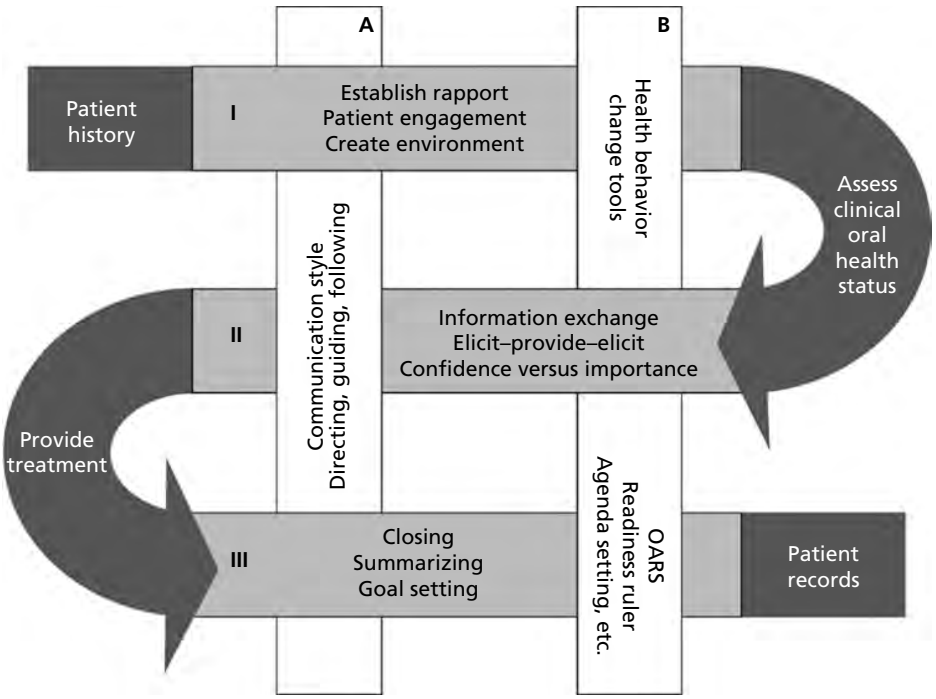

Fig. 27-4 Patient Activation Fabric for the Dental Visit (Implementation Model) from Suvan *et al*. (2010). The patient history and patient records positioned at the start and end depict the critical elements of documentation that serve to weave one dental visit into the next. The horizontal bands depict the three core strands of conversations constituting the visit. These bands labelled as "Establish Rapport", "Information Exchange", and "Closing" transition directly into the curves, representing the clinical assessment or treatment that takes place between the conversations as part of the flow of the appointment. The bands are woven together through the vertical ribbons (A, B) that signify the specific elements of the communication and interaction characterizing the approach. These vertical ribbons represent communication style and health behavior change tools and are consistent, yet flexible, recurring throughout the appointment ready to provide stability. OARS, *O*pen-ended questions, *A*ffirm the patient, *R*eflect, and *S*ummarize. (Source: Suvan *et al*. 2010. Reproduced with permission from John Wiley & Sons.)

Fig. 27-5 Appropriate position for a conversation: the clinician is facing the patient on the same seating level.

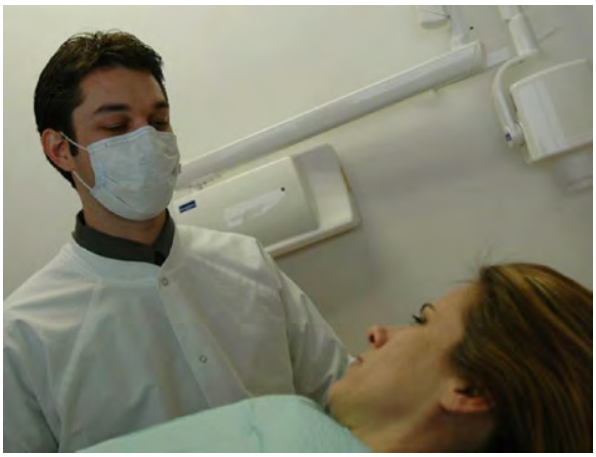

Fig. 27-6 Inappropriate position for a conversation: the clinician is wearing the face mask and is at a higher level to the supine patient.

on patient engagement using the elicit-provide-elicit method described above. Starting with what the patient already knows (elicit) immediately encourages patients to think, reflect, and acknowledge their own expertise. From that starting point the clinician can then, with permission, tailor the information offered to each patient (provide). Perhaps the most important step is the question that follows exploring what sense the patient makes of information provided (elicit). This question can open the door to dialogue rich with opportunity for discussions about possible change.

Leading into and moving on from this middle phase of the visit the clinician may be performing a number of clinical tasks including assessment and treatment. Conversations about behavior change are most valuable when the clinician and the patient are able to speak freely. Be mindful not to have these conversations when the patient is unable to be an equal participant, such as when the patient is physically incapable of speaking, or may be feeling pain or discomfort during or after clinical procedures.

Band III: closing

The third band takes place and functions as a closing to the visit. It may involve a brief summary of the clinical treatment that has been provided together with any expected side effects or post-treatment discomfort. Equally as important is that it serves to briefly summarize behavior change discussions. It provides the clinician with the opportunity to review the agreed goals or plan of action suggested by the patient in Band II. To ensure this is collaborative, the clinician should ask the patient if there is anything they would like to add to the plan and confirm with them that the most important points have been covered. Further treatment options may also be discussed if the patient is not too tired. However, this is not typically the best time for most patients to discuss important facts as they are usually focused on leaving the dental chair as soon as the appointment has concluded.

Ribbon A: communication style

Earlier in this chapter, styles of communication were presented highlighting that a spectrum exists with directing and following at opposite extremes and guiding in the middle as an intermediary style engaging both parties equally. A skilful movement between the three styles constitutes the well-managed interaction with the patient. In the model, communication style is labelled as a vertical ribbon interwoven through the entire visit. This portrays that at certain times during the visit, a particular style will tend to be more advantageous than the others. Maximum patient engagement without compromising the clinician's responsibility and ability to provide important information will be facilitated through use of a guiding style. Fundamental communication techniques such as asking open questions can encourage the two-way communication that characterizes a guiding style. However, this does not infer that it is the only style of communication used during the visit.

Ribbon B: health behavior change tools

The second vertical ribbon represents the many behavior change tools presented in this chapter to facilitate patient activation or interaction throughout the visit. Like Ribbon A, clinicians may choose the tool they feel will be most beneficial at certain points in the visit or conversation. The choice is driven by the goal to provide a relaxed atmosphere where conversations can be spontaneous and individualized to each patient.

Case examples

Oral hygiene motivation I

Using the following case example, MI is demonstrated in a dialogue for oral hygiene motivation between a clinician (C) and a patient (P) diagnosed with periodontitis at the beginning of periodontal therapy.

C	"Would you mind if we talk about methods to improve your oral hygiene during and after your gum treatment?"	*Raising the topic* *Asking permission*
P	"No, I don't mind."	
C	"Good. Could you let me know a little bit about how you usually clean your teeth?"	*Asking open questions (eliciting what the patient already does)*
P	"I usually brush once or twice a day."	
C	"So you brush your teeth regularly. What are you using when you clean your teeth?"	
P	"I use a toothbrush and toothpaste."	
C	"Very good. Could you let me know how you use your toothbrush?"	
P	"I brush all upper and lower teeth on the outside and the inside as I was shown a long time ago."	
C	"And how do you feel about brushing your teeth that way?"	
P	"I generally feel quite good about it. But since I have been told I have gum disease, I'm wondering if I haven't been brushing enough?"	
C	"So you have been making efforts to keeping your teeth clean but you're worried that maybe you haven't been brushing enough. It can be difficult to get to all the areas of your teeth and gums to remove the plaque that causes gum disease. I have some information related to prevention of gum disease that you might be interested in. Would you like to hear about it?"	*Reflective listening* *Showing empathy* *Asking permission*
P	"Yes."	
C	"The gum or periodontal disease you are diagnosed with was caused by bacterial plaque attached to your teeth over time. Plaque has to be entirely removed from all the tooth surfaces on a daily basis in order to prevent and control this disease. How confident are you that you were cleaning all the surfaces on a regular basis?"	*Providing information* *Assessing confidence*
P	"Not so much, although I thought that I was doing enough."	
C	"Well actually, research indicates that using a toothbrush alone is not sufficient to clean between the teeth. In order to clean these areas, an interdental device is needed such as a dental floss, a toothpick, or an interdental brush. Are you using any one of these devices?"	*Providing information*
P	"Yes, I've tried using dental floss."	
C	"How did you find the use of dental floss?"	*Asking open questions*
P	"I had some trouble getting to some of the spaces between my teeth. In other areas, the floss used to rip up too, so I quit using it."	
C	"I am sorry to hear that you had trouble using the dental floss. The floss can rip up at the edges of dental fillings or crowns. In spaces with extensive tartar built-up, the gap between your teeth may even be blocked out with tartar. Are you using anything else for cleaning?"	*Showing empathy*
P	"Yes, I use a toothpick whenever I have something stuck between my teeth."	*Asking open questions*
C	"So in addition to your regular brushing with toothpaste you are also using a toothpick from time to time to clean your teeth?"	*Reflective listening*
P	"That's right."	
C	"Good. During gum treatment, fillings and crowns with rough edges will be smoothed over and tartar can be removed which should make it easier to use things like dental floss or a toothpick between your teeth. Thinking of a 10-point scale where 0 is not at all important and 10 is extremely important, how important is it to you to floss or use a toothpick every day to clean the gaps between your teeth?	*Providing information* *Using readiness ruler on importance*
P	"Probably a 7."	
C	"That sounds quite important. What makes this so important to you?"	
P	"I want to do everything needed to keep my teeth. However, I am not quite sure if I will be able to keep doing it over time."	
C	"So you are quite motivated now because you want to look after your teeth, but you are worried about the long term. If you were to use the same 10-point scale to rate how confident you are that you can do it over the long term, where would rate yourself?"	*Using readiness ruler on self-efficacy*
P	"I would be at a 6."	

(*Continued*)

C	"That sounds fairly confident. What gives you that level of confidence?"	
P	"Well, taking care of my teeth and gums is part of my routine already so this would just need to be added to it. But it does take extra effort, so it's a matter of realizing that it's really that important for my gums."	
C	"So the fact that it can be part of your existing routine will help. But perhaps I can help you remain motivated in the long run by showing you at your follow-up visits the benefits you are achieving with your treatment by doing it regularly. How do you think that might help you to stick with it over time?"	*Supporting self-efficacy*
P	"Well, yes I think that would probably help a lot to see or learn from you that it really is making a difference to the success of my treatment."	
C	"Great! So, let me summarize what we have discussed. You plan to keep brushing on a regular basis with toothbrush and toothpaste and you will start to use a device for cleaning the gaps between your teeth after the issues with the rough filling and crown margins have been resolved. Then, each time you visit we will see how you are progressing with your cleaning at home and see if we need to find any other ways to help. Does that sound like it would work for you?"	*Summarizing*
P	"Yes, that sounds like it would work."	

Oral hygiene motivation II

In this second case example dialogue, MI is used in a conversation about oral hygiene at a visit for supportive periodontal therapy (SPT).

C	"From looking at your plaque-index, I noticed today that compared with your last visit 3 months ago there is more plaque around the areas between your teeth. I was wondering if you could tell me a little bit about how you find the cleaning between your teeth."	*Raising the topic* *Asking permission*
P	"Oh… I guess that I do not do it as often as I should. I barely have time now to do it every day, you know."	
C	"I understand. It takes time to clean all the areas between your teeth, you are right. May I ask you a few questions about your current oral hygiene habits so I could understand your situation better?"	*Showing empathy*
P	"Sure you can."	*Asking permission*
C	"Good. So, what do you use to clean your teeth currently?"	*Asking open questions (eliciting what the patient already does)*
P	"I am using an electric toothbrush and the interdental brushes you showed me."	
C	"Ok. How often do you use these?"	
P	"I use the electric toothbrush every day and I use the interdental brushes from time to time."	
C	"So you are using the toothbrush on a regular basis, but only occasionally using the interdental brushes. What is prompting you when you do decide to use the interdental brushes?"	
P	"Well, sometimes I just feel guilty that I haven't been using them and sometimes I can see the tartar on my teeth and am reminded to use them again."	
C	"So you sometimes worry that you are not using them enough and sometimes you can see on your teeth that you are not using them enough."	*Reflecting on ambivalence*
P	"Right, I suppose I should be doing better."	
C	"Well, let me ask you this. If you had to rate how important it is for you to use the interdental brushes every day on a scale from 0 to 10, 0 being not important at all and 10 being very important, where would you place yourself?"	*Using readiness ruler on importance*
P	"I guess the use of these brushes is pretty important. I'd say an 8."	
C	"Well that sounds very motivated. What makes it that important for you?"	
P	"Well I don't want to have a lot of problems with my teeth – I hate having fillings and of course I don't want to lose any teeth in the long run."	
C	"So avoiding pain and discomfort and keeping your teeth is important to you. So how confident are you that you can use the brushes on a daily basis? Where would you rate yourself on that 0 to 10 scale?"	*Using readiness ruler on self-efficacy*
P	"As I said, I know that I should use them more often, but finding the time is hard and I even just forget sometimes. I'd give it a 3."	
C	"Using them daily seems quite hard for you. Out of curiosity, though, it seems you do have little bit of confidence in doing this – may I ask you why a 3 instead of a 0 or a 1?"	
P	"Well, I just think that I would use them more often if they would become a part of my routine tooth cleaning, you know? I used to have toothpicks on my dinner table too and so I used them whenever I saw them sitting there. I could think about putting my interdental brushes on my sink next to my toothbrush. So, I would be reminded to use them after brushing my teeth with the electric toothbrush."	

C	"That sounds like a really good plan. Can you see any problems with doing that?"	*Supporting self-efficacy*
P	"No, not really. Once I have that reminder in place it's just a matter of staying committed to doing it."	
C	"Very good. So if I can summarize, it sounds like you feel quite motivated to use the interdental brushes every day, and that you think that if you put your interdental brushes on your sink next to your electric toothbrush that would help you remember to actually do it."	*Summarizing*
P	"Yes, that's right."	
C	"Well does that sound like something you want to do?"	
P	"Yes, I'll do that tonight."	

Conclusion

Sustained unhealthy behaviors not only affect general and oral health for individuals but also impact the burden of these diseases on a community level. Hence, services aiming at the improvement of prevention on an individual level oriented towards the change of inappropriate behavior have become a professional responsibility for all oral health care providers. Moving beyond oral hygiene instruction, health behavior change approaches specifically targeted at self-performed oral hygiene have become useful methods that can be incorporated into every day periodontal practice during both active and supportive periodontal therapy to encourage the modification of all common risk factors for periodontal diseases such as insufficient oral hygiene, tobacco use, unhealthy dietary habits, and alcohol abuse.

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Chapter 28

Mechanical Supragingival Plaque Control

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Importance of supragingival plaque removal

People clean their teeth for a number of reasons: oral well-being, to feel fresh and confident, to have a nice smile, and the perception of fresh breath. A healthy smile is more than cosmetic. Oral cleanliness is the cornerstone for the preservation of oral health because it removes microbial plaque, preventing it from accumulating on the teeth and gingiva (Löe *et al*. 1965). Dental plaque is a bacterial biofilm that is not easily removed from the surface of the teeth. Biofilms consist of complex communities of bacterial species that reside on tooth surfaces or soft tissues. It has been estimated that between 400 and 1000 species can, at various times, colonize oral biofilms. In these microbial communities, there are observable associations between specific bacteria, due in part to synergistic or antagonistic relationships and in part to the nature of the available surfaces for colonization or nutrient availability (see Chapter 9). The products of biofilm bacteria are known to initiate a chain of reactions leading not only to host protection but also to tissue destruction (see Chapter 10). Plaque can be supragingival or subgingival and can be adherent or non-adherent to teeth or tissue. In addition, the microbial composition of plaque varies from person to person and from site to site within the same mouth (Thomas 2004). Plaque removal and/or control is fundamentally important in any attempt to prevent and control periodontal diseases (Chapple *et al*. 2015). In fact, without the continuous collaboration of patients, periodontal treatment has little success and results obtained do not last long.

Supragingival plaque is exposed to saliva and to the natural physiologic forces existing in the oral

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

cavity. Natural self-cleansing mechanisms include tongue movement, by which the tongue contacts the lingual aspects of the posterior teeth and, to a lesser extent, also cleans their facial surfaces. The cheek covers the buccal aspects of the posterior maxillary teeth and can thereby help to prevent the copious build-up of dental plaque on these surfaces. Saliva flow has some limited potential for cleaning debris from interproximal spaces and occlusal pits, but it is less effective in removing and/or washing out plaque. Friction through mastication might have a limiting effect on occlusal and incisal extensions of plaque although, for instance, chewing gum has no effect on plaque and gingivitis scores (Keukenmeester *et al*. 2013). These defenses can best be classified as superficial actions in controlling or mediating plaque build-up. Natural cleaning of the dentition is virtually non-existent. To be controlled, plaque must be removed frequently by active methods. Hence, the dental community continues to encourage proper oral hygiene and more effective use of mechanical cleaning devices (Cancro & Fischman 1995; Löe 2000).

Therefore, to maintain oral health, regular personal plaque removal measures must be undertaken. The most widespread means of actively removing plaque at home is toothbrushing. There is substantial evidence that demonstrates that toothbrushing and other mechanical cleansing procedures can reliably control plaque, provided that this cleaning is sufficiently thorough and is performed at appropriate intervals. Evidence stemming from large cohort studies has demonstrated that high standards of oral hygiene ensure the stability of periodontal tissue support (Hujoel *et al*. 1998; Axelsson *et al*. 2004). Based on a longitudinal study of the natural history of periodontitis in a dentally well-maintained male population (Schätzle *et al*. 2004), Lang *et al*. (2009) concluded that persistent gingivitis represents a risk factor for periodontal attachment loss and tooth loss.

Given the great importance that has been placed on plaque and personal oral hygiene in the periodontal therapy hierarchy, evidence is needed to support this leading role. In a review, Hujoel *et al*. (2005) systematically searched for evidence from randomized controlled trials regarding whether improved personal oral hygiene was associated with a decreased risk of periodontitis initiation or progression. These reviewers were unable to find randomized controlled trial evidence indicating that improved personal oral hygiene prevented or controlled chronic periodontitis. By itself, this finding is not surprising because, based on common sense, it would be unethical to provide periodontal treatment without oral hygiene instruction. Furthermore, almost 60 years of experimental research and clinical trials in different geographic and social settings have confirmed that effective removal of dental plaque is essential for dental and periodontal health (Löe 2000). The reduction of plaque mass through good oral hygiene will reduce the injurious load on these tissues.

As meaningful as oral hygiene measures are for disease prevention, they are relatively ineffective when used *alone* for the treatment of moderate and severe forms of periodontitis (Loos *et al*. 1988; Lindhe *et al*. 1989). Without an adequate level of oral hygiene in periodontitis-susceptible subjects, periodontal health tends to deteriorate once periodontitis is established, and further loss of attachment can occur (Lindhe & Nyman 1984).

Meticulous, self-performed plaque removal measures can modify both the quantity and composition of subgingival plaque (Dahlén *et al*. 1992). Oral hygiene acts as a non-specific reducer of plaque mass. This therapeutic approach is based on the rationale that any decrease in plaque mass benefits the inflamed tissues adjacent to bacterial deposits. The Socransky group (Haffajee *et al*. 2001) reported that a permanent optimal supragingival plaque control regimen could alter the composition of the pocket microbiota and lower the percentage of putative bacterial pathogens.

Currently, both primary prevention of gingivitis and primary and secondary prevention of periodontitis are based on the achievement of sufficient plaque removal. The concept of primary prevention of gingivitis is derived from the assumption that gingivitis and periodontitis are a continuum of the same inflammatory disease and that maintenance of healthy gingiva will prevent periodontitis. Consequently, preventing gingivitis could have a major impact on periodontal care expenditure (Baehni & Takeuchi 2003). Primary prevention of periodontal diseases includes educational interventions for periodontal diseases and related risk factors, and regular, self-performed plaque removal and professional, mechanical removal of plaque and calculus. Optimal oral hygiene requires appropriate motivation of the patient, adequate tools, and professional oral hygiene instruction.

Patient-administered mechanical plaque control is also considered the standard of care in the management of peri-implant disease (Salvi & Ramseier 2015). There is, however, a lack of evidence with regard to the most effective self-performed oral hygiene around dental implants. At present, home care recommendations can therefore only be based on the knowledge that is available with regard to home-based care of natural teeth (Louropoulou *et al*. 2014). However, there are various implant-supported prosthetic designs and the anatomic structure of the marginal gingival tissues is different from that around natural teeth. For instance, in case of exposed rough surfaces of the dental implant, the peri-implant conditions may even be jeopardized by the application of dental floss (Montevecchi *et al*. 2016; Van Velzen *et al*. 2016). The authors therefore strongly suggest further well-performed clinical trials in the near future to examine different aspects of oral hygiene around dental implants.

Self-performed plaque control

Maintenance of oral health has been an objective of humans since the dawn of civilization. Self-care has been defined by the World Health Organization as all of the activities that the individual undertakes to prevent, diagnose, and treat poor personal health though self-support activities or referral to health care professionals for diagnosis and care. Personal oral hygiene refers to the effort of the patient to remove supragingival plaque. The procedures used to remove supragingival plaque are as old as recorded history. The use of mechanical devices for the cleaning of teeth dates back to the ancient Egyptians 5000 years ago, who made brushes by fraying the ends of twigs. People often chewed on one end of a stick until the fibers of the wood formed a brush, which was then rubbed against the teeth to remove food. These chewing sticks were the ancestors of the *miswak*, which is still used today and is especially popular in Muslim communities. Salvadorine, an alkaloid content of the *miswak*, has proven antibacterial activity (Sofrata *et al*. 2008). A recent systematic review indicated that when used 3–5 times a day it can be as effective on plaque and gingivitis scores as a regular manual toothbrush (Adam *et al*. 2021). The Chinese are believed to have invented the first toothbrush in approximately 1600 BC. This primitive toothbrush was made of natural hog bristles from pigs' necks with the bristles attached to a bone or bamboo handle (Carranza & Shklar 2003). In his writings, Hippocrates (460–377 BC) included commentaries on the importance of removing deposits from the tooth surfaces. The observation that self-performed plaque removal is one of the foundations of periodontal health was clearly described in 1683 by the well-known Dutch scientist Antonie van Leeuwenhoek, who wrote, "Tis my wont of a morning to rub my teeth with salt and then swill my mouth out with water; and often, after eating, to clean my back teeth with a toothpick, as well as rubbing them hard with a cloth; wherefore my teeth, back and front, remain as clean and white as falleth to the lot of few men of my years, and my gums never start bleeding" (Carranza & Shklar 2003). Van Leeuwenhoek examined under the lens of an early microscope the scrapings from his own teeth. He observed tiny moving organisms floating and spinning through the soft mass. This centuries-old discovery seems primitive by today's standards, but this early description of the dental biofilm was the basis for modern-day microbiology.

Currently, toothbrushes of various kinds are important aids for mechanical plaque (dental biofilm) removal, and their use is almost universal. Furthermore, a fluoridated dentifrice is an integral component of daily home oral care. Over the past 60 years, oral hygiene has improved; in industrialized countries, 80–90% of the population brushes its teeth once or twice a day (Saxer & Yankel 1997). The use of interdental cleaning devices, mouth rinses, and other oral hygiene aids is less well documented, but the available evidence tends to suggest that only a small percentage of the population uses such additional measures on a regular basis (Bakdash 1995). The benefits of optimal home-use plaque-control measures include the opportunity to maintain a functional dentition throughout life; reduction of the risk of loss of periodontal attachment; optimization of esthetic values, such as appearance and breath freshness; and a reduced risk of complex, uncomfortable, and expensive dental care (Claydon 2008). There is increasing public awareness in the Western world of the value of good oral health practices. This fact has been demonstrated by the recorded increases in both public spending on oral hygiene products and industry spending on consumer-related advertising (Bakdash 1995). Dental care professionals must make daily decisions about the clinical care and the recommendations that they provide for their patients. The significant variety of oral hygiene products makes it difficult to choose the most appropriate oral hygiene devices. In this chapter various devices for mechanical supragingival plaque control will be discussed.

Brushing

Different cleaning devices have been used in different cultures over the centuries (toothbrushes, chewing sticks, chewing sponges, tree twigs, strips of linen, bird feathers, animal bones, porcupine quills, etc.). Toothbrushing is currently the most commonly implemented measure in oral hygiene practices. The toothbrush, when used properly, has no side effects, is easy to use, and is inexpensive. Used with toothpaste it removes tooth stain and is the vehicle to deliver therapeutic agents in toothpaste. According to the Lemelson-MIT Invention Index (2003), the toothbrush was selected as the number 1 invention that Americans could not live without; when they were asked to select from among five choices – toothbrush, automobile, personal computer, cell phone, and microwave – more than one-third of teens (34%) and almost half of adults (42%) cited the toothbrush. Toothbrushing alone, however, does not provide adequate interdental cleaning because a toothbrush can only reach the facial, oral, and occlusal tooth surfaces. It was suggested (Frandsen 1986) that the outcomes of toothbrushing are dependent on: (1) the design of the brush; (2) the skill of the individual using the brush; (3) the frequency of brushing; and (4) the duration of brushing. Also, the uniformity of the dentition and a person's attitude and commitment towards brushing play a role, and together mean that there is no single toothbrush suitable for all populations. Dental professionals must become familiar with the variety in shapes, sizes, textures, and other characteristics of available toothbrushes to provide their patients with proper advice. From the numerous products currently available on the market, only a few should be selected for any individual patient. It is important that the dental care provider understands the advantages and

disadvantages of the various toothbrushes (and other aids) to provide the patient with proper information during oral hygiene instruction sessions. It is quite possible that a given patient will obtain better results with one particular toothbrush than with another. Therefore, the provision of oral hygiene information should be tailored to the individual.

Motivation

Oral hygiene education is essential to the primary prevention of gingivitis. Improvement in a patient's oral hygiene is often accomplished through cooperative interaction between the patient and the dental professional. The role of the patient is to seek education regarding efficient self-performed plaque removal and to undergo regular check-ups to ensure a high level of oral hygiene. The patient must be involved in maintaining the health of the tissues, interested in a proposed treatment plan, and motivated to participate. Without compliance, which has been described as the degree to which a patient follows a regimen prescribed by a dental professional, a good treatment outcome will not be achieved. In this context, it should be realized that compliance with treatment recommendations is generally poor, particularly in patients with chronic diseases for which the risk of complications is not immediate or life threatening. Also, compliance with oral hygiene recommendations is generally poor (Thomas 2004).

Thus, however effective any toothbrushing method is, it will only be of any real value if the patient is prepared to use the technique on a regular basis (Warren & Chater 1996). The patient's positive attitude toward treatment can have positive long-term effects on her/his tooth cleaning efforts. Thus, well-motivated patients who are compliant with professional advice and instructions are likely to achieve and sustain ideal levels of plaque control. Good oral hygiene should form an integral part of overall health practices, along with regular exercise, stress management, diet and weight control, smoking cessation, and moderation in alcohol consumption. If the clinician can establish the link between oral health and general health for the patient, then the individual might be more willing to establish proper oral hygiene measures as part of her/his lifestyle. The issue of changing a patient's lifestyle is the more difficult part of motivational sessions (see Chapter 27). The principles of brushing and flossing are easy to learn. Integrating them into a person's daily routine is far more difficult. This difficulty can become a source of frustration for the clinician who has provided a patient with information about the necessity of personal oral hygiene measures.

Oral hygiene instruction

Oral hygiene education consists not only of knowledge transfer; it must also consider current habits and personal skills. Patients often present with non-specific brushing techniques and need sufficient support to establish methods that are appropriate for their respective needs. Ganss *et al*. (2009a) assessed toothbrushing habits in uninstructed adults and observed that when using a strict definition of appropriate brushing habits (defined as brushing at least twice daily for 120 seconds with a brushing force not exceeding 3 N and with circling or vertical sweeping movements), only 25.2% of the participants fulfilled all of the criteria.

Twice-daily brushing with fluoridated toothpaste is now an integral part of most people's daily hygiene routines in Western societies. However, it appears that most patients are unable to achieve total plaque control at each cleaning (Van der Weijden & Slot 2011). A systematic review was initiated to assess the effect of mechanical plaque control and was then refined to address the effect of manual toothbrushing on plaque and gingivitis parameters. It was concluded that in adults with gingivitis, the quality of self-performed mechanical plaque removal was not sufficiently effective and needed to be improved. Based on studies of 6 months or longer in duration, it appears that a single oral hygiene instruction session, during which the use of a mechanical toothbrush is described, in addition to a single professional session of "oral prophylaxis" at baseline, had a significant, albeit small, positive effect on the reduction of gingival inflammation in adults with gingivitis (Van der Weijden & Hioe 2005). A study evaluated the effects of yearly oral hygiene instructions during dental check-ups of 284 patients over a 5-year period (Furusawa *et al*. 2011). It was shown that these repeated instructions significantly contributed to improved plaque control compared with control in patients not receiving these instructions. An individually tailored oral health educational program, based on aspects of psychological interventions such as cognitive/behavioral models and motivational interviewing, are effective in achieving proper long-term oral hygiene behavior resulting in reduced plaque and gingivitis, specifically interproximally (Renz *et al*. 2007; Jönsson *et al*. 2009).

Oral mHealth

Mobile apps are software programs that run on smartphones and other mobile devices. There are thousands of mobile health apps available, and hundreds of them focus on dentistry. It is important to know that the majority is not reviewed by regulatory authorities. The US Food and Drug Administration (FDA) does not review or monitor health apps unless they are connected to or intended to be used as a medical device. An app that is intended for maintaining or encouraging a healthy lifestyle (and unrelated to the diagnosis, cure, prevention or treatment of a disease or condition), is not considered a medical device.

The National Health Service (NHS) in the UK has approved one app for dentistry. The app Brush DJ plays two minutes of music during which the teeth can be brushed. The app has short videos with instructions

for brushing and how to clean in between teeth. This app has been scientifically evaluated and 88% reported that the app motivated them to brush longer and 92% would recommend the app to their friends and family (Underwood *et al*. 2019). Also, text messages can be used to motivate and encourage positive oral hygiene behavior. It can even be used as a method to send messages regarding aligned topics such as dental visits, sugar, and fluoride. Self-performance monitoring systems are now available to track the areas being brushed and the pressure applied by use of video recognition and a motion sensor. Such feedback systems can lead to a prolonged learning effect resulting in improved oral hygiene (Graetz *et al*. 2013). Evidence suggests that teledentistry, particularly mHealth (messages and apps), is a promising clinical tool for preventing and promoting oral health, especially under the accelerated virtualization of dentistry (Fernández *et al*. 2021). Thus, a mobile app can be a promising tool to acquire oral health knowledge and improve oral hygiene (Toniazzo *et al*. 2019). Because most studies focus on children and orthodontic patients, further detailed evaluations are needed in order to recommend mHealth for daily use in particular among periodontitis patients.

Toothbrushing

Manual toothbrushes

The exact origins of mechanical devices for cleaning teeth in the Western world are unknown. The Chinese are given credit for developing the first handheld bristle toothbrush, as the earliest record of a toothbrush was found in Chinese writing from approximately 1000 AD. It was made from hairs from the neck of Siberian wild boar, which were fixed to a bamboo or bone handle. It was brought to Europe by traders. In 1698, Cornelis van Solingen, a doctor from The Hague, published a book in which he presented the first illustration of a toothbrush in Europe (Fig. 28-1). Over the past 350 or so years, toothbrushes have been crafted with bone, wood, or ivory handles that held the stiff bristles of hogs, boars, or other animals. The nobility used toothbrushes fashioned from silver.

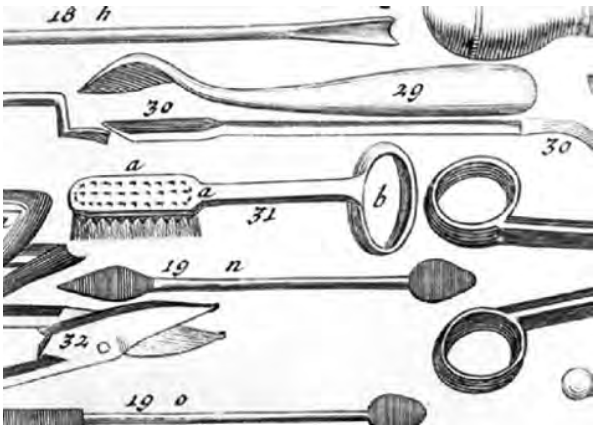


Fig. 28-1 Illustration of a toothbrush and tongue scraper from a book by Cornelis van Solingen. (Source: Courtesy of the University Museum of Dentistry in Utrecht, the Netherlands.)

The toothbrush was reinvented in the Western world in the late eighteenth century. The first mass-produced toothbrush was made by William Addis of Clerkenwald, England, circa 1780. The idea of the bristle bone toothbrush came to William Addis while in prison. In 1770, he had been sent to jail for causing a riot. Addis noticed that the prison floor was swept with a broom and reasoned that the current method to clean teeth with a cloth was highly ineffective and could thus be improved. Boredom and necessity drove Addis to take a small animal bone left behind from one of his meals and drilled holes into it. He then obtained some bristles from one of his guards. He tied the bristle filaments in tufts and passed them through the holes in the animal bone. Finally, he sealed the holes with glue. Upon his release from jail, he launched a business to manufacture toothbrushes. His business evolved into the company "Wisdom", which continues to manufacture toothbrushes today. The Addis version of the toothbrush had natural hog bristles. While acceptable at the time and no doubt efficacious in terms of plaque removal, natural products are inherently unhygienic, as the bristle fibers allow the accumulation and proliferation of orally derived bacteria. The first American to patent a toothbrush was H.N. Wadsworth (in 1857), and many American companies began to produce toothbrushes after 1885. In the early 1900s, celluloid began to replace the bone handle, a change that was hastened by World War I when bone and hog bristles were in short supply. Nylon filaments were introduced in 1938 by Du Pont de Nemours because World War II prevented the exportation of wild boar bristles from China. Nearly all current toothbrushes are made exclusively of synthetic materials. Their nylon filaments and plastic handles are easy to manufacture and are therefore more affordable. This ease of manufacture has made toothbrushing a common practice in most societies.

During toothbrushing, the removal of dental plaque is achieved primarily through direct contact between the filaments of the toothbrush and the surfaces of teeth and the soft tissues. At the European Workshop on Mechanical Plaque Control, it was agreed that the features of an ideal manual toothbrush are (Egelberg & Claffey 1998):

- Handle size appropriate to user's age and dexterity so that the brush can be easily and efficiently manipulated
- Head size appropriate to the size of the individual patient's requirements
- End-rounded nylon or polyester filaments not larger than 0.23 mm (0.009 inches) in diameter
- Soft filament configurations, as defined by the acceptable international industry standards (ISO)
- Filament patterns that enhance plaque removal in the appropriate spaces and along the gum line.

Additional characteristics could include an inexpensive price, durability, imperviousness to moisture, and easy to clean.

Modern toothbrushes have reached a certain stage of sophistication. Much imagination and inventiveness has been applied to toothbrush design and now numerous models are available. Combinations of different filaments and tuft arrangements are appealing for consumers but often not scientifically evaluated. To improve patient comfort, over time the shape of the brush head, the filaments, and the placement of filaments in the handles has changed (Voelker *et al*. 2013). Modern toothbrushes have filament patterns designed to enhance plaque removal from hard-to-reach areas of the dentition, particularly from proximal areas. A major shortcoming of the conventional flat-trim toothbrushes has been the "blocking effect" of tight bristle tufts, which prevents individual tufts from reaching interproximal areas. Filaments with crimped and tapered filaments are the most recent improvements. The designs are based on the premise that the majority of subjects in any population use a simple horizontal brushing action. Multiple tufts of filaments, sometimes angled in different directions, are also used (Jepsen 1998). These multilevel toothbrushes have alternating rows of taller and shorter bristle tufts acting independently, so they are not influenced by the adjacent bristles during brushing. Once independent motion is achieved, the longer bristles can effectively reach further between the teeth. Multilevel or angled toothbrush designs (Fig. 28-2) yield genuinely improved performance characteristics when compared with flat-headed brushes (Cugini & Warren 2006; Slot *et al*. 2012). Double- and triple-headed toothbrushes have been proposed to reach the lingual surfaces more easily, especially in molar areas, which are normally the tooth surfaces hardest to reach with regular toothbrushes. Although some studies have indicated that the use of such multiheaded toothbrushes might improve plaque control in lingual areas (Agerholm 1991; Yankell *et al*. 1996), their use is not widespread. The use of a triple-headed manual toothbrush was found to be favorable with respect to plaque removal in case a care-dependent individual is brushed by a caregiver (Kalf *et al*. 2018).

Fig. 28-2 Flat-trim, multilevel and angled manual toothbrush bristle tuft design.

Whereas handles used to be straight and flat, round and curved handles are more common today. The modern toothbrush has a handle size that is appropriate to the hand size of the prospective user, and greater emphasis has been placed on new ergonomic designs (Löe 2002). Several studies have investigated differences in plaque removal between brushes with different handle designs. In such studies, brushes with long and contoured handles appear to remove more plaque than brushes with traditional handles (Saxer & Yankell 1997).

Obviously, there can be no single "ideal" toothbrush for all populations. The choice of brush is usually a matter of individual preference, rather than governed by a demonstrated superiority of any one type. In the absence of clear evidence, the best toothbrush is the one that is (properly) used by the patient (Cancro & Fischman 1995; Jepsen 1998).

For a toothbrush company to qualify a toothbrush for the American Dental Association (ADA) Seal of Acceptance, it must be shown that:

- All of the toothbrush components are safe for use in the mouth
- Bristles are free of sharp or jagged edges and end points
- Handle material is manufacturer tested to show durability under normal use
- Bristles will not fall out with normal use
- Toothbrush can be used without supervision by the average adult to provide a significant decrease in mild gum disease and plaque
- Size and shape of the brush should fit in the mouth comfortably, allowing the user to reach all areas easily.

A company earns the ADA seal for its product by producing scientific evidence that the product is safe and effective, claims that are evaluated by an independent body of scientific experts – the ADA Council on Scientific Affairs – according to objective guidelines.

Efficacy

Toothbrush manufacturers have made great efforts to consider many different aspects when designing new models to meet the challenges of enhancing plaque biofilm removal through improved toothbrushing efficacy. Few toothbrush manufacturers have also attempted to evaluate toothbrush efficacy. The enthusiastic use of a toothbrush is not synonymous with a high standard of oral hygiene. Adults, despite their apparent efforts, do not appear to be as effective in their plaque removal as might be expected. The daily experience in dental practice is that patients exhibit plaque even though they reportedly engage in oral hygiene practices. De la Rosa *et al*. (1979) studied the patterns of plaque accumulation and removal with daily toothbrushing over a 28-day period following

dental prophylaxis. On average, approximately 60% of the plaque remained after self-performed brushing. Morris *et al*. (2001) reported on the 1998 UK Adult Dental Health Survey and observed that the mean proportions of teeth with plaque deposits were 30% in the 25–34-year-old age group and 44% in those aged 65 years and older.

Brushing exercise studies are commonly used for toothbrush evaluations. This study model provides useful indications of the plaque removal capacity of toothbrushes and facilitates the control of confounding variables, such as compliance. A systematic review was initiated by Slot *et al*. (2012) to assess the effect of a single brushing exercise using a manual toothbrush. In total, 212 brushing exercises as separate legs of experiments in 10 806 participants, were used to calculate a weighted mean overall percentage plaque reduction score. The sheer magnitude of the number of participants and the heterogeneity observed in the various study designs yielded results of particular value because they reflected what might be generally expected from a routine oral hygiene exercise as encountered among patients in everyday practice. Based on the baseline and end scores, a plaque reduction percentage was calculated for each of the eligible experiments taken from the selected studies. Using these data, a weighted mean difference was calculated as a 42% reduction in plaque index scores from baseline indices.

An interesting aspect of this analysis was that the estimated magnitude of the effect size of toothbrushing appeared to be dependent on the plaque index score used to assess the magnitude of the effect. Compared to the Quigley & Hein plaque index, the estimate with the Navy index resulted in a greater difference between pre- and post-brushing scores: 30% versus 53%, respectively.

The Navy plaque index (Elliott *et al*. 1972) and the Quigley & Hein plaque index (Quigley & Hein 1962) and their modifications are the two indices most commonly used for assessing plaque removal efficacy with toothbrushes. Although these indices score plaque in different ways, there appears to be a strong correlation between them (Cugini *et al*. 2006). The Quigley & Hein plaque index emphasizes the differences in plaque accumulation in the gingival third of the tooth, and it tends to overscore the incisal half of the crown at the expense of the gingival margin. The Navy plaque index gives greater weight to plaque in the immediate gingival area. The scores from both indices are descriptive. They do not represent strictly linear scales; rather, they ascend in severity. A score of 0 is given when no plaque is found. Higher scores are assigned in ascending order, corresponding roughly to increasing areas of tooth surfaces covered by plaque. Because plaque is colorless, it is usually visualized by staining prior to scoring. Plaque is then defined, in an operational sense, as "stainable material" (Fischman 1986). Such practices do not result in precise estimates of the dental biofilm because they fail to evaluate qualitative features.

Methods of toothbrushing

Although the toothbrush is the most used tool to remove dental plaque its proper use is not trivial and requires some skill. The ideal brushing technique is the one that allows for complete plaque removal in the least possible time, without causing any damage to tissues (Hansen & Gjermo 1971). There is no single oral hygiene method that is correct for every patient. The morphology of the dentition (crowding, spacing, gingival phenotype, etc.), the type and severity of periodontal tissue destruction, and the patient's own manual dexterity determine what kind of hygiene aids and cleaning techniques should be recommended. It should also be realized that during the course of periodontitis therapy, the techniques might have to be changed or adapted to the morphologic situation (longer teeth, open interdental spaces, exposed dentin).

Wainwright and Sheiham (2014) assessed methods of toothbrushing recommended for both adults and children by dental associations, toothpaste and toothbrush companies, and professional sources such as in dental textbooks and by experts. There appeared to be a wide diversity between recommendations on toothbrushing techniques, how often people should brush their teeth, and for how long. The most common method recommended was the (modified) Bass technique. The different toothbrushing methods that have been proposed over time can be proposed based on the position and motion of the brush.

Horizontal brushing is probably the most commonly used toothbrushing method. It is most frequently used by individuals who have never had instruction in oral hygiene techniques. Despite the efforts of the dental profession to instruct patients to adopt other, more efficient brushing techniques, most individuals use horizontal brushing because it is simple. The head of the brush is positioned perpendicular to the tooth surface, and then a horizontal back-and-forth scrubbing movement is applied (Löe 2000). The occlusal, lingual, and palatal surfaces of the teeth are brushed with an open mouth. To reduce the pressure of the cheek on the brush head, the vestibular surfaces are cleaned with the mouth closed.

Vertical brushing (Leonard [1939] technique) is similar to the horizontal brushing technique, but the movement is applied in the vertical direction, using up-and-down strokes.

Circular brushing (Fones [1934] method) is performed with the teeth closed, the brush placed inside the cheek, and a fast circular motion applied that extends from the maxillary gingiva to the mandibular gingiva, using light pressure. Back-and-forth strokes are used on the lingual and palatal tooth surfaces.

The *scrubbing method* includes a combination of horizontal, vertical, and circular strokes.

Sulcular brushing (Bass [1948] method) (see Box 28-1) emphasizes cleaning of the area directly

beneath the gingival margin. The head of the brush is positioned in an oblique direction toward the apex. The filament tips are directed into the sulcus at approximately 45° to the long axis of the tooth. The brush is moved in a back-and-forth direction using short strokes, without disengaging the tips of the filaments from the sulci. On the lingual surfaces in the anterior tooth regions, the brush head is kept in the vertical direction. The Bass method is widely accepted as an effective method for removing plaque, not only at the gingival margin but also subgingivally. A few studies have been conducted on teeth affected with periodontal disease and scheduled for extraction, in which the gingival margin was marked with a groove, and the depth of subgingival cleaning was measured. These studies showed that with the use of this brushing method, plaque removal could reach a depth of approximately 1 mm subgingivally (Waerhaug 1981a).

The *vibratory technique* (Stillman [1932] method), was designed for the massage and stimulation of the gingiva and for cleaning the cervical areas of the teeth. The head of the brush is positioned in an oblique direction toward the apex, with the filaments placed partly in the gingival margin and partly on the tooth surface. Light pressure, together with a vibratory (slight rotary) movement, is then applied to the handle, while the filament tips are maintained in position on the tooth surface.

The *vibratory technique* (Charters [1948] method) was originally developed to increase cleansing effectiveness and gingival stimulation in the interproximal areas. Compared with the Stillman technique, the position of the brush head is reversed. The head of the brush is positioned in an oblique direction, with the filament tips directed toward the occlusal or incisal surfaces. Light pressure is used to flex the filaments and gently force the tips into the interproximal embrasures. A vibratory (slight rotary) movement is then applied to the handle, while the filament tips are maintained in position on the tooth surface. This method is particularly effective in cases with receded interdental papillae because the filament tips can easily penetrate the interdental space and in orthodontic patients (Fig. 28-3).

With the *roll technique*, the head of the brush is positioned in an oblique direction toward the apex of the teeth, with the filaments placed partly in the gingival margin and partly on the tooth surface. The sides of the filaments are pressed lightly against the gingiva. Next, the head of the brush is rolled over the gingiva and teeth in an occlusal direction.

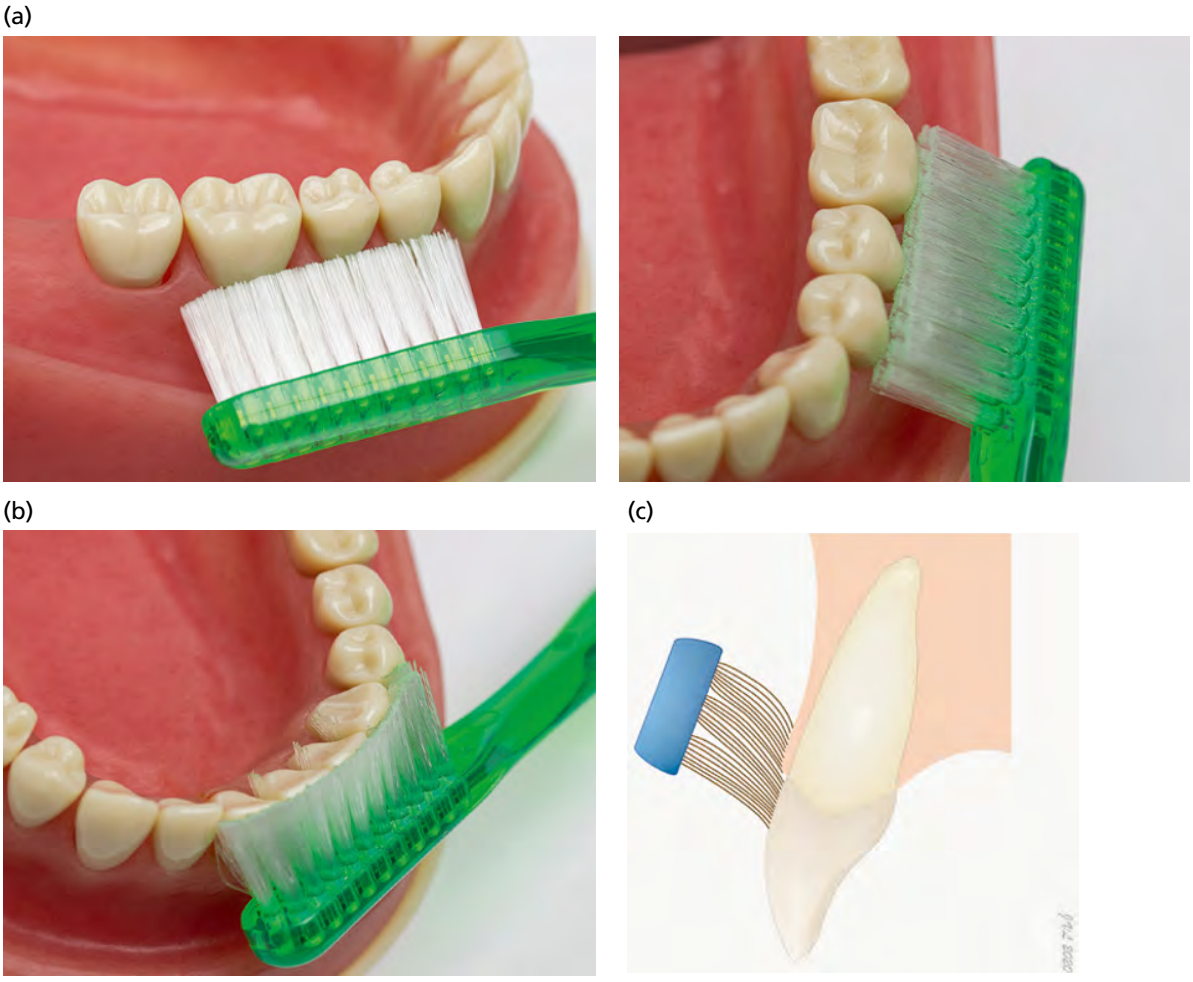


Fig. 28-3 Charters method of toothbrushing. (a) Note how the head of the toothbrush is placed in the right and left mandible. (b) The bristles are forced into the interproximal areas. (c) Note the angulation of the bristles against the buccal tooth surface. (Source: Schematic drawing courtesy of Joep Laverman. Printed with permission.)

Finally, the *modified Bass/Stillman technique* emerged because the Bass and Stillman methods were both designed to concentrate on the cervical portion of the teeth and the adjacent gingival tissues and could be modified to add a roll stroke. The brush is positioned similarly to in the Bass/Stillman technique. After activation of the brush head in a back-and-forth direction, the head of the brush is rolled over the gingiva and teeth in the occlusal direction, making it possible for some of the filaments to penetrate interdentally.

In the 1970s, several investigators compared various methods of brushing. Because of varying experimental conditions, the outcomes of these studies are difficult to compare. To date, no method of toothbrushing has been shown to be clearly superior to others. As early as 1986, Frandsen commented on this issue, stating, "Researchers have realized that improvement in oral hygiene is not as dependent upon the development of better brushing methods as upon improved performance by the persons using any one of the accepted methods." Therefore, because no particular toothbrushing method has been found to be clearly superior to the others, there is no reason to introduce a specific toothbrushing technique with each new periodontal patient. In most cases, small changes in the patient's own method of toothbrushing will suffice, always bearing in mind that more important than the selection of a certain method of toothbrushing is willingness and thoroughness on the part of the patient to clean his/her teeth effectively. Implementation of the toothbrushing methods described above must be made according to a patient's needs. For example, because the Bass method has been associated with gingival recession (O'Leary 1980), it is not be indicated in individuals with energetic toothbrushing habits who also have a thin gingival phenotype. Van der Sluijs *et al*. (2017, 2018 a, b) evaluated various recommendation related to toothbrushing methods. As the lingual surfaces in general demonstrate more plaque and bleeding on probing than other areas of the mouth it has been suggested that the toothbrush should therefore first be applied to these surfaces. This presumption, however, was not supported by the outcome of a split-mouth study (Van der Sluijs *et al*. 2018a). Rinsing before brushing has also been proposed in order to hydrate the biofilm, reduce adherence, and render plaque more readily detached by mechanical cleaning methods. This pre-rinsing with water does not contribute significantly to toothbrushing efficacy (Van der Sluijs *et al*. 2017).

Frequency of use

Although the ADA recommends that teeth should be brushed twice per day with a fluoride toothpaste and cleaned in between daily with floss or an interdental cleaner, there is no true consensus as to the optimal frequency of toothbrushing. How often teeth must be brushed and how much plaque must be removed to prevent dental disease from developing are not known. The majority of individuals, including periodontal patients, are usually unable to remove dental plaque completely with daily brushing. However, complete plaque removal does not seem to be necessary. Theoretically, the proper level of oral hygiene is the extent of plaque removal that prevents gingivitis/periodontal disease and tooth decay in the individual patient. The prevention of gingival inflammation is important because inflammatory conditions of soft tissues also favor plaque accumulation (Lang *et al*. 1973; Ramberg *et al*. 1994; Rowshani *et al*. 2004).

Results from cross-sectional studies have been equivocal when the self-reported frequency of tooth cleaning has been related to caries and periodontal disease. A survey, using a questionnaire to assess oral hygiene practices, observed no statistically significant differences in periodontal health measurements (gingival inflammation, probing pocket depth, attachment loss) between subjects performing acceptable (brushing at least once a day) and unacceptable self-reported brushing behavior (Lang *et al*. 1994). However, correlation coefficients have revealed a weakly positive, but significant, relationship between the frequency of tooth brushing and oral hygiene and gingival health (Addy *et al*. 1990). Disease appears to be related more to the quality of cleaning than to its frequency (Bjertness 1991). Kressin *et al*. (2003) evaluated the effect of oral hygiene practices on tooth retention in a longitudinal study with 26 years of follow-up. They observed that consistent brushing (at least once per day) resulted in a 49% reduction in the risk of tooth loss, compared with a lack of consistent oral hygiene habits.

If plaque is allowed to accumulate freely in the dentogingival region, subclinical signs of gingival inflammation (gingival fluid) appear within 4 days (Egelberg 1964). The minimum frequency of tooth cleaning needed to reverse experimentally induced gingivitis is once every day or every second day. Bosman and Powell (1977) induced experimental gingivitis in a group of students. Signs of gingival inflammation persisted in those students who removed plaque only every third or fifth day. In the groups who properly cleaned their teeth once per day or every second day, the gingiva healed within 7–10 days.

Based on the observation that the onset of gingivitis appears to be more closely related to the maturation and age of the plaque than to its amount, the minimum frequency of brushing needed to prevent the development of gingivitis was investigated in a prospective study. Dental students and young dental faculty members with healthy periodontal conditions were assigned to study groups with different cleaning frequencies over periods of 4–6 weeks. The results indicated that students who thoroughly removed plaque once daily or even every second day did not develop clinical signs of gingival inflammation over

a 6-week period. This tooth cleaning included the use of interproximal aids (dental floss and woodsticks) and toothbrushes (Lang *et al*. 1973). Caution should be exercised in extrapolating the results obtained from studies including dentally aware subjects to the average patient.

As a point of principle, it is reasonable to state that meticulous mechanical removal of plaque by toothbrushing, combined with the removal of interdental plaque once every 24 hours, is adequate to prevent the onset of gingivitis and interdental caries (Axelsson 1994; Kelner *et al*. 1974). From a practical standpoint, it is generally recommended that patients brush their teeth at least twice daily, not only to remove plaque but also to apply fluoride through the use of a dentifrice to prevent caries. This advice also considers feelings of oral freshness. For most patients, it might be desirable to perform all necessary procedures (e.g. brushing and interdental cleaning) at the same time and in the same manner each day. Unfortunately, for subjects who live busy, stressful lives, this level of dedication can be difficult to achieve (Thomas 2004). Despite most individuals claiming to brush their teeth at least twice per day, it is clear from both epidemiologic and clinical studies that mechanical oral hygiene procedures, as performed by most subjects, are insufficient to control supragingival plaque formation and to prevent gingivitis and more severe forms of periodontal disease (Sheiham & Netuveli 2002).

Duration of brushing

Patients usually believe that they spend more time on toothbrushing than they actually do. A cause of insufficient oral hygiene in the general population is therefore often too short brushing time (Saxer *et al*. 1998). The least amount of time spent on brushing was observed in a study performed on English school children; in the 13-year-old group, the children spent approximately 33 seconds on brushing (MacGregor & Rugg-Gunn 1985). Approximately one-third of the studies that were reviewed reported an average brushing time of <56 seconds, whereas two-thirds of the studies reported brushing times of between 56 and 70 seconds. Two investigations reported an average brushing time of ± 90 seconds (Ayer *et al*. 1965; Ganss *et al*. 2009a). MacGregor and Rugg-Gunn (1979) reported that of a mean 50-second brushing time, only 10% of that time was spent on the lingual surfaces.

The best estimates of actual manual brushing time range between 30 and 60 seconds (Van der Weijden *et al*. 1993; Beals *et al*. 2000). Some caution regarding these estimates should be exercised, as the act of measuring brushing time has been shown to affect brushing behavior (MacGregor & Rugg-Gunn 1986).

The toothbrushing in the study by Van der Weijden *et al*. (1993) was performed by a dental professional. This study compared the effect of brushing time on plaque removal using manual and electric toothbrushes, utilizing five different brushing times (30, 60, 120, 180, and 360 seconds). The results indicated that 2 minutes of electric toothbrushing was as effective as 6 minutes of manual toothbrushing. The authors furthermore observed that at 2 minutes, an optimum in plaque-removing efficacy was reached with both manual and electric toothbrushes. Two systematic reviews have evaluated in a subanalysis the effect of a single brushing exercise with a manual or an electric toothbrush relative to the toothbrushing time (Slot *et al*. 2012; Rosema *et al*. 2016) and found that brushing duration contributed to the observed range in results. For the manual toothbrush, based on the Quigley & Hein plaque index scores, the estimated weighted mean efficacy as represented in plaque score reduction was 27% after 1 minute and 41% after 2 minutes (Slot *et al*. 2012).

A number of studies in the literature address the question of whether, in adult patients, the duration of toothbrushing correlates with the efficacy of plaque removal. Some of these studies evaluated the use of electric toothbrushes (Van der Weijden *et al*. 1996a; McCracken *et al*. 2003, 2005) while others compared manual toothbrushes with electric toothbrushes (Preber *et al*. 1991) or evaluated only manual toothbrushes (Hawkins *et al*. 1986; Gallagher *et al*. 2009). The results from these studies indicated that the duration of brushing was consistently correlated with the amount of plaque that was removed.

Based on the above observations, the duration of toothbrushing is likely to be an important determinant of plaque removal in the general population; therefore, it should be stressed during toothbrushing instruction sessions. As plaque removal is strongly correlated with brushing time for any given toothbrush, brushing for 2 minutes or longer should be encouraged, regardless of the brush used. Brushing time is also likely the most easily controlled parameter of effective everyday brushing.

Toothbrush filaments

The characteristics of an effective toothbrush correspond to the primary functional properties of the filaments. Most modern toothbrushes have nylon filaments. The end of a toothbrush filament can be cut in either a blunt or a rounded manner (see Filament end-rounding later). Today, many manufacturers vary the length or diameter of the filaments mounted in the head. The degrees of hardness and stiffness of a toothbrush depend on the filament characteristics, such as material, diameter, and length. Toothbrushes with thinner filaments are softer, while thicker-diameter filaments are stiffer and less flexible. Curved filaments can be more flexible and less stiff than straight filaments of equal length and diameter. Also, the density of the filaments in a tuft influences its stiffness, as each filament provides support to adjacent filaments, and each tuft provides support to adjacent tufts.

Consequently, the number of filaments per tuft also determines the hardness of a toothbrush. Increased stiffness will prevent the filament ends from bending back during brushing, avoiding the potential risk of damaging the gums. However, the filament must be sufficiently stiff so that during brushing, sufficient pressure (shear force) is exerted to allow for proper plaque removal.

Concern about toothbrush filaments relates primarily to the potential for hard and soft tissue abrasion. Consider that a rod represents a filament of a toothbrush. While brushing, a vertical upward load is exerted, which, in turn, exerts an effect of the same order of magnitude on the oral mucosa. The force of the brush, acting on the individual filament, is thus always as great as the load exercised by the filament on the mucosa. If the load is increased, then the load increases to the same extent. Consequently, the risk of soft tissue damage increases as the filament's tip can penetrate into the mucosa. However, elastic rods demonstrate a peculiarity in their behavior. They suddenly fold back laterally when a certain load limit is exceeded. When folding back, the rod suddenly gives way elastically (without breaking), and the load on the oral mucosa diminishes abruptly. Thus, a load greater than this fold-back limit cannot be transferred to the mucosa by the rod via its tip.

As late as 1967, most people were buying hard brushes (Fanning & Henning 1967). The shift in preference to soft brushes of a specific design paralleled the change that occurred in oral health care when calculus was identified as the prime etiologic agent in periodontal disease (Mandel 1990). The concentration on plaque, especially in the crevicular area, and attention to intrasulcular brushing strongly influenced the change from hard to soft filaments, primarily because of the concern for trauma to the gingival tissues (Niemi *et al*. 1984). Soft filaments are universally recommended for sulcular brushing, such as with the Bass method. Patients can brush at the cervical areas without fear of discomfort or soft tissue laceration. However, various studies have shown that subjects cleaned significantly better with medium and hard brushes than with soft-bristled brushes (Robertson & Wade 1972; Versteeg *et al*. 2008a). Therefore, it appears that the filaments must have a degree of stiffness to create sufficient abrasion to dislodge plaque deposits. There is no point in using a brush with very thin filaments that merely stroke across the tooth and, as a result of the lack of load, no longer clean the tooth surface. However, to avoid damaging the gums when positioning the toothbrush, they must not be too hard: the harder the toothbrush filaments, the greater the risk of gingival abrasion (Khocht *et al*. 1993). People also tend to prefer medium-to-hard brushes because they feel that their teeth are cleaner after brushing with a stiffer brush. Versteeg *et al*. (2008a) showed that when there is no clinical indication for a soft toothbrush, the professional advice with regard to effectiveness should indeed be for a toothbrush of medium stiffness. Soft-filament brushes are particularly recommended for brushing shortly after periodontal surgery for patients with highly inflamed gingiva and for patients with naturally finely textured atrophic or sensitive mucosa. However, the topic of filament stiffness should not be addressed by itself; brush–toothpaste interaction should also be considered. The capacity of a toothbrush to hold and move polish/abrasive over the tooth surface affects the amount of hard tissue abrasion (see Toothbrush abrasion later).

Filament end-rounding

End-rounding has become increasingly common in the toothbrush-manufacturing process to reduce gingival abrasion (Fig. 28-4). The logic that smooth filament tips would cause less trauma than filament tips with sharp edges or jagged projections has been validated in both animal and clinical studies (Breitenmoser *et al*. 1979). Danser *et al*. (1998) evaluated two types of end-rounding and observed their effects on the incidence of abrasion. The form to which the ends were rounded had no effect on the level of plaque removal. Tapered filaments (Fig. 28-5) have endings in the shape of an extreme rotational ellipsoid instead of a hemisphere. This shape has been suggested to give the filaments very soft endings, combined with good stability of the filament corpus. As a result, more flexibility is introduced into the filaments, which are presumably less harmful. The efficacy of tapered toothbrush filaments has been tested in laboratory studies, and it has been found that they were able to reach into the interproximal areas of the teeth, under the gum line, and into the fissures. A recent systematic review, however, found no firm evidence in support of a tapered filament toothbrush over the use of an regular toothbrush with

Fig. 28-4 Filament end-rounding.

Fig. 28-5 Tapered toothbrush filaments.

end-rounded filaments (Hoogteijling *et al*. 2018). The outcomes of clinical studies comparing end-rounded filaments with flat-trimmed toothbrush head configurations have been equivocal (Dörfer *et al*. 2003; Versteeg *et al*. 2008b).

Wear and replacement

Common sense dictates that toothbrushes should be replaced because the filaments and tufts do not retain their shape forever. Completely worn brushes lose the capacity to remove plaque effectively. This result most likely occurs because of a loss of shear force, as the tips of the filaments can no longer disrupt the plaque adequately. The exact moment at which a toothbrush should be replaced is difficult to determine. In general, dental associations, professionals, and the oral care industry advocate toothbrush replacement every 3–4 months. While this advice would seem reasonable, there is little actual clinical proof that this recommendation is correct. Patients do not appear to heed this advice; the evidence indicates that the average age at which a toothbrush is replaced ranges from 2.5 to 6 months (Bergström 1973). On average, each person in the USA purchases three toothbrushes every 2 years.

Common sense would suggest that a worn toothbrush with splayed or frayed filaments loses its resilience and is less likely to be as effective in removing plaque as a new brush. Because of the variability in subjects' brushing techniques and the force applied to the teeth while brushing, the degree of wear varies significantly from subject to subject. It is also likely that different brushes, made from various materials, would exhibit differences in longevity.

Because many patients use their brushes for periods significantly longer than the recommended time of 3 months, it is important to know whether excessive wear is of clinical relevance. There is inconclusive evidence about the relationship between toothbrush wear and plaque removal. The age of the toothbrush by itself appears not to be the critical parameter that is crucial to plaque removal efficacy. Studies with laboratory-worn toothbrushes have reported that such toothbrushes had inferior plaque removal efficacy compared with new brushes (Kreifeldt *et al*. 1980; Warren *et al*. 2002). However, artificially worn toothbrushes might not properly mimic the characteristics of naturally worn brushes. The wear of laboratory-worn toothbrushes will inevitably be highly uniform and will not reflect the variations in wear seen in normal toothbrush use. Most studies in which naturally worn toothbrushes were studied reported no statistically significant decreases in the reduction of whole-mouth plaque scores after brushing compared with when using new toothbrushes (Daly *et al*. 1996; Sforza *et al*. 2000; Tan & Daly 2002; Conforti *et al*. 2003; Van Palenstein Helderman *et al*. 2006). Toothbrush wear per individual patient is fairly consistent (Van Leeuwen *et al*. 2019). Rosema *et al*. (2013) evaluated the plaque-removing efficacy of new and used manual toothbrushes and found that wear rate seemed to be the determining factor with regard to loss of efficacy. Similarly, Van Leeuwen *et al*. (2019) found toothbrushes with extreme wear to be less effective than those with no or light wear. They suggested that bristle splaying is a more appropriate measure of brush replacement time than the commonly used toothbrush age. Splaying of the outer tufts beyond the base of the toothbrush is a condition that indicates it is time to change the brush.

Kreifeldt *et al*. (1980) studied tapering of toothbrush filaments with regard to toothbrush wear and reported that new brushes were more efficient in removing dental plaque than old brushes. They also examined worn toothbrushes and observed that, as a result of wear, the filaments exhibited tapering that proceeded from the insertion to the free end. For example, filaments were seen that tapered from 0.28 mm at one end to 0.020–0.015 mm at the free end. They concluded that, among wear factors, tapering contributed the most to loss of effectiveness. Their explanation for this observation was that as tapering results in a reduction of filament diameter, the brush will become softer and remove less plaque. Based on this tapering phenomenon, some commercially available brushes have filaments that change color after a certain amount of use. These wear indicator filaments serve to remind patients that it is time to replace the brush.

Electric (powered) toothbrushes

In well-motivated and properly instructed individuals who are willing to invest the necessary time and effort, mechanical measures using traditional toothbrushes and adjunctive manual (interdental) devices are effective in removing plaque. Maintaining a

dentition that is close to plaque-free is not easy, however. The high prevalence of gingivitis indicates that toothbrushing is not as effective in practice as it is in supervised studies. The electric toothbrush represents an advance that has the potential to enhance both plaque removal and patient motivation (see Box 28-2). Electric toothbrushes have been around since the 1940s, starting with devices such as the Motodent (circular brush head) and the Toothmaster (straight brush head). An example of the latter can be found in the National Museum of Dentistry in Baltimore, Maryland, USA. The first successfully marketed electric toothbrushes were introduced more than 50 years ago. In 1954, the Swiss inventor Dr Philippe Guy E. Woog invented an oscillating, motorized electric toothbrush. This toothbrush was further developed by Bemann and Woog and first appeared in 1956 in Switzerland. In 1959, it was introduced in the USA as the Broxodent at the centennial celebration of the ADA by E.R. Squibb and Sons. This early electric brush was a plug-in device that featured bristles that moved from side to side. In 1961, a cordless, rechargeable model was introduced by General Electric, the so-called Automatic Toothbrush, which soon took the lead in what was turning out to be a very competitive market.

The first electric toothbrushes were basically mechanized versions of manual toothbrushes, with the bristles moving back and forth in an imitation of the way people brushed by hand. Studies of the use of these early electric toothbrushes showed that there was no difference in plaque removal when compared with manual toothbrushes, although they had mixed effects on gingivitis. In 1966, the consensus from the research reports on toothbrushing of the World Workshop in Periodontics stated, "in non-dentally oriented persons, in persons not highly motivated to oral health care, or in those who have difficulty in mastering suitable hand brushing technique, the use of an electric brush with its standard movements may result in more frequent and better cleansing of the teeth".

Since the 1980s, tremendous advances have been made in the technology of electrically powered toothbrushes. Various electric toothbrushes have been developed with unique motions to improve the efficiency of plaque removal, using increased filament velocity and brush stroke frequency, and various filament patterns and motions. Whereas older electric toothbrushes used a combination of horizontal and vertical movements, mimicking closely the back-and-forth motion of traditional brushing methods, the more recent designs have incorporated a variety of actions, such as vibrating at ultrasonic frequencies, and have heads that rotate, heads that move from side to side, or sets of bristles that move one way and then the other way. The electric toothbrush that in the 1980s successfully steered away from a conventional brushing mode and instead mimicked the small round rotating brush head of dental prophylaxis instruments was the Rotadent (Zila, Fort Collins, CO, USA) (Boyd *et al*. 1989). It was sold with three different brush heads in different shapes to facilitate access to all areas of the oral cavity. However, the consumer found it difficult to control. In the 1980s the Interplak was introduced (Conair, Stamford, CT, USA), with independent tufts of bristles that performed rotary and counter-rotary movements (Van der Weijden *et al*. 1993). Although being effective it lost popularity because of the complicated gearing system which could not cope with the abrasive nature of toothpaste.

The development of an oscillating–rotating round brush head by Braun (Kronberg, Germany) made control of the brush easier. Oscillating–rotating brushes are designed with round heads that move back and forth, with alternating one-third turns clockwise and counterclockwise. The original oscillating–rotating toothbrush, the Braun Oral-B Plaque Remover (D5), featured a small, round brush head that made rotating and oscillating movements at a speed of 2800 oscillating rotations/min. A further development of this brush, the Braun Oral-B Ultra Plaque Remover (D9), maintained the oscillating–rotating action but at an increased speed (3600 rotations/min). A clinical study with the D9 demonstrated equivalence in safety and a trend toward greater plaque removal (Van der Weijden *et al*. 1996b). Newer developments in oscillating–rotating brush technology are the addition of high-frequency vibrations in the direction of the bristles, creating three-dimensional movements during brushing. This modification was developed to enhance penetration and the removal of plaque from the proximal spaces of the dentition. Studies have shown that the three-dimensional movements performed by the brush are safe and more efficient regarding plaque removal (Danser *et al*. 1998).

Another advance in this technology has been the development of sonic toothbrushes, which have a high frequency of filament movement in excess of approximately 30 000 strokes/min. For example, the rechargeable Oral-B Sonic Complete® (Oral-B Laboratories, Boston, MA, USA) and the Philips Sonicare® Elite (Philips Oral Healthcare, Snoqualmie, WA, USA) both use a side-to-side motion operating at a frequency of 260 Hz, but are based on different technologies. Toothbrushes with bristle motion at a high frequency can generate a turbulent fluid flow in the oral cavity. This flow can cause hydrodynamic forces (wall shear forces) that act parallel to a surface. The vibration of toothbrush bristles could further enable energy transfer in the form of sound pressure waves. *In vitro* studies have indicated that non-contact biofilm reduction can be obtained by these hydrodynamic effects. However, *in vivo*, the additional beneficial effects of higher amounts of non-contact biofilm removal have not yet been shown clinically (Schmidt *et al*. 2013).

The electric toothbrush should not be considered a substitute for a specific interdental cleaning method,

such as flossing, but it can offer advantages in terms of an overall approach to improved oral hygiene. The use of an electric toothbrush was found to improve plaque removal from the surfaces of implant-supported fixed partial dentures, especially from the area of the prostheses touching the alveolar ridge (Maeda *et al*. 2019).

Electric brushes versus manual toothbrushes

To some extent, modern design features of electric brushes have overcome the limitations of manual dexterity and skill of the user (Fig. 28-6). These modern toothbrushes remove plaque in a shorter time than a standard manual brush. It takes 6 minutes to remove the same percentage of plaque using a manual toothbrush that is removed in 1 minute using a powered toothbrush in the hands of a professional operator (Van der Weijden *et al*. 1993, 1996a). The new generation of electric brushes has better plaque removal efficacy and gingival inflammation control on the proximal tooth surfaces (Egelberg & Claffey 1998). Of this latter aspect the superiority was clearly demonstrated in a study conducted on extracted teeth (Rapley & Killoy 1994).

A systematic review of single brushing exercises showed that the efficacy in plaque removal using an electric toothbrush provides a weighted mean plaque score reduction of 46% on average, with a range of 36–65%, dependent on the index scale to score plaque. Power supply (rechargeable or replaceable battery), mode of action, as well as brushing duration and type of instructions are factors which contribute to the variation in the observed efficacy (Rosema *et al*. 2016). The collective evidence also shows that electric toothbrushes have superior efficacy over manual toothbrushes in reducing plaque and gingivitis (Sicilia *et al*. 2002; Yaacob *et al*. 2014; De Jager *et al*. 2017; Elkerbout *et al*. 2020; Wang *et al*. 2020). The conclusion from a Cochrane Oral Health Group review was that in the long term, electric toothbrushes reduced plaque by 21% and gingivitis by 11%, when compared with manual brushes (Yaacob *et al*. 2014). Any reported side effects were localized and temporary. The greatest body of evidence was found for oscillating–rotating brushes the effect of which has recently been summarized in a systematic review of studies up to 3 months in duration. This provided evidence supporting recommendations for patients with various degrees of gingival bleeding to use oscillating–rotating electric toothbrushes (Grender *et al*. 2020). Collective evidence for high-frequency, high-amplitude sonic powered toothbrushes showed that these also decreased plaque and gingivitis significantly more effectively than manual toothbrushes in everyday use in studies lasting up to 3 months (De Jager *et al*. 2017).

Modern electric toothbrushes are known to enhance long-term compliance. In a study involving periodontitis patients with persistently poor compliance, Hellstadius *et al*. (1993) found that switching from a manual to an electric toothbrush reduced plaque levels and that the reduced levels were maintained over a period of between 12 and 36 months. The electric brush significantly improved compliance, and patients expressed a positive attitude toward the new brush. Another study reported 62% of people continuing to use their electric toothbrushes on a daily basis 36 months after purchase (Stålnacke *et al*. 1995). In a survey conducted in Germany, most dentists stated that the time their patients spent on toothbrushing was too short (Warren 1998). Approximately half of the dentists stated that they recommended that their patients use an electric toothbrush, and the vast majority of the dentists believed that changing to an electric toothbrush would improve the condition of their patients' teeth and gums. The findings from a US practice-based study, involving a large number of subjects who switched from manual toothbrushes to the Braun Oral-B Ultra Plaque Remover

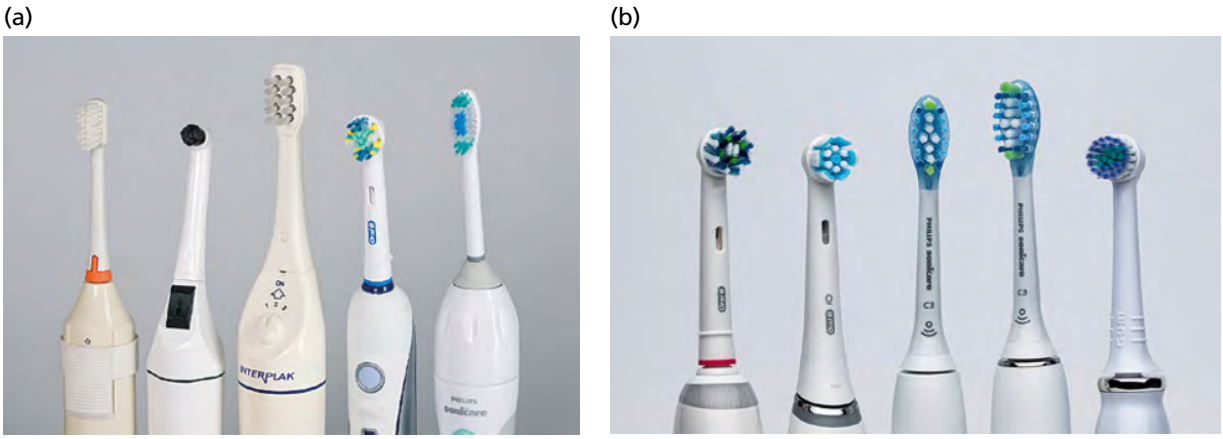


Fig. 28-6 (a) Overview of the development of electric toothbrushes, from brushes mimicking a manual toothbrush to high-frequency brush head movement. From left to right: the Braun D3® (courtesy of Braun), Rotadent® (courtesy of Rotadent), Interplak® (courtesy of Conair), Braun/Oral-B Triumph® (courtesy of Braun and Oral-B), and Sonicare Elite® (courtesy of Philips). (b) The latest versions of modern electric toothbrushes.

(D9), confirmed those from a German study (Warren *et al*. 2000).

Comparison of different electric toothbrushes

Today's marketplace is crowded with dozens of electric brushes. The choices range from inexpensive, disposable, battery-operated, rotating brushes to sophisticated, rechargeable electric brushes. To establish the superiority of electric brushing over any other mode, the most well-known review, from a decade ago, performed in collaboration with the Cochrane Oral Health Group, assessed the collective evidence on efficacy of electric brushes and their effects on oral health (Deacon *et al*. 2011). The selection criteria were studies that were randomized, involved at least 4 weeks of unsupervised brushing, enrolled participants who had no impairment of manual dexterity, and compared two or more electric brushes with different modes of action. Brushes with a rotation–oscillation action reduced plaque and gingivitis more than those with side-to-side action in the short-term. However, the difference was small and its clinical importance unclear. Due to the low numbers of trials using other types of electric brushes, no other definitive conclusions can be drawn regarding the superiority of one type of electric toothbrush over another. However, it must be emphasized that absence of evidence is not evidence of absence, and it might be that future trials show the superiority of specific toothbrush designs. The most recent review based on single brushing exercises evaluated dental plaque removal using an oscillating–rotating power toothbrush as compared with a high-frequency sonic power toothbrush. It was concluded that there is some evidence of a very small but significant beneficial effect of an oscillating–rotating power toothbrush (Van der Sluijs *et al*. 2021). In addition, the difference in efficacy of oscillating–rotating power toothbrushes compared with other powered toothbrushes was recently systematically reviewed and analyzed (Clark-Perry & Levin 2020; El-Chami *et al*. 2021; Van der Sluijs *et al*. 2021). Altogether this shows that there is some evidence to suggest that oscillating–rotating power toothbrushes might remove more plaque and reduce the number of bleeding sites better than other powered toothbrushes, including high-frequency, high-amplitude sonic-powered toothbrushes. Based on studies with at least a 4-week duration, little to no difference in plaque and gingivitis scores was found with oscillating–rotating power toothbrushes compared with side-to-side powered toothbrushes (El-Chami *et al*. 2021). Further research is required before evidence-based advice concerning the relative performances of different electric toothbrushes can be provided by health care professionals to the public.

Safety

The safety of electric toothbrushes has been a concern of dental care professionals. One fear was that they would be used excessively and compulsively. For example, enthusiastic electric brush users could apply too much force and compromise their gingival tissues, thereby promoting recession. In a systematic review of the effects of oscillating–rotating and manual brushes on hard and soft tissues, the authors determined the safety of this design of electric toothbrush as comprehensively as possible (Van der Weijden *et al*. 2011). They searched the existing literature, using a variety of electronic databases, for any study that compared the safety of oscillating–rotating brushes to that of manual brushes, including all but the weakest levels of evidence. Having extracted the relevant data from the 35 most appropriate original papers, the data were grouped by research design (randomized controlled trials with safety as the primary outcome, trials in which safety was a secondary outcome, studies that used a surrogate marker of safety, and laboratory-based studies). Within these groups, the designs of the original studies were usually so diverse that it was impossible to bring the results together into a single statistical analysis. Nevertheless, the original data consistently failed to indicate problems with the safety of rotation–oscillation brushes. However, the majority of the trials considered safety as a secondary outcome. Therefore, the evidence was usually anecdotal rather than quantitative. The review authors concluded, "This systematic review of a large body of published research in the preceding two decades consistently showed oscillating–rotating toothbrushes to be safe when compared with manual brushes, and collectively indicated that there is no evidence that they do pose a clinically relevant concern to either hard or soft tissues". The outcomes were consistent with the observations in the reviews of Yaacob *et al*. (2014), Deacon *et al*. (2011) and El-Chami *et al*. (2021) reporting only minor and transient side effects.

Electrically active (ionic) toothbrush

Several toothbrushes (ionic, electronic, and electrically active) have been marketed over the years that are designed to send a small, imperceptible electronic current through the brush head onto the tooth surfaces, presumably to disrupt the attachment of dental plaque and to damage the electrostatic bonding of plaque proteins to tooth surfaces. Thus, these currents could enhance the efficacy of brushes in plaque elimination. Electrons should eliminate H^+ ions from the organic acid in the plaque, which could result in decomposition of the bacterial plaque (Hoover *et al*. 1992). The first record of a charged toothbrush, "Dr. Scott's Electric Toothbrush", was found in the

February 1886 issue of *Harper's* weekly magazine. The handle of Dr Scott's toothbrush was purportedly "charged with an electromagnetic current which acts without any shock, immediately upon the nerves and tissues of the teeth and gums. . .arresting decay. . .and restoring the natural whiteness of the enamel".

Hotta and Aono (1992) studied an electrically active manual toothbrush that was designed with a piezoelectric element in the handle. This brush generated a voltage potential corresponding to the bending motion of the handle as the teeth were brushed. In this study, no difference in the amount of remaining plaque after brushing was observed between the placebo and the electrically active brush. Other toothbrushes that have claimed an "electrochemical" effect on dental plaque have had semiconductors of titanium oxide (TiO_2) incorporated into the brush handle. In the presence of light, saturated low-energy electrons in the wet semiconductor are transformed into high-energy electrons. An electron current of approximately 10 nA was measured to run from the semiconductor to the tooth (Weiger 1988). Some short-term clinical studies of the use of these kinds of brushes have documented beneficial effects in terms of plaque reduction and gingivitis resolution (Hoover *et al*. 1992; Galgut 1996; Weiger 1998; Deshmukh *et al*. 2006), while others have failed to do so (Pucher *et al*. 1999; Moreira *et al*. 2007). One 6-month study reported lower plaque scores and improvement of gingivitis with the ionic brush compared with the control, but these findings were not substantiated in subsequent 6- and 7-month studies (Van der Weijden *et al*. 1995, 2002b).

Interdental cleaning

There is confusion in the literature regarding the definitions of the proximal, interproximal, interdental, and proximal sites. Commonly used indices are not suitable for assessing interdental plaque (directly under the contact area), thereby limiting the interpretation of interdental plaque removal. In 1998, the European Workshop on Mechanical Plaque Control proposed the following definitions. *Proximal* areas are the visible spaces between teeth that are not under the contact area. These areas are small in healthy dentition, although they can increase after periodontal attachment loss. The terms *interproximal* and *interdental* can be used interchangeably and refer to the area under and related to the contact point.

Based on consensus, interproximal cleaning is essential to maintain interproximal gingival health, in particular for secondary prevention (Chapple *et al*. 2015). The rationale for considering interdental cleaning under a separate heading is related to toothbrushing alone being considered optimally capable of thoroughly cleaning the *flat* surfaces of the teeth, that is the buccal, lingual, and occlusal surfaces, with the exceptions of pits and fissures. Toothbrushes do not reach the proximal surfaces of teeth as efficiently, nor do they reach into the interproximal areas between adjacent teeth. Therefore, measures for interdental plaque control should be selected to complement plaque control by toothbrushing (Lang *et al*. 1977; Hugoson & Koch 1979). The interdental gingiva fills the embrasure between two teeth apical to their contact point. This is a "sheltered" area which is difficult to access when the teeth are in their normal position. In populations that use toothbrushes, the interproximal surfaces of the molars and premolars are the predominant sites of residual plaque. The removal of plaque from these surfaces remains a valid objective because in patients susceptible to periodontal diseases, gingivitis and periodontitis are usually more pronounced in these interdental areas than on the oral or facial aspects (Löe 1979). Dental caries also occur more frequently in the interdental region than on the oral or facial smooth surfaces. A fundamental principle of prevention is that the effect is greatest where the risk of disease is greatest. Therefore, interdental plaque removal, which cannot be achieved with a toothbrush alone, is of critical importance for most patients.

A number of interdental cleaning methods have been developed, ranging from flossing to the more recently introduced electrically powered cleaning aids. Flossing is the most universally applicable method. However, not all interdental cleaning devices suit all patients or all types of dentitions. Apart from the ease of use, the ability and motivation of the patient should be taken into consideration when recommending an interdental cleaning method. The most appropriate patient-specific interdental cleaning devices must be selected to enable each individual patient to achieve a safe and high standard of interdental cleaning (Amarasena *et al*. 2019).

The selection made from among the numerous commercially available devices is dependent for the most part on the contour of the papilla, size of the interdental space, morphology of the proximal tooth surfaces, and tooth alignment. In subjects with normal gingival contours and embrasures, dental floss or tape can be recommended. At sites where soft tissue recession has become pronounced, flossing becomes progressively less effective. Thus, an alternative method (either woodsticks, rubber/elastomeric interdental cleaning sticks, or interdental brushes) should be recommended. In addition, it should be borne in mind that the advice offered might need to change as the effectiveness of treatment and improved oral hygiene change the shapes of the interproximal regions.

A review of interdental cleaning methods (Warren & Chater 1996) concluded that all conventional devices are effective, but each method should be suited to a particular patient and to a particular situation in the mouth (Table 28-1). Furthermore, for maximum effectiveness, the level of oral

Table 28-1 Interdental cleaning methods recommended for particular situations in the mouth.

Situation	Interdental cleaning method
Intact interdental papillae; narrow interdental space	Dental floss or small woodstick/rubber/elastomeric interdental cleaning stick
Moderate papillary recession; slightly open interdental space	Dental floss, woodstick/rubber/elastomeric interdental cleaning stick or small interdental brush
Complete loss of papillae; wide open interdental space	Interdental brush
Wide embrasure space; diastema, extraction diastema, furcation or posterior surface of most distal molar, root concavities or grooves	Single-tufted/end-tufted brush or gauze strip

hygiene advice delivered to the patient must contain enough information to enable the patient to be able to identify each site in turn, to select a device, and to clean all interdental surfaces effectively (Claydon 2008). The starting point is an evaluation of existing products. An ideal interdental cleaning device should be user-friendly, remove plaque effectively, and have no deleterious soft tissue or hard tissue effects. Gingival bleeding during interdental cleaning can be the result of trauma, such as lacerations and gingival erosions, or it can be an indication of inflammation. Patients must be aware that bleeding *per se* is not a sign that interdental cleaning should be avoided but is more likely an indicator of inflammation that needs to be treated (Gillette & Van House 1980).

Dental floss and tape

Of all the methods used for removing interproximal plaque, dental flossing is the most frequently recommended. Levi Spear Parmly, a dentist based in New Orleans, USA is credited with being the inventor of modern dental floss. As early as 1815, Parmly recommended tooth flossing with a piece of silk thread. In 1882, the Codman and Shurtleft Company of Randolph, Massachusetts, USA, started to mass-produce unwaxed silk floss for commercial home use. In 1898, the Johnson & Johnson Company of New Brunswick, New Jersey, USA, was the first to patent dental floss. During the 1940s nylon floss, which was more resistant to shredding, replaced silk as the material for dental floss. Dr Charles C. Bass is considered to be for making teeth flossing an important part of dental hygiene.

Dental floss and tape (see Box 28-3) – the latter a broader type of dental floss – are most useful where the interdental papillae completely fill the embrasure space. When properly used, effective flossing removes up to 80% of proximal plaque. Even subgingival plaque can be removed because dental floss can be introduced 2–3.5 mm beyond the tip of the papilla (Waerhaug 1981b). Several types of floss (waxed, unwaxed) are available. Studies have shown no difference in the effectiveness of unwaxed versus waxed dental floss. Unwaxed dental floss is generally recommended for patients with normal tooth contacts because it slides through the contact area easily. It is the thinnest type of floss available, yet when it separates during use it covers a larger surface area of the teeth than waxed floss. Waxed floss is recommended for patients with tight proximal tooth contacts.

Ease of use is the most important factor that influences whether patients will use floss on a daily basis. Many people find using dental floss difficult to master because of the manual complexity of the technique which in turn has a negative effect on compliance (Graziani *et al*. 2018). Unlike toothbrushing, few people have learned how to use dental floss properly. However, like any other skill, flossing can be taught, and those patients who are given appropriate instruction will increase their flossing frequency (Stewart & Wolfe 1989). Patients benefit from step-by-step instructions (see Box 28-3) and frequent re-instruction and reinforcement in the use of floss are necessary. Because many people think that the purpose of flossing is to remove particles of food, they must be advised that the objective is to remove plaque that adheres to the tooth surface.

To facilitate flossing, a special floss holder can be used. These holders can be re-used and are normally made of a plastic that is durable, lightweight, and easy to clean. Research has revealed that reductions in bacterial plaque biofilm and gingivitis are equivalent with either hand flossing or the use of a floss holder. Powered flossing devices have been introduced. In comparison with manual flossing, no differences were found in terms of plaque removal or gingivitis reduction, although patients preferred flossing with the automated device (Gordon *et al*. 1996).

Flossing is also time-consuming. When a patient is unwilling to use dental floss, alternative interdental hygiene aids should be recommended, even if these aids are less efficient. If a patient finds a particular method or device more appealing to use, long-term compliance becomes an achievable goal. Although it is clear that flossing, when properly used, removes plaque in a very efficient manner, there is no evidence that flossing in adult patients with preserved interproximal periodontal tissues should be routinely indicated (Burt & Eklund 1999).

Three systematic reviews and one meta-review are available concerning the efficacy of dental floss. The first, by Berchier *et al*. (2008), evaluated the collective evidence to determine the effectiveness of dental floss, in combination with toothbrushing, on plaque and the clinical parameters of gingivitis in adults. The majority

of the included studies showed that there was no benefit from flossing. The meta-analysis of plaque and the gingival index scores also showed no significant differences between groups. Advocacy for flossing as an interdental cleaning method hinges, in large part, on common sense. However, common sense arguments are the lowest level of scientific evidence. A Cochrane review included a variety of floss-related products and, based on the combined evidence, concluded that there was some evidence that flossing, in addition to toothbrushing, reduced gingivitis compared with toothbrushing alone (Sambunjak *et al*. 2011). The most recent Cochrane review summarized the evidence for all interdental cleaning devices and included 15 trials evaluating floss plus toothbrushing versus toothbrushing alone. It was concluded that low-certainty evidence suggested that flossing, in addition to toothbrushing, may reduce gingivitis (Worthington *et al*. 2019). A meta-review based on evidence gathered from existing systematic reviews concluded that the majority of available studies fail to demonstrate that flossing is generally effective in plaque removal (Salzer *et al*. 2015). Thus, there is weak, very unreliable evidence that flossing plus toothbrushing could be associated with a small reduction in plaque. This is also confirmed in two Bayesian Network Meta-Analysis concerning the efficacy of interdental oral hygiene aids. It quantitatively provided a global ranking of efficacy where, with respect to the reduction of gingival bleeding, dental floss ranked last (Kotsakis *et al*. 2018; Liang *et al*. 2020).

That dental floss has no additional effects on toothbrushing is apparent from more than one review. Hujoel *et al*. (2006) found that flossing was only effective in reducing the risk of interproximal caries when applied professionally. High-quality professional flossing, performed in first-grade children on school days, reduced the risk of caries by 40%. In contrast, self-performed flossing failed to show a beneficial effect. The lack of an effect on caries and the absence of an effect on gingivitis in the systematic review by Berchier *et al*. (2008) were most likely the consequences of plaque not being removed efficiently.

That flossing does not appear to be effective in the hands of the general public does not preclude its use. For instance, in interdental situations that only allow for the penetration of a string of dental floss, floss is the best available tool. Although floss should not be the first tool recommended for cleaning open interdental spaces, if the patient does not like any other tool, flossing could still be part of oral hygiene instruction. Floss can also still be advised in interdental sites, where other interdental cleaning devices will not pass through the interproximal area without trauma (Chapple *et al*. 2015). The dental professional should realize that proper instruction, sufficient motivation of the patient, and a high level of dexterity are necessary to make the flossing effort worthwhile. Routine instruction in using floss is not supported by scientific evidence.

Woodsticks

While flossing is the most widely advocated interdental cleaning method, picking of teeth may well be one of humanity's oldest habits and the toothpick one of our earliest tools. The toothpick might date back to the days of cave people, who probably used sticks to pick food from between their teeth. A 1.2 million-year-old hominin jawbone was recently discovered at an excavation site in northern Spain. The jawbone had an interproximal groove with fragments of non-edible wood, which suggests that picking at teeth may be one of humanity's earliest interdental oral hygiene activities (Hardy *et al*. 2016). The ancient Romans made use of toothpicks fabricated from bone and metal. Saxon women carried ivory toothpicks. The evolution of the primitive toothpick took a second pathway in more acquisitive societies, becoming part of personal care kits, along with depilatory tweezers and earwax scoops (Mandel 1990). In 1872, Silas Noble and J. P. Cooley patented the first toothpick-manufacturing machine.

Originally, dental woodsticks were advocated by dental professionals as "gum massagers" used to massage inflamed gingival tissue in the interdental areas, to reduce inflammation, and to encourage keratinization of the gingival tissue (Galgut 1991).

The key difference between a toothpick and a woodstick (wooden stimulator/cleaner) relates to the triangular (wedge-like) design of the latter. Woodsticks should not be confused with toothpicks, which are simply intended to remove food debris after meals (Warren & Chater 1996). Woodsticks are inserted interdentally, with the base of the triangle resting on the gingival side (see Box 28-4). The tip should point occlusally or incisally, with the triangle against the adjacent tooth surfaces. Triangular, wedge-like woodsticks have been found to be superior in plaque removal compared with round or rectangular woodsticks, because they fit the interdental area more snugly (Bergenholtz *et al*. 1980; Mandel 1990). Woodsticks are usually made of soft wood to prevent injury to the gingiva. Their tapered form makes it possible for the patient to angle the woodstick interdentally and even clean the lingually localized interdental surfaces. Unlike floss, woodsticks can be used on the concave surfaces of the tooth roots. Some are handheld, while others are designed to be mounted in a handle, which facilitates access to the interdental areas in the posterior region of the mouth (Axelsson 2004). The wood can store fluoride crystals, both on the surface and in the porosities. These crystals readily dissolve when woodsticks are moistened with saliva (Axelsson 2004).

Woodsticks have the advantage that they are easy to use and can be used throughout the day, without the need for special facilities, such as a bathroom or a mirror. They are also environmentally friendly. A national dental survey showed that the Swedish population prefers using woodsticks to dental floss

for the removal of interdental plaque: approximately 46% of adults used woodsticks sporadically and 12% used woodsticks daily. In contrast, dental floss was used occasionally by 12% of adults and daily by only 2%. In other words, adults used woodsticks as oral hygiene aids four to six times more frequently than dental floss (Axelsson 1994). Woodsticks can be used in primary prevention, including in posterior areas, even in cases of poor manual dexterity. To use woodsticks, there must be sufficient interdental space available; in these cases, woodsticks are an excellent substitute to dental floss. Woodsticks can clearly be recommended for patients with open interdental spaces for secondary prevention of periodontal diseases.

Although woodsticks have good cleansing capacity in the central part of the interproximal surfaces of teeth in contact, their effect is reduced on the lingual side of these surfaces. Woodsticks are somewhat difficult to use in the far posterior regions of the jaws because of the lack of accessibility and because the triangular cross-section must pass into the embrasure space at a specific angle (Bassiouny & Grant 1981). When used in healthy dentition, woodsticks can depress the gingival margin. Long-term use can cause permanent loss of the papilla and opening of the embrasure, which can have important esthetic implications for the anterior dentition.

Hoenderdos *et al*. (2008) performed a systematic review to evaluate and summarize the available evidence on the effectiveness of using woodsticks in combination with toothbrushing, to reduce both plaque and clinical inflammatory symptoms of gingival inflammation. The evidence as collected only refers to triangular-shaped woodsticks. No data were gathered with respect to other shapes of woodsticks such as round or square toothpicks. The heterogeneity of the data precluded quantitative analysis and only allowed for a descriptive analysis. In seven studies, improvement in gingival health represented a significant incremental benefit realized by the use of triangular woodsticks. None of the studies that scored visible interdental plaque demonstrated any significant advantage of using woodsticks, as opposed to alternative methods (toothbrushing only, dental floss, or interdental brushes), in patients with gingivitis. The latest Cochrane review (Worthington *et al*. 2019), with only one included study on woodsticks, also concluded that this device reduced gingivitis but had no effect on plaque scores.

A series of histologic investigations in patients with periodontitis has shown that the papillary area with the greatest inflammation corresponds to the middle of the interdental tissue. It is difficult to assess the mid-interdental area clinically, as it is usually not available for direct visualization (Walsh & Heckman 1985). When used on healthy dentition, woodsticks depress the gingiva by up to 2–3 mm (Morch & Waerhaug 1956) and therefore clean part of the subgingival area. Thus, woodsticks can specifically remove subgingivally located interdental plaque that is not visible and therefore not evaluated by the plaque index. This physical action of woodsticks in the interdental area could produce a clear, beneficial effect on interdental gingival inflammation.

The studies included in the review by Hoenderdos *et al*. (2008) showed that changes in gingival inflammation were as apparent as changes in bleeding tendency as indicators of disease. Numerous studies have shown that sulcular bleeding is a very sensitive indicator of early gingival inflammation. Bleeding following the use of woodsticks can also be used to increase patient motivation and awareness of gingival health. The dental care professional can also demonstrate the gingival condition to the patient, using an interdental bleeding index (Eastman Interdental Bleeding Index; Caton *et al*. 1988). This method is a reliable and validated clinical indicator for detecting interdental inflammatory lesions (Barendregt *et al*. 2002). It can be used as a self-assessment tool for gingivitis patients because the presence of bleeding provides immediate feedback on the level of gingival health. This could encourage patients to include woodsticks as part of their oral hygiene regimens (Walsh *et al*. 1985).

Rubber/elastomeric interdental cleaning sticks

The most recent development for interdental cleaning is the rubber/elastomeric interdental cleaning stick (RICS) (see Box 28-5). The first product was Soft-pick®, marketed by the GUM® Company (Sunstar Europe S.A., Etoy, Switzerland). Its plastic core with soft elastomeric bristles is said to massage the gum and dislodge food. It is presented as an alternative to flossing and should improve patient compliance. A more recent development is a comparable product called EasyPick™ from the TePe® Company (Tepe Munhygienprodukter AB, Malmö, Sweden) where the core is firm covered by a flexible silicone coating and lamellae. Only a handful of clinical trials have evaluated this new device. In gingivitis patients, adjuvant use to toothbrushing of RICS as compared with dental floss, showed no difference of plaque and gingivitis scores (Yost et al. 2006; Abouassi *et al*. 2014; Graziani *et al*. 2017). In four studies with a follow-up design, no differences with respect to plaque score reduction was observed for the RICS compared with interdental brushes (Yost *et al*. 2006; Abouassi *et al*. 2014; Graziani *et al*. 2017; Hennequin-Hoenderdos *et al*. 2017). In addition, for overall bleeding scores no difference was found, but one study that analyzed the accessible sites in a separate analysis found RICS to be preferable to interdental brushes (Hennequin-Hoenderdos *et al*. 2017). In contrast, one study evaluating efficacy of RICS compared with interdental brushes according to the gingival index scores showed that the interdental brush achieved a significant greater reduction (Yost *et al*. 2006). Moreover, the RICS led to less abrasions of

the gingiva (Hennequin-Hoenderdos *et al*. 2017) and was preferred by the study participants (Abouassi *et al*. 2014; Hennequin-Hoenderdos *et al*. 2017). So far, no comparisons to woodsticks have been published. Overall, the evidence suggests that RICS may be recommended as an alternative interdental cleaning device for patients with gingivitis (Van der Weijden *et al*. 2021). The evidence supports user safety and participants' preference.

Interdental brushes

Interdental brushes (see Box 28-6) were introduced in the 1960s as an alternative to woodsticks. They are effective in the removal of plaque from the proximal tooth surfaces (Bergenholtz & Olsson 1984). Interdental brushes consist of soft nylon filaments twisted into a fine stainless steel wire. This "metal" wire can prove uncomfortable for patients with sensitive root surfaces. For such patients, the use of plastic-coated metal wires might be recommended. The support wire is continuous or inserted into a metal/plastic handle. The most common forms are cylindrical or conical/tapered (like a Christmas tree). In patients receiving supportive periodontal therapy the conical interdental brushes were found to be less effective than cylindrical ones with respect to lingual approximal plaque removal (Larsen *et al*. 2017). Less common are those with a waist-shape (like a diabolo). It is suggested that it may result in more contact at the lingual and buccal line angles because of the larger diameter at the base and tip section than in the middle (Chongcharoen *et al*. 2011). The waist-shaped interdental brush was found to more effective in plaque removal as compared with a cylindrical interdental brush among patients receiving supportive periodontal therapy (Schnabl *et al*. 2020). The development of triangular interdental brushes was generated by the inconsistency between the form of the interdental space and the shape of the interdental brush which creates insertion resistance. The triangular brushes were found to penetrate the interdental space more easily than conventional cylindrical interdental brushes (Wolff *et al*. 2006a).

Whereas bristle filament stiffness appears to have no statistically significant influence on the cleaning efficacy (Wolff *et al*. 2006b) the length of the filaments in cross-section should be tailored to the interdental space. Interdental brushes are available for the smallest to the largest interdental spaces (Fig. 28-7). Although unconfirmed in the scientific literature, it is believed that the most efficient cleaning is achieved if the brush selected is slightly larger than the embrasure space, as long as they can be inserted into the interdental space (Wolff *et al*. 2006a). Patients require interdental brushes of various sizes. Schmage *et al*. (1999) assessed the relationship between the interdental space and the position of the teeth. Most of the interproximal spaces in the anterior teeth were small and of an appropriate size for the use of floss. Premolars and molars have larger interproximal spaces and are accessible with interdental brushes. The brush can be inserted obliquely into the interdental space from the apical direction leaning towards the mesial and distal aspect of the interproximal space (Schnabl *et al*. 2020). As the posterior proximal spaces have wider lingual embrasures, conical-shaped interdental cleaners are not the first choice. Approaching then from the lingual side will result in more effective plaque removal, but this technique is not easy. Cleaning is performed with a back-and-forth motion. The interdental brush is the aid of choice when root surfaces with concavities or grooves have been exposed. Interdental brushes are also the most suitable cleaning devices for "through-and-through" furcation defects.

Fig. 28-7 With interdental brushes, the diameter of the metal wire core is a determining factor with regard to access. A close fit of the brushing filaments influences the cleaning capacity.

Like woodsticks, interdental brushes are easy to use. They come with different types of handles. This can be the metal wire core itself or handles/holders that are round or flat. The wire, or the handles that have a flexible neck can be bent to form the best insertion angle. Also angled handles are available which have been found to be less effective in plaque removal than straight interdental brushes (Jordan *et al*. 2014). When not used properly, interdental brushes can elicit dentin hypersensitivity. To minimize the risk of hard tissue abrasion, interdental brushes should be used without dentifrice except in special cases, and then only for the short term. Interdental brushes can also be used as carriers to apply fluoride or antimicrobial agents, for example chlorhexidine gel, into the interdental space to prevent caries or the recolonization of residual pockets. Brushes should be discarded when the filaments become loose or deformed.

Interdental brushes represent the ideal interdental cleaning tool, especially for periodontitis patients. Waerhaug (1976) showed that individuals who habitually used interdental brushes were able to maintain supragingival proximal surfaces free of plaque and

to remove some subgingival plaque below the gingival margin up to a depth of 2–2.5 mm below the gingival margin. In a study in patients with moderate-to-severe periodontitis, Christou *et al*. (1998) demonstrated that interdental brushes were more effective than dental floss in the removal of plaque and in promoting pocket reduction. Patients reported that the use of interdental brushes was easier than using dental floss. This finding is in agreement with those of previous studies (e.g. Wolffe 1976). Additionally, the perception of efficacy was better for interdental brushes. Significantly fewer patients reported problems with using interdental brushes. Even if the efficacy of interdental brushes were not better than that of floss, the long-term use of interdental brushes might be more easily implemented in patients' routines than floss. Patient acceptance is a major issue to be considered when it comes to the long-term use of interdental cleaning devices. Interdental brushes are considered to be less time-consuming and more efficacious than floss for interdental plaque removal.

Slot *et al*. (2008) systematically reviewed the literature to determine the effectiveness in patients with gingivitis or periodontitis of interdental brushes used as adjuncts to toothbrushes in terms of plaque and clinical parameters of periodontal inflammation. The majority of the studies showed a positive significant difference in plaque index when using interdental brushes compared with floss. No differences were identified for gingival or bleeding indices. Meta-analysis revealed a significant effect with the Silness and Löe plaque index in favor of the interdental brush group compared with the floss group. Most of the included studies did not discuss the different interdental brush sizes, nor did they indicate whether interdental brushes were used in all available proximal sites. Two of the included studies showed a significant effect on pocket depth reduction with the use of interdental brushes compared with the use of floss. That interdental cleaning with interdental brushes is the most effective method for interdental plaque removal is supported by a meta-review (Saelzer *et al*. 2015), the latest Cochrane review (Worthington *et al*. 2019), and a Bayesian Network Meta-Analysis (Kotsakis *et al*. 2018). A network meta-analysis of studies with participants in periodontal maintenance demonstrated that for plaque removal the adjuvant use of interdental brushes was significantly more effective than the manual toothbrush alone (Slot *et al*. 2020). The reduced pocket depth might have been related to the reduction in swelling with concomitant recession (Jackson *et al*. 2006). However, the effect on pocket depth cannot readily be explained by a reduction in the level of gingival inflammation (Slot *et al*. 2008). As an alternative explanation for the observed effect, which seems conceivable, Badersten *et al*. (1975) suggested that mechanical depression of the interdental papilla is induced by interdental brushes, which, in turn, causes recession of the marginal gingiva. This result, together with the good plaque removal, could have been the origin of the improved reduction in pocket depth.

Single-tufted/end-tufted brushes

Single-tufted brushes have smaller brush heads, which have a small group of tufts or a single tuft (see Box 28-7). The tuft can be 3–6 mm in diameter and can be flat or tapered. The handle can be straight or contra-angled. Angled handles permit easier access to lingual and palatal aspects. The filaments are directed into the area to be cleaned and are activated with a rotating motion. Single-tufted toothbrushes are designed to improve access to the distal surfaces of the posterior molars and to tipped, rotated or displaced teeth; to clean around and under fixed partial dentures and pontic, orthodontic appliances or precision attachments; and to clean teeth affected by gingival recession and irregular gingival margins or furcation involvement. Little research has been performed with this type of brush. A cross-over study compared the single tuft to a flat-trim toothbrush. The results indicated that the single-tuft brush was effective in removing plaque from relatively hard-to-reach sites. More plaque was removed on the buccal side of the maxillary molars and on the lingual interproximal side of the mandibular molars (Lee & Moon 2001).

Dental water jets/oral irrigators

The dental water jet was developed by a hydraulic engineer, John Mattingly, and a dentist, Gerald Moyer. It was introduced to the dental profession in 1962 and has been studied extensively for the past several decades. Prior to 1964, Mattingly built the units at home, and they were sold exclusively through Dr Moyer's practice. In 1964, a patient who loved the device raised thousands of dollars to help make the units available in stores. A few years later, Waterpik® devices could be found in drug stores and department stores. In 2001, the American Academy of Periodontology stated, "Among individuals who do not perform excellent oral hygiene, supragingival irrigation with or without medicaments is capable of reducing gingival inflammation beyond that normally achieved by toothbrushing alone. This effect is likely due to the flushing out of subgingival bacteria". The pulsating, hydrodynamic forces produced by irrigators can rinse away food debris from interdental spaces and plaque-retentive areas (see Box 28-8). An *ex vivo* scanning electron microscopy study demonstrated that the hydraulic forces of a dental water jet can remove the biofilm above and below the cementoenamel junction (Gorur *et al*. 2009). It has been reported that a pulsating stream of water is better than a continuous flow. Irrigation is not, however, a monotherapy but an adjunct designed to supplement or enhance other home oral care methods (brushing and flossing) intended for mechanical plaque removal (Hugoson 1978; Cutler *et al*. 2000) (Fig. 28-8).

Fig. 28-8 Dental water jet. Fluid flow can be either continuous or pulsated.

Husseini *et al*. (2008) performed a systematic review of the existing literature to evaluate the effectiveness of oral water irrigation as an adjunct to toothbrushing on plaque and clinical parameters of periodontal inflammation compared with toothbrushing alone or to regular oral hygiene. The heterogeneity of the data prevented quantitative analysis; therefore, a descriptive approach was undertaken. None of the included studies showed a significant difference between toothbrushing and the use of a dental water jet in combination with toothbrushing. When observing visual signs of gingival inflammation, three of the four studies reported a significant effect with the use of a dental water jet as an adjunct to regular oral hygiene. Two of the four studies showed a significant reduction in probing depth as a result of using a dental water jet as an adjunct to regular oral hygiene. The authors concluded that there is evidence that suggests a positive tendency toward improved gingival health when using a dental water jet as an adjunct to toothbrushing, as opposed to regular oral hygiene (i.e. self-performed oral hygiene without any specific instructions). A 4-week evaluation showed (within the limits of this short evaluation period) that when combined with manual toothbrushing, the daily use of an oral irrigator is significantly more effective in reducing gingival bleeding scores than the use of dental floss (Rosema *et al*. 2011). A 2-week evaluation found that the oral irrigator is more effective than interdental brushes for the reduction of gingival bleeding (Goyal *et al*. 2016). A Bayesian Network Meta-Analysis concerning the efficacy of interdental oral hygiene aids quantitatively provided a global ranking of efficacy where, with respect to the reduction of gingival bleeding, oral irrigators together with interdental brushes ranked highest (Kotsakis *et al*. 2018). The Waterpik® Water Flosser (Water Pik Inc, Fort Collins, Colorado, USA) received the ADA seal of acceptance in February 2017.

The selected papers for this systematic review reported no statistically significant reduction in plaque with use of a dental water jet (Husseini *et al*. 2008). Plaque reduction is a prerequisite for an oral hygiene device to be considered valuable. Despite the lack of an effect on the plaque index, these studies did find a significant effect on the bleeding index. The mechanisms underlying these clinical changes in the absence of a clear effect on plaque are not understood. Different hypotheses have been put forward by authors to explain the results. One hypothesis is that when patients with gingivitis perform supragingival irrigation on a daily basis, the populations of key pathogens (and their associated pathogenic effects) are altered, reducing gingival inflammation (Flemmig *et al*. 1990). There is also the possibility that water pulsations alter specific host–microbial interactions in the subgingival environment and that inflammation is reduced independent of plaque removal (Chaves *et al*. 1994). Another possibility is that the beneficial activity of a dental water jet is at least partly due to removal of food deposits and other debris, flushing away of loosely adherent plaque, removal of bacterial cells, interference with plaque maturation, and stimulation of immune responses (Frascella *et al*. 2000). Other explanations include mechanical stimulation of the gingiva or a combination of previously reported factors. Irrigation can reduce plaque thickness, which might not be easily detected using two-dimensional scoring systems. This fact could explain the absence of an effect on plaque but a positive effect on gingival inflammation.

Irrigation devices can increase the delivery of fluid beneath the gingival margin (Flemmig *et al*. 1990). Greater penetration of a solution into periodontal pockets was achieved by patient-applied supragingival irrigation compared with mouth rinsing (Flemmig *et al*. 1995). Studies evaluating the capacity of supragingival irrigation to project an aqueous solution subgingivally have determined that supragingival irrigation with a standard irrigation tip was capable of delivering water or a medicinal fluid 3 mm subgingivally or to approximately half the probing depth of a 6-mm pocket (Larner & Greenstein 1993). Irrigation devices can be used with water or with disinfectant solutions (Lang & Räber 1982). The use of chlorhexidine in suboptimal concentrations (e.g. 0.06%) has resulted in improved plaque inhibition and has had anti-inflammatory effects (Lang & Räber 1982; Flemmig *et al*. 1990).

Success with pulsating oral irrigators with regular tips is limited to the subgingival area and periodontal pockets (Wennström *et al*. 1987). With a specially designed tip (Pik Pocket® subgingival irrigation tip; Water Pik Inc.), the pulsating stream of fluid can penetrate more deeply into the pocket areas (Cobb *et al*. 1988). These blunt-ended cannulas can also be used to inject antimicrobial agents into shallow-to-moderate periodontal pockets.

Supragingival irrigation applies considerable force to the gingival tissues. Irrigation was shown to have the potential to induce bacteremia. However, given the collective evidence, it appears that irrigation is safe for healthy patients (Husseini *et al*. 2008).

Another oral irrigator device is the Sonicare AirFloss (Philips Oral Healthcare, Snoqualmie, WA, USA), which uses a spray of microbubbles and a small dose of fluid to generate the interdental cleaning action, through which it is claimed disrupts plaque biofilm structures. The nozzle tip is designed to act as a guide to the spaces between teeth. When the two commercially available oral irrigators are compared, the Water Flosser was found to be significantly more effective than the AirFloss for reducing gingivitis and plaque (Sharma *et al* 2012a, b; Goyal *et al*. 2015). There is clearly a need for more published clinical research studies regarding this device to establish its clinical value.

Tongue cleaners

Regular tongue cleaning has been performed since ancient times and is still carried out by the native populations of Africa, the Arab countries, India, and South America. Many ancient religions emphasized the cleanliness of the entire mouth, including the tongue. Indian people's daily ritual of oral hygiene was not confined to brushing of the teeth; the tongue was also scraped, and the mouth was rinsed with concoctions of betel leaves, cardamom, camphor, or other herbs.

The dorsum of the tongue, with its papillary structure, furrows and crypts, harbors a great number of microorganisms. It forms a unique ecologic oral site with a large surface area (Danser *et al*. 2003). The tongue is said to act as a reservoir, which permits the accumulation and stagnation of bacteria and food residues (Outhouse *et al*. 2006). Tongue bacteria can serve as a source of bacterial dissemination to other parts of the oral cavity, for example the tooth surfaces, and can contribute to dental plaque formation. These bacteria make the greatest contribution to the bacteria found in the saliva. Therefore, tongue brushing has been advocated as part of daily home oral hygiene, together with toothbrushing and flossing (Christen & Swanson 1978). Tongue brushing has also been advocated as a component of the so-called "full-mouth disinfection" approach in the treatment of periodontitis, with the aim of reducing possible reservoirs of pathogenic bacteria (Quirynen *et al*. 2000).

A large variety of tongue cleaners are commercially available. A modern tongue-scraping instrument can consist of a long strip of plastic ribbon. This strip is held in both hands and is bent so that the edge can be pulled down over the dorsal surface of the tongue. A study that evaluated preference and perception of effectiveness with respect to nine commercially available tongue scrapers found this to vary the tongue-cleaning device designs. No single feature stood out as being specifically related to perception of effectiveness although sharpness and comfort were negatively correlated (Beekmans *et al*. 2017). Tongue brushing also appears to be an easy method of cleaning the tongue surface, provided that the gag reflex can be controlled. However, in a systematic review, it was concluded that scrapers or cleaners are more effective than toothbrushes for tongue cleaning (Outhouse *et al*. 2006) and with them the gag reflex is reduced (Van der Sleen *et al*. 2010). Patients should be informed that it is most important to clean the posterior portion of the tongue dorsum, but in reality, it is likely that many patients do not reach far enough to contact the posterior dorsum during tongue cleaning because extended reaching causes the gag reflex.

Tongue cleaning is a simple and fast procedure that helps to remove microorganisms and debris from the tongue (see Box 28-9). When tongue cleaning is practiced on a daily basis, the process becomes easier. Eventually, the patient can indeed feel "unclean" when tongue debris is not removed on a regular basis. In a study by Gross *et al*. (1975), the test group was instructed to brush the tongue as an adjunct to normal oral hygiene measures. The control group was not instructed to clean the tongue. A reduction of 40% in the presence of tongue coating was noted in the test group compared with the control group. In a group of systemically healthy young adults self-reported tongue cleaning behavior was associated with slightly lower bleeding on probing scores (Van Gils *et al*. 2019).

Some studies have shown that tongue brushing, in combination with other methods of oral hygiene, is an effective method for reducing the formation of dental plaque. In contrast, Badersten *et al*. (1975) found no difference in *de novo* plaque accumulation between a 4-day period of tongue brushing and a 4-day period of no oral hygiene procedures. The authors suggested that the majority of the important plaque-forming bacteria might not originate from the tongue. Another reason for not finding an effect of tongue brushing on plaque formation might be that brushing the posterior part of the dorsum of the tongue is difficult due to inaccessibility and discomfort.

Yaegaki and Sanada (1992) observed six times more tongue coating in patients with periodontal problems than in those who were periodontally healthy. Consequently, individuals with periodontal diseases will likely present with microbial flora more favorable to exacerbating the formation of volatile sulfur compounds than healthy individuals. Over the years, oral malodor has become a topic of interest to both the scientific community and to people who suffer from it. Regular mechanical tongue cleaning can play a role in controlling bacterial numbers and removing tongue coating. Individuals with coated tongues showed significantly higher malodor scores than individuals with non-coated tongues (Quirynen *et al*. 2004). Van der Sleen *et al*. (2010) demonstrated in their systematic review that mechanical approaches, such as tongue brushing or tongue scraping to clean the dorsum of the tongue, have the potential to reduce tongue coating and oral malodor. This systematic review detected only one study that

included patients with chronic oral malodor, with an unknown evaluation period and a high potential risk of bias. This study stood in contrast to the other included studies, which evaluated the effect of tongue cleaning in cases of morning bad breath. Consequently, no firm statement can be made as to whether mechanical tongue cleaning contributed to a reduction in oral halitosis (Slot *et al*. 2015). More research is needed to assess the effect of mechanical tongue cleaning, particularly in true halitosis populations.

Foam brushes, swabs, or tooth towelettes

Tooth towelettes are being marketed as a method of plaque removal when toothbrushing is not possible. Their use is not meant to replace a daily toothbrushing regimen.

Finger brushes, such as the I-Brush®, are mounted on the index finger of the brushing hand and use the agility and sensitivity of the finger to clean the teeth. Consequently, the pressure with which they are applied can be well controlled because the finger can actually feel the tooth and gingival surfaces and help position the brush for more effective scrubbing. During a 3-week clinical trial (Graveland *et al*. 2004), no adverse effects were found with the I-Brush®. The results showed that the finger brush removed less plaque than a regular manual toothbrush. In particular, proximal plaque reduction was poor in comparison with manual toothbrushing. Based on these results, it was concluded that there were no beneficial effects of the finger brush in comparison with regular manual toothbrushes.

Foam brushes resemble a disposable soft sponge on a stick, and they have been dispensed to hospital patients for intraoral cleansing and refreshing since the 1970s. They are used in particular for oral care in medically compromised and immunocompromised patients to reduce the risk of oral and systemic infection (Pearson & Hutton 2002). Lefkoff *et al*. (1995) studied the effectiveness of such a disposable foam brush on plaque. In this study, regular manual toothbrushes were found to be significantly more effective in retarding the accumulation of plaque from a plaque-free baseline on both facial and lingual surfaces. However, the foam brush did show some plaque-preventive capabilities by maintaining plaque formation below 2 mm at the cervical margin of the tooth. Nevertheless, according to most authors, foam brushes should not be considered a substitute for regular toothbrushes. In a study by Ransier *et al*. (1995), foam brushes were saturated with a chlorhexidine solution. The authors found foam brushes that had been soaked in chlorhexidine to be as effective as regular toothbrushes in controlling plaque and gingivitis levels. Therefore, if hospitalized patients cannot use a toothbrush, an alternative could be the use of chlorhexidine applied with a foam brush.

Dentifrices

The use of a toothbrush is usually combined with that of a dentifrice, with the intention of facilitating plaque removal and applying agents to the tooth surfaces for therapeutic or preventive reasons, to produce fresh breath, and to make the toothbrushing procedure more pleasant. The term dentifrice is derived from the Latin words *dens* (tooth) and *fricare* (to rub). A simple, contemporary definition of a dentifrice is a mixture used on the tooth in conjunction with a toothbrush. Dentifrices are marketed as powders, pastes, and gels. Dentifrice was used as early as 500 BC in both China and India; modern toothpastes were developed in the 1800s. In 1824, a dentist named Peabody was the first person to add soap to toothpaste. John Harris first added chalk to toothpaste in the 1850s. Colgate mass-produced the first toothpaste in a jar. In 1892, Dr. Washington Sheffield of Connecticut, USA manufactured toothpaste in a collapsible tube (Dr. Sheffield's Creme Dentifrice). Advancements in synthetic detergents made after World War II have allowed the replacement of the soap used in toothpaste with emulsifying agents, such as sodium lauryl sulfate. Later, fluoride was added.

Traditionally, it was believed that dentifrices should contain an abrasive. The addition of abrasives supposedly facilitated plaque and stain removal without producing gingival recession/tooth abrasion or altering the remaining components of the dentifrice. For many decades, abrasive systems, such as calcium carbonate, alumina, and dicalcium phosphate, have been used. Today, most dentifrices contain silica. Although more expensive, silica can be combined with fluoride salts, and it is very versatile. It has also been shown to increase the abrasiveness of dentifrices, resulting in even more plaque removal (Johannsen *et al*. 1993).

Conflicting reports have been published concerning the added value of using dentifrice for plaque removal. Studies by de la Rosa *et al*. (1979) and by Stean and Forward (1980) validated the use of dentifrice because they found that there was a reduction in plaque growth after brushing with a dentifrice as opposed to brushing with water. Similarly, Eid and Talic (1991) reported overall reductions in plaque of 67% for manual toothbrushing with a dentifrice and 59% for toothbrushing with water. In contrast, in a study by Gallagher *et al*. (2009), the use of 1.5 g of dentifrice showed no additional effect after 1 minute of brushing compared with brushing without dentifrice. Paraskevas *et al*. (2006) also studied whether dentifrice had a beneficial effect on plaque removal and whether an abrasive additive was a contributor. Their results showed that among 40 subjects using three different hydrated, silica-based dentifrices in a crossover study, the difference in abrasiveness (RDA 80 and 200) did not play a role in plaque removal. Moreover, significantly more plaque (3%) was removed when the

brushing procedure was performed without dentifrice. In another study by Paraskevas *et al*. (2007), the group that used dentifrice removed a significant 6% less plaque compared with the group that did not use dentifrice. Furthermore, in a study by Jayakumar *et al*. (2010), a 9% difference in plaque removal, in favor of the non-dentifrice group, was observed. The results of a study by Rosema *et al*. (2013) showed a difference in plaque removal of 2% in favor of the non-dentifrice group. Although this difference in plaque score reduction did not reach the level of significance, it is noteworthy that the use of dentifrice did not seem to increase the amount of "instant" plaque removal (i.e. the immediate effect of brushing, as opposed to prolonged effects beyond the brushing exercise). These results are also supported by a report from the ADA Division of Science (American Dental Association 2001), which accepts that "plaque removal is associated minimally with abrasives." The effectiveness of plaque removal during toothbrushing with dentifrice appears to be essentially a function of the access of brush filaments, rather than dentifrice abrasives (Gallagher *et al*. 2009). Also, a recent systematic review demonstrated that there is moderate certainty evidence that toothbrushing with a dentifrice does not provide an added effect for the mechanical removal of dental plaque (Valkenburg *et al*. 2016). In 1998, the concept of "dry brushing" was introduced: brushing without dentifrice and a toothbrush not wetted with water (O'Hehir & Suvan 1998). The purpose of this was to avoid the smooth perception of tooth surfaces being the results of reduced surface tension, as provided by surfactants of a dentifrice. A recent study indicated that dry brushing did not contribute significantly to toothbrush efficacy. The participants did not perceive that pre-wetting a toothbrush influenced filament stiffness and cleaning capability. Moreover, they found brushing without dentifrice to be uncomfortable (Van der Sluijs *et al*. 2018b).

Another factor that might be involved in the process of plaque removal is the detergent (or surfactant) contained in the dentifrice formulation. Detergents are surface-active compounds that are added to the formulation because of their foaming properties. This foaming effect could be beneficial in clearing loosened plaque from the teeth and also in providing the pleasant feeling of cleanness. Today, dentifrice formulations also contain ingredients that could help improve oral health. Fluoride is almost omnipresent in commercially available toothpastes. Problems with dentifrice formulation have involved finding compatible constituents to combine with the active ingredients in dentifrice formulas. Over the years, many dentifrice formulations have been tested and become well established because of their antiplaque and/or antigingivitis properties (Valkenburg *et al*. 2019). Nowadays toothpastes also carry cosmetic functions such as the whitening of teeth (Soeteman *et al*. 2018). For additional information, see Chapter 29.

Some substances in dentifrices can induce local or systemic side effects. Chlorhexidine in dentifrices can foster tooth staining. Pyrophosphates, flavorings, and detergents, especially sodium lauryl sulfate which is present in most commercially available dentifrices, have been implicated as causative factors in certain oral hypersensitive reactions, such as aphthous ulcers, stomatitis, cheilitis, burning sensations, and oral mucosal desquamation. In such cases, the dental professional should identify these conditions and advise the patient to discontinue use of the suspected dentifrice.

Side effects

A toothbrush is one of the most familiar devices of everyday use and few people would ever think about its associated risks. However, in view of the universal availability and presence, and the frequency with which toothbrushes are used, adverse events can be expected. A systematic review of case reports found that the oral use of a toothbrush can be related to serious adverse events such as ingestion, impaction, instant trauma, gingival traumatic injury, and seizures. Given the incidence of reporting, important recommendations are that a toothbrush should not be used to induce vomiting, nor should people walk or run with this device in their mouths, especially children (Oliveira *et al*. 2014).

Brushing force

In a study evaluating toothbrushing habits in unstructed adults, the mean brushing force was 2.3 ± 0.7 N, with a maximum of 4.1 N (Ganss *et al*. 2009a). Brushing force with electric toothbrushes has consistently been shown to be lower than that with a manual toothbrush (by approximately 1.0 N) (Van der Weijden *et al*. 1996c). McCracken *et al*. (2003) observed, for a range of pressures from 0.75 to 3.0 N, that the improvement in plaque removal when forces in excess of 1.5 N with an electric toothbrush were used was negligible. In a feedback study, a professional brusher was asked to brush with a pressure of 1.0 N, 1.5 N, 2.0 N, 2.5 N, and 3.0 N, during which time the efficacy with regard to brushing force was determined. An increase in efficacy was observed when the brushing force was raised from 1.0 N to 3.0 N (Van der Weijden *et al*. 1996c). Hasegawa *et al*. (1992) evaluated the effects of different toothbrushing forces on plaque reduction by brushing at 100-*g* force intervals on a scale from 100 to 500 *g*. The results of their study corroborated the findings of earlier studies that with increasing force, more plaque is removed. In addition, they observed that 300 *g* seemed to be the most effective brushing force when using a manual toothbrush for both children and adults. Forces exceeding 300 *g* caused pain and gingival bleeding in the test patients. As shown in a manual brushing study in which efficacy was plotted against brushing force, the relationship between force and efficacy does not appear to be linear (Van der Weijden *et al*. 1998). Using a manual toothbrush, a positive correlation was

identified between efficacy and force (up to 4.0 N). The greater the force used, the more effective was the plaque removal. However, efficacy decreased when forces of >4.0 N were used. Indeed, there appeared to be a negative correlation. The hypothesis is that this negative correlation was due to the distortion of the brushing filaments. Beyond 4.0 N, brushing was no longer performed with the tip of the filament but, due to bending, with its side, indicating that brushing force is not the sole factor that determines efficacy. Other factors, such as the action of the brush, the size of the brush head, brushing time, and manual dexterity, could be of greater importance.

Excessive brushing force has been mentioned as a factor that is partly responsible for toothbrush trauma (gingival abrasion). For patients who use excessive force, manual and electric toothbrush manufacturers have introduced toothbrush designs that can limit the amount of force used and thus reduce the chance of damage to soft and hard tissues. There appears to be no linear correlation between brushing force and gingival abrasion. An *in vitro* experiment revealed that under severe erosive conditions, neither total mineral loss nor the spatial loss of mineralized dentin (measured using profilometry) significantly increased after brushing, regardless of the force applied. The demineralized organic dentin matrix was strikingly resistant to mechanical impact, although it was compressed with greater brushing forces (Ganss *et al*. 2009b).

Mierau and Spindler (1989) performed a quantitative assessment of patterns of toothbrushing habits in 28 subjects over nine sessions. The least variations among individuals were observed with regard to brushing force. Brushing force ranged from 1.0 to 7.4 N between individuals. The authors did not observe any (visual) lesions from brushing in those individuals using a brushing force of <2 N. If the brushing force was >2 N, co-factors such as brushing time, brushing method, and frequency of brushing appeared to be associated with acute brushing lesions. Burgett and Ash (1974) argued that the potentially detrimental effect of brushing is related to the force applied at a particular point, that is the pressure. It should be recognized that the head of a manual brush is larger than the head of an electric brush. Because the forces are given as a total of the force over the entire brush, it could be that the unit pressure is less for manual brushes than for electric brushes. Van der Weijden *et al*. (1996c) observed no difference in pressure between soft manual (11.32 g/mm^2) and electric toothbrushes (11.29 g/mm^2), demonstrating that the pressures for the electric and the manual brushes were similar.

Toothbrush abrasion

Because various mechanical products are used in personal control of supragingival plaque, the possibility exists that some deleterious effects can occur as a consequence of these oral hygiene practices (Echeverría 1998). The simple act of removing deposits from teeth requires that the toothbrush–dentifrice combination possess some level of abrasiveness. The filaments must have a sufficient degree of stiffness to create abrasion to dislodge plaque deposits. This stiffness must be balanced against potentially detrimental effects on dental hard and soft tissues. The wear on a tooth consists of a combination of attrition (tooth-to-tooth contact wear), erosion (acid-mediated surface softening), and abrasion (wear because of toothbrushing with toothpastes). Toothbrush abrasion is modified by toothbrush filament stiffness (Wiegand *et al*. 2008).

It has long been known that toothbrushing can have some unwanted effects on the gingiva and hard tooth tissues (Kitchin 1941). Trauma to hard tissues leads to cervical abrasion of the tooth surfaces (Fig. 28-9). These lesions have been associated with toothbrush stiffness, the method of brushing, and brushing frequency. Cervical tooth abrasions have a multifactorial etiology, but in most cases, they are the consequence of toothbrushing with excessive brush pressure and an excessive number of toothbrushing episodes/time. Both situations are likely linked to personality traits (*compulsive brushers*). Tooth wear has also been associated with toothbrush characteristics, especially with the finishing and hardness of the filaments (Fishman 1997). It has been stated that hard tissue damage is mainly caused by the abrasives in dentifrice (Axelsson *et al*. 1997; Meyers *et al*. 2000). The capacity of a toothbrush to hold and move polish/abrasive over the tooth surface particularly affects the amount of hard-tissue abrasion. The influence of the type of toothbrush was negligible when water was used as a substrate, but when toothpaste was added the abrasion values diverged by more than ten-fold depending on the toothbrush. A softer toothbrush might have caused similar or even more abrasions than a harder brush (Tellefsen *et al*. 2011).

In many instances, *tooth abrasion* is found in combination with *gingival recession*. Whereas gingival recession is associated with different etiologic/risk factors, for example periodontal inflammation, smoking, gingival phenotype, or repeated periodontal instrumentation, inadequate use of the toothbrush is likely the most significant cause (Björn *et al*. 1981). Clinical experience supports the idea that, with improper use, toothbrushing can cause superficial damage to the gingival tissues. Patients with good oral hygiene have been found to have more gingival recession and more dental abrasions than patients with poor oral hygiene. Unfortunately, there have been few studies in the dental literature concerning gingival lesions resulting from toothbrushing. Thus, the extent to which oral hygiene procedures can traumatize the gingival tissues is not clear. An experimental study investigated the healing time of a freshly induced abrasion lesion. An area away from the gingival margin at the palate was brushed with a manual toothbrush. Lesions caused by 30 seconds of brushing needed at least 24 hours to heal in 40% of cases (De Nutte *et al*. 2018).

Gingival abrasions as a result of brushing are often reversible, localized, superficial lesions. It is unlikely that gingival abrasion is induced by a single factor. One

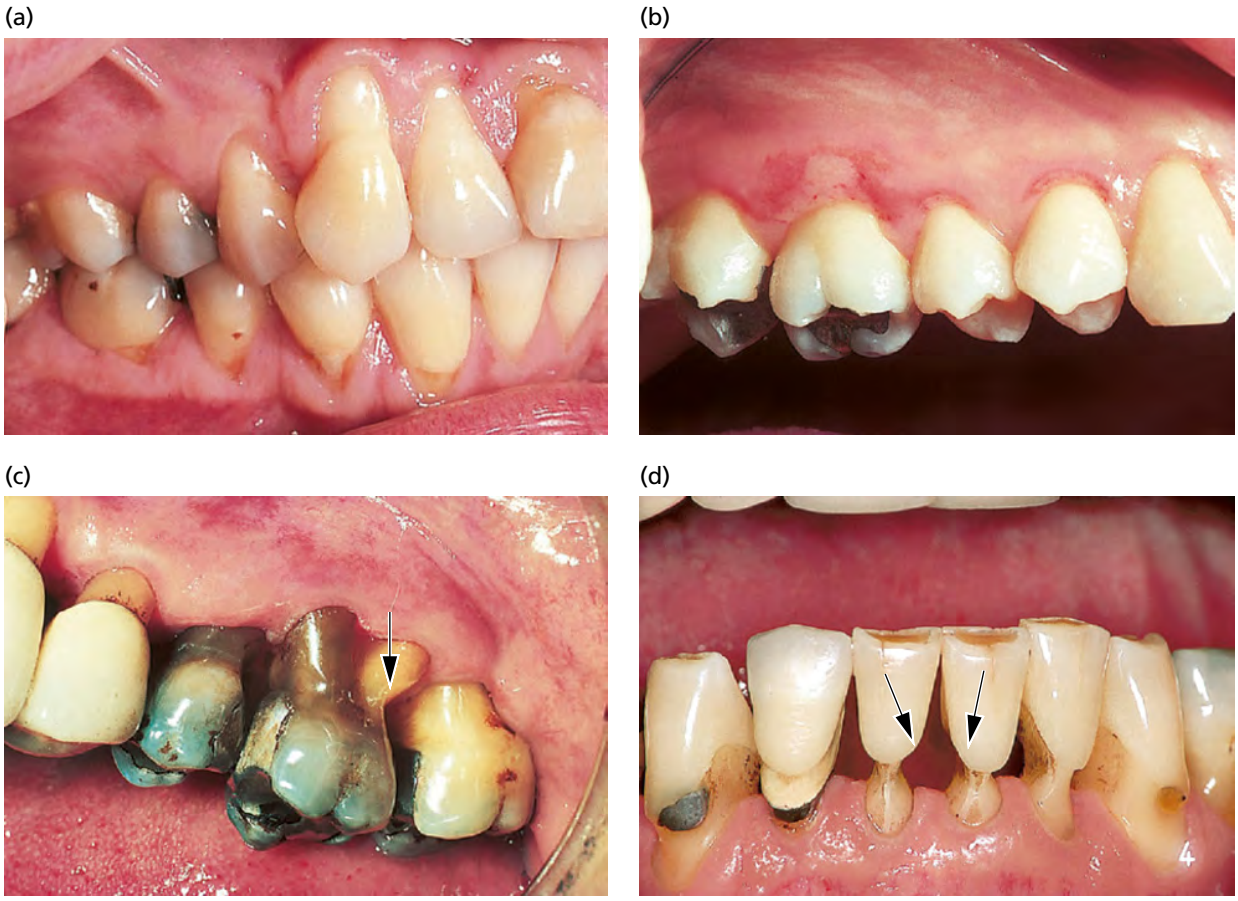


Fig. 28-9 (a) Soft tissue damage as a result of extensive toothbrushing. Note the gingival recession on the buccal gingival surface of tooth 13. (b) Note the multiple ulcerations of the buccal gingival margin in the right maxilla. (c, d) Hard tissue damage (arrows) has resulted after extensive use of interdental brushes.

factor, which has already been mentioned as related to gingival abrasion, is brushing force. In the literature, other factors have been suggested, such as brushing method (e.g. the Bass method), abusive toothbrush use, toothbrushing duration, manual or powered toothbrushing, toothbrush grip, brush head shape, stiffness of the filaments, end-rounding of toothbrush filaments, and toothbrushing frequency (Van der Weijden & Danser 2000, Hennequin-Hoenderdos *et al*. 2018).

Toothbrushes with hard bristles remove plaque better but can also cause more soft-tissue trauma compared with brushes with softer bristles (Ranzan *et al*. 2019). Zimmer *et al*. (2011) investigated the effectiveness and potential harmfulness of manual toothbrushes of the same type but with different bristle stiffnesses. Based on their observations, they suggested that in general a toothbrush with medium stiffness can be advised. For subjects with poor oral hygiene, a toothbrush with hard bristles should be considered. If a patient already shows soft tissue damage, a soft toothbrush should be recommended (Versteeg *et al*. 2008a). Sharp-edged and unacceptably rounded filament tips represent a greater threat to dental tissues. Breitenmoser *et al*. (1979) evaluated the effects of filament end forms on the gingival surface. It was found that manual toothbrushes with cut filament ends resulted in significantly greater gingival lesions than rounded ends. Further research has shown in several studies that filaments with sharp edges can cause soft tissue injury. The depth of epithelial lesions caused by toothbrushing was influenced by the quality of filament end-rounding (Plagmann *et al*. 1978). End-rounded filaments showed significantly less abrasion to soft tissues compared with non-end-rounded filament tips (Alexander *et al*. 1977; Hennequin-Hoenderdos *et al*. 2017). Oral soft tissue injuries are similar for both tapered and end-rounded bristles (Ranzan *et al*. 2019).

The pattern of toothbrushing is that most right-handed people begin on the buccal surfaces of the anterior teeth on the left side. Accordingly, the most severe gingival recession and abrasion defects are localized to the buccal surfaces on the left side (MacGregor & Rugg-Gunn 1979).

Interestingly, there has been little debate regarding the role of dentifrice in the abrasion of soft tissues. This fact is somewhat surprising when abrasion of dental hard tissues is almost entirely a function of dentifrice. Detergents in dentifrice, agitated over a mucosal surface, can enhance the removal of the protective salivary glycoprotein layer and exert cytotoxic action on the overlying epithelial cells (Addy & Hunter 2003). No statistically significant differences in the incidence of gingival abrasions were identified between brushing with dentifrice or without dentifrice (Versteeg *et al*. 2005; Rosema *et al*. 2013). This finding was in agreement with those of Alexander *et al*. (1977), who

used hamster cheek pouch tissue that was brushed mechanically for various intervals. The results showed that the dentifrice/polishing agent applied to the tissue with a brush did not increase the abrasive effects of the brush (using protein removed during brushing as an index of tissue abrasion). Meyers *et al*. (2000) investigated the effects of three commercially available dentifrices on tooth and gingival surfaces by means of scanning electron microscopy quantification. The results indicated that none of the dentifrices tested was harmful to teeth or soft tissues.

Toothbrush contamination

Toothbrushes may be the cause of disease transmission and increase the risk of infection since they can serve as a reservoir for microorganisms in healthy, diseased, and medically ill adults (Agrawal *et al*. 2019). Commonly, after oral use, toothbrushes are rinsed with plain water and stored in the bathroom. There is a high chance of cross-infection by sharing or keeping them in close proximity. Review of the literature showed that toothbrushes of healthy and oral diseased adults become contaminated with pathogenic bacteria from the dental plaque, design, environment, or a combination of factors (Frazelle & Munro 2012). However, potential impact of this contamination on disease transmission was not researched (Van der Weijden & Slot 2015). Decontaminating a toothbrush by exposing it to (microwave or ultra-violet) radiation and disinfecting agents reduces bacterial load (Agrawal *et al*. 2019).

Importance of instruction and motivation in mechanical plaque control

A fundamental principle for all preventive action is that the effect is greatest when the risk of the development of disease is greatest. Needs-related instruction in oral hygiene should therefore aim to intensify mechanical plaque removal on those individual teeth and surfaces that are at risk. A prerequisite for establishing needs-related tooth-cleaning habits is a well-motivated, well-informed, and well-instructed patient (Axelsson 2004). Mechanical plaque control demands active participation of the individual subject; therefore, the establishment of proper home oral care habits is a process that greatly involves and depends on behavioral changes. As toothbrushing is a daily habit, it is not easily altered, even after professional instruction. When implementing behavioral changes, dental professionals should try to ensure that the patient recognizes his/her oral health status and the role of his/her personal oral hygiene procedures in the prevention of caries and periodontal diseases. The patient should be informed about the casual relationship that led to the disease process and should be encouraged to take responsibility for his/her own oral health. The dental team has numerous opportunities to demonstrate to the patient the soft tissue alterations elicited by inflammation and the responsible etiologic factors. Most commonly, as with sports coaching, a one-to-one professional–patient approach should be employed.

Many patients spend too little time brushing, or they brush haphazardly. The importance of thorough plaque removal should be stressed. Toothbrushing instruction for a patient involves teaching what, when, where, and how. A recommended toothbrushing regimen should take into account the characteristics of the toothbrush and dentifrice, and the individual's behavior with regards to brushing frequency, duration, pattern, force, and method. Toothbrushing habits are locally acquired at home and can be supplemented periodically with more formal instruction from the dental professional. Training of toothbrushing skills requires many repetitions of the same movements to incorporate them into an individuals' habitual motor program (Hayasaki *et al*. 2014). In addition, instruction should also involve a description of specific toothbrushing methods, the grasp of the brush, the sequence and amount of brushing, the areas of limited access, and supplementary brushing for occlusal surfaces and the tongue. The possible detrimental effects from improper toothbrushing and variations for special conditions can be described (Wilkins 1999). The design of toothbrushes or a specific toothbrushing method is of secondary importance to the skills of the individual in using the brush (Frandsen 1986). The simplest, least time-consuming procedures that will effectively remove bacterial plaque and maintain oral health should be recommended. If a patient prefers a specific oral hygiene strategy, the clinician can evaluate this and modify the technique to maximize effectiveness rather than changing it. Although it is necessary to give all patients honest feedback on their plaque removal efforts, it is also important to reward positive performance and not entertain unrealistic expectations, so that the patient will not dread each maintenance visit.

Oral hygiene instruction should also include components such as self-assessment, self-examination, self-monitoring, and self-instruction. With this purpose, several devices and chemical agents have been used to make dental plaque more evident to the patient. The interested patient can be informed and motivated, for example, through the use of disclosing agents to visualize plaque at the gingival margin or in the interdental spaces (Oliveira *et al*. 2021). Disclosing agents are chemical compounds, such as erythrosine, fuchsine or fluorescein-containing dye, that stain dental plaque and thus make it fully evident to the patient using either regular or ultraviolet light. Erythrosine has been used for many years as a means of motivating patients and evaluating the effectiveness of oral hygiene, and it has received Food and Drug Administration (FDA) approval (Arnim 1963) (Fig. 28-10). When applied immediately before toothbrushing, the patient can identify the amount of plaque formed since the last toothbrushing episode, thus receiving immediate feedback about his/her cleaning performance. This procedure is useful during the early phase of plaque control. Later, the disclosing agent should be applied after toothbrushing, which allows the patient to identify those areas

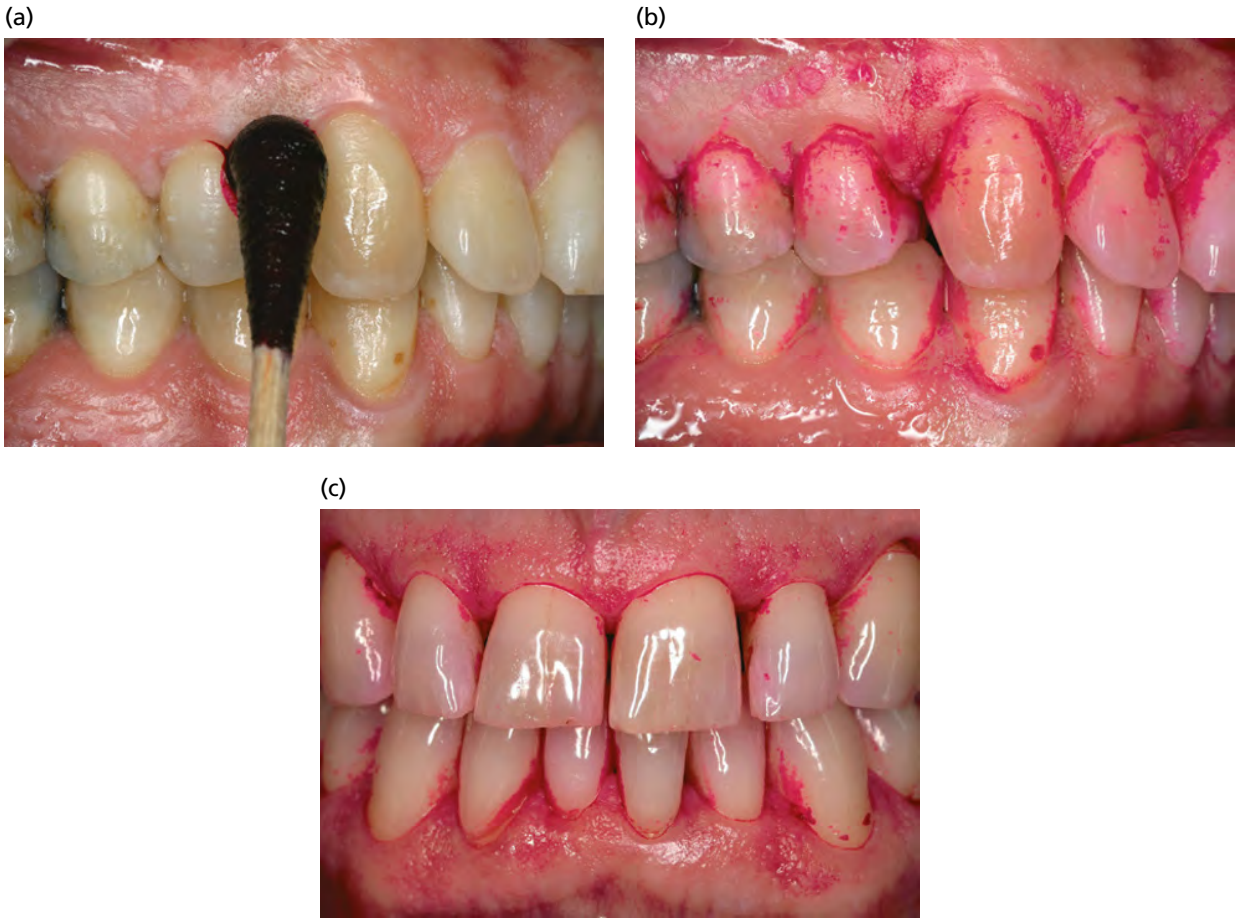


Fig. 28-10 (a) Disclosing solution is often used to identify plaque. (b) Note the remaining plaque on the buccal tooth surfaces after staining. (c) After self-performed tooth cleaning, remaining plaque can be identified by the patient following rinsing with a disclosing solution.

needing additional cleaning efforts. Disclosing solution is available in liquid and tablet forms. The liquid form might offer some advantages in that the operator can ensure that all surfaces are adequately covered. Red disclosing solution remains in the mouth for some time and can temporarily stain the lips and gingiva. This may create an esthetic problem for some patients but can be eliminated by protecting the lips with petroleum jelly. Two-tone agents (containing methylene blue and erythrosine) are also available that distinguish an old plaque accumulation from a more recent one.

Disclosing plaque in the patient's mouth is usually not sufficient to establish good oral hygiene habits. Other factors might influence the individual to modify or determine his/her behavior. These factors could be more or less beyond the control of the dental professional (such as social and personal factors, environmental settings, and past dental experiences), or they may lie within the control of the professional (such as the conditions of treatment and the instruction and education of the patient). All of these factors should be considered in the design of an individualized oral hygiene program.

A variety of methods can be used to deliver advice and instructions. The effects of various oral hygiene instruction programs, administered individually or in groups, have been evaluated in a number of clinical studies. These studies have evaluated whether instruction given during one visit only is similar to step-by-step instruction provided over several visits, and whether the use of pamphlets or videotapes is superior to self-instruction manuals and to personal instruction given by a dental professional. In a study by Renton-Harper *et al*. (1999), an instructional video for an oscillating–rotating electric toothbrush was evaluated. The subjects who followed the instructional video benefited significantly and considerably in terms of plaque removal compared with subjects who received only written instructions. Different types and amounts of feedback given to the patients using disclosed plaque scores and phase-contrast demonstrations have also been investigated. These studies have usually reported similar improvements in plaque and gingivitis scores, irrespective of the mode of instruction. However, these results should be interpreted with caution because the subjects participating in these studies were examined at regular intervals; therefore, it is difficult to separate the effects of repeated examinations from the effects of the instructions (Renvert & Glavind 1998).

If oral hygiene motivation, information, and instruction are combined with professional tooth cleaning, the effects in terms of reduction of plaque levels and levels of gingival inflammation can persist even after 6 months (Van der Weijden & Hioe 2005). Rylander and

Lindhe (1997) recommended that oral hygiene instruction be provided over a series of visits, allowing for the possibility of giving the patient immediate feedback and reinforcing the patient in his/her home oral care activities. The protocol below is based on the one used in several clinical trials by Lindhe and Nyman (1975), Rosling *et al*. (1976), and Lindhe *et al*. (1982) in which the role of plaque control in preventing and arresting periodontal diseases was clearly demonstrated.

First session

1. Apply a plaque-disclosing solution to the teeth and, with the aid of a hand mirror, demonstrate all sites with plaque to the patient (see Fig. 28-10b). The plaque score can be recorded using a plaque control record (Fig. 28-11).
2. Ask the patient to clean his/her teeth using his/her traditional technique. With the aid of a hand mirror, demonstrate the results of the toothbrushing to the patient, again identifying all sites with plaque (see Fig. 28-10c).
3. Without changing the technique, ask the patient to clean the surfaces with plaque.

Depending on the plaque remaining after this second toothbrushing, the dental professional should either improve the technique or introduce an alternative system of toothbrushing. So as not to overload the patient with too much information during the first session, the use of adjunctive devices for interproximal cleaning can be introduced or improved in the second session.

Second session

1. A few days after the first session, the disclosing solution is again applied. The results, in terms of plaque deposits, are identified in the mouth, recorded in the plaque control record, and discussed with the patient.
2. The patient is then invited to clean his/her teeth, according to the directions previously provided during the first session, until all staining is removed. In many cases, toothbrushing instructions will need to be reinforced. Positive recognition should be given to the patient at the same time.

If necessary, the use of interproximal cleaning aids can now be introduced or improved.

Third and subsequent sessions

1. One or 2 weeks later, the procedure used in the second session is repeated. However, the efficacy of self-performed plaque control should be evaluated and presented to the patient at each appointment. This repeated instruction, supervision, and evaluation aims to reinforce the necessary behavioral changes.

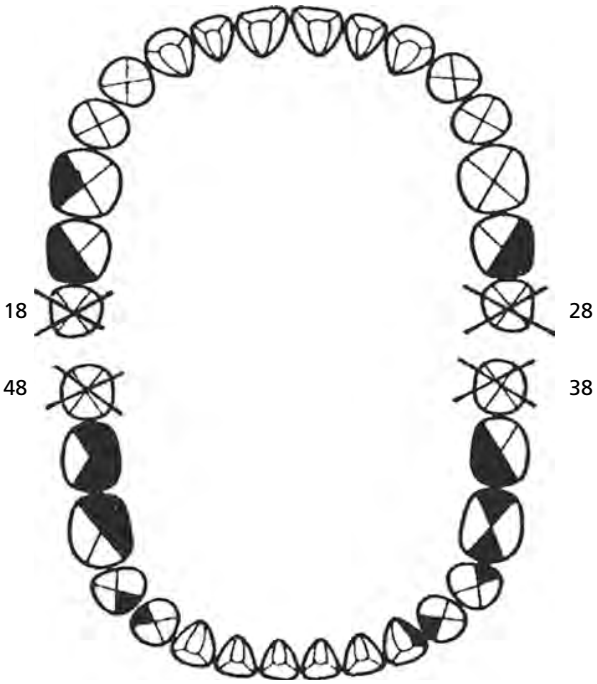


Fig. 28-11 Chart showing the teeth and tooth surfaces in the maxilla and mandible. The distribution of tooth surfaces with dental plaque (shadowed areas) is identified. In this case, the plaque score is 17%.

The long-term results of oral hygiene instruction are dependent on behavioral changes. Patients might fail to comply with given instructions for many reasons, ranging from unwillingness to perform oral self-care, poor understanding, lack of motivation, poor dental health beliefs, and unfavorable dental health values due to stressful life events or poor socioeconomic status. Although the use of behavior-modification techniques can offer an advantage over traditional instruction techniques, there is limited research in this area to clarify the relationship between health beliefs and compliance.

Conclusion

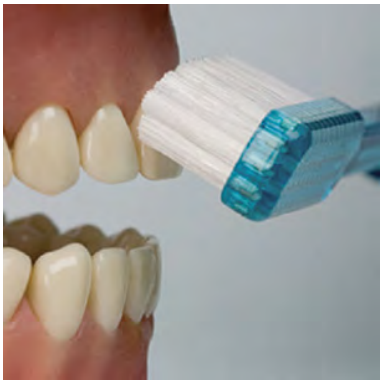
- Ultimately, the goal of a patient's self-care program is to prevent, arrest, and control periodontal disease and caries. The patient's ability to remove plaque from all areas, including interproximal areas, is an essential part of this.
- Oral hygiene instruction should be tailored to each individual patient on the basis of his/her personal needs and other factors.
- The patient should be involved in the instructional process.
- An individualized maintenance program should follow basic oral hygiene instruction.

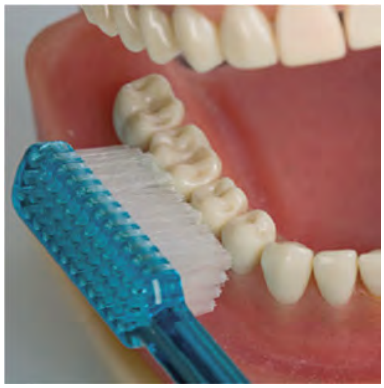
Acknowledgments

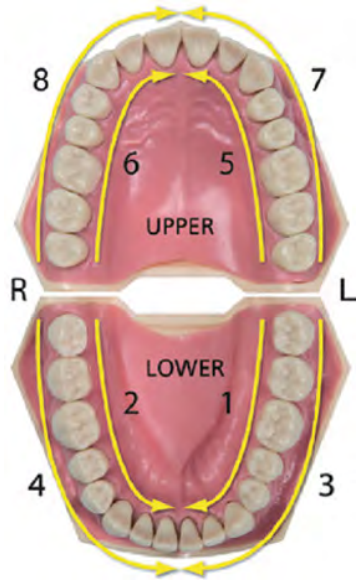
All of the figures illustrating the procedures in Boxes 28-1 to 28-9 are used with permission from the Paro Praktijk Utrecht.

Box 28-1 Instructions for manual toothbrushing.

It is of the utmost importance, in addition to using the correct toothpaste and also brushing for at least 2 minutes, to brush the teeth in a set sequence. This technique prevents certain areas from being missed. Areas untouched by the brush will allow plaque to continue to grow. Try to choose a brush with medium or soft bristles and a small head.







Instructions

- Hold the brush firmly and place the bristles at an angle against the edge of your gums (use a 45° angle). Take care to ensure that the bristles are in contact with a small part of the gum margin.
- Place the brush against the molar or tooth at the back of the mouth and make short back-and-forth scrubbing movements. Brush from the back to the front of the mouth and try to overlap the strokes. Do not brush more than two teeth simultaneously. Always start at the back and work slowly forward.
- Always hold the brush head horizontally when cleaning the outside surfaces of the teeth. It is easier to hold the head vertically when brushing the inside surfaces of the top and bottom teeth.
- Avoid too much pressure and fast movements, and be aware of feeling contact with the gum margin. Also, avoid brushing too vigorously, thereby preventing damage to the gums.

When cleaning the teeth, keep using the same sequence of brushing. For example, brush the inside of the lower left jaw (15 seconds) and then the inside right (15 seconds). Then, brush the left on the outside (15 seconds), followed by the right on the outside (15 seconds). Repeat the same sequence in the upper jaw. Finally, brush the chewing surfaces with small scrubbing movements. Replace the brush when the bristles start to bend or splay.

Box 28-2 Instructions for electric (power) toothbrushes.

The importance of using a set sequence of brushing movements is applicable when using an electric toothbrush. The question of whether or not an electric brush is better than a manual one has been asked many times. Both brushes allow a high level of oral hygiene to be achieved. However, research has shown that electric toothbrushes are more efficient, and many people report that they are easier to use.

Instructions

- Place the brush firmly on the hand piece. Grip the brush in the palm so that the bristles of the head are somewhat angled toward the gums (at an angle of approximately 70°). Try to allow the longer bristles to penetrate between the teeth and take care that the bristles contact your gums.
- Switch on the brush, place the head on the last tooth in the mouth (check the angle), and move the head gradually (over approximately 2 seconds) from the back to the front of this tooth.
- Try to follow the contours of both the teeth and the gums. Place the brush head on the next tooth and repeat this process.
- Allow the electric toothbrush to do the work. It is not necessary to press hard or make brushing movements.
- Use a timer! Many brushes will provide some form of signal after 30 seconds (the apparatus stops for a moment). This is the point at which to move on to a new part of the mouth.

Remember to clean the brush and its head thoroughly when finished.

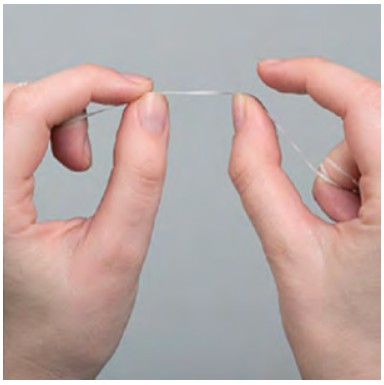
Box 28-3 Instructions for use of dental floss.

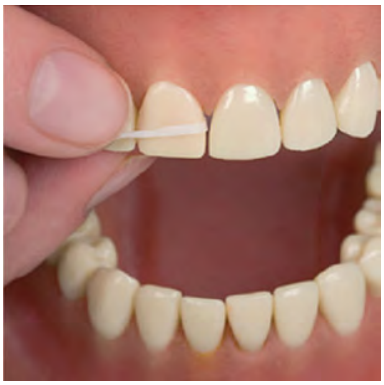
The use of dental floss has become part of oral care, in addition to correct, more frequent, and longer tooth brushing. Floss can be purchased in a variety of thicknesses and types and with or without a layer of wax. If there is sufficient space between the front and back teeth, it is advisable to use the somewhat thicker tape rather than the thinner floss.

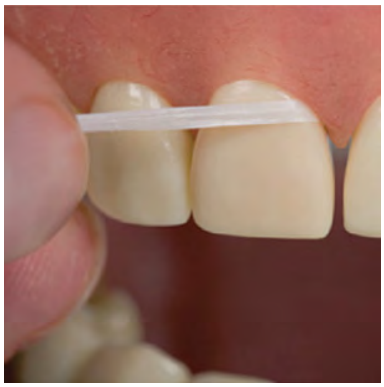
Instructions

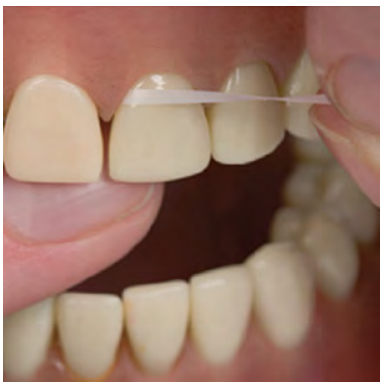
- Take approximately 40 cm of floss and wind the ends loosely around the middle fingers. Allow for 10 cm between the middle fingers. Then, hold the floss taut between the thumb and first finger so that roughly 3 cm remains between the thumbs. Alternatively, a loop or circle of dental floss can be created.
- Using a sawing movement, allow the tightly stretched piece of floss to pass between the contact of the front and back teeth. This action might be difficult where the teeth are so close together that the space between them is limited. Avoid allowing the floss to slip so quickly between the teeth because through this "snapping" the gums may be damaged.
- Stretch the floss in a "U" shape around one of the teeth, press firmly against the side of the tooth surface and carefully allow the floss to pass just under the gum, once again with a sawing movement.
- Draw the floss up to the contact point with a sawing movement, and then repeat the process on the other tooth bordering the space filled with gum tissue.
- Remove the floss from between the teeth, once again with a sawing movement, and repeat this process for all of the other spaces in the mouth.
- Use a clean piece of floss for each separate space by unwinding part of it from around one middle finger while winding it around the other middle finger.

Do not worry if at first your gums bleed slightly. This bleeding will stop after using the floss a number of times. Do not give up!







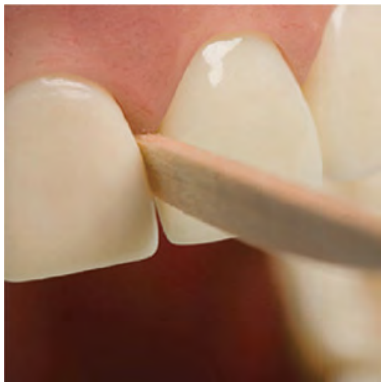


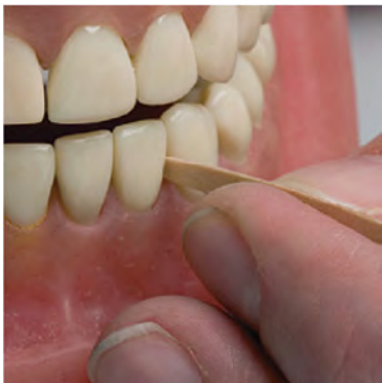
Box 28-4 Instructions for use of woodsticks.

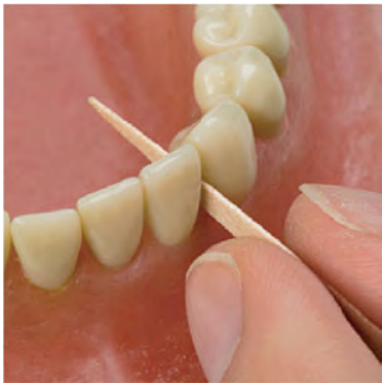
Most adults have sufficient space available between the incisors and molars to allow woodsticks to be used. These sticks come in different thicknesses, they are made from wood, and they have a triangular cross-section, mimicking the shape of the space between the teeth. Woodsticks can only be used once and are ideal for use when you have a few spare moments – for example, when sitting in traffic!

Instructions

- Hold the woodstick firmly between the thumb and first finger, roughly halfway along its length. When possible, place the other fingers for support on the chin. Moisten the tip of the woodstick by sucking on the point of it, thus making it softer and more flexible.
- Place the flat side of the woodstick (i.e. not the sharp side) against the gum. In the upper jaw, the flat surface will face upward, and in the lower jaw, it will face downward.
- Push the woodstick firmly from the outer side of the space into the space until the stick just becomes wedged. Then, pull it back slightly, and push it back once again, using a light, sawing motion at right angles to the outer surfaces of the teeth. Light pressure can also be applied simultaneously to the gums. Repeat this action a few times, angling the woodstick to contact the surfaces of the teeth enclosing the space.
- When using a woodstick between the premolars and molars, close the mouth slightly to reduce tension in the cheeks, thus making the movements easier.





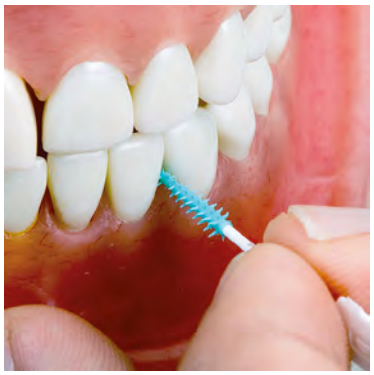


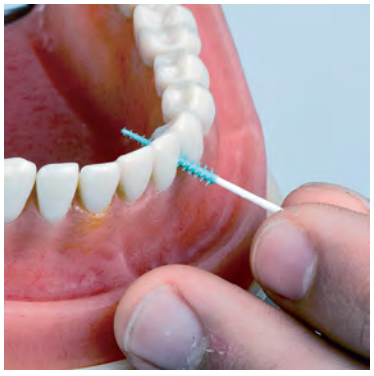
With this method, all of the spaces between the teeth throughout the mouth can be cleaned. Should the woodstick prick the surface of the gums with the point, angle it a little differently – in the upper jaw, the point will face downward, and in the lower jaw, it will face upward. During use, the soft wood can become splayed. As soon as the first signs of splaying are evident, the woodstick should be discarded.

Do not be concerned if your gums bleed a little at first – this bleeding will disappear after using the woodsticks repeatedly for a period of time. Do not give up!

Box 28-5 Instructions for use of rubber/elastomeric interdental cleaning sticks.

Most adults have sufficient interdental space to allow rubber/elastomeric interdental cleaning sticks to be used. The sticks have a firm but flexible conical plastic core that is either covered with a soft rubber/elastomeric coating and bristles or a flexible silicone coating and lamellae. Although they resemble an interdental brush the working effect is that of a toothpick. They come in different sizes and for the best result, it is important to choose the right size. They are intended for single-use and are ideal to bring along and use on-the-go.





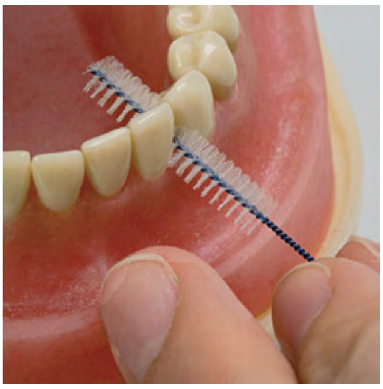
Instructions

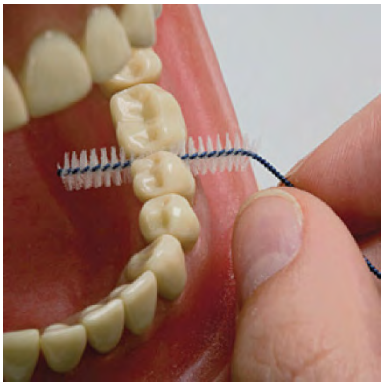
- Detach an interdental cleaning stick from the strip.
- Hold the stick between the thumb and first finger, at the grip. When possible, place the other fingers for support on the chin.
- Place the point of the stick in the interdental space.
- Push the stick into the space as far as possible and then pull it back slightly. Repeat this a few times moving it back and forth using a light, sawing motion.
- Use a straight insertion angle into the interdental space.
- Simultaneously, light pressure can also be applied against the gums.
- Do not force the stick into tight spaces between teeth
- When cleaning between the premolars and molars, close the mouth slightly to reduce tension in the cheeks, thus making the movements easier.
- Try to clean all interdental spaces with one stick but if it bends use a new one.
- After use, deposit the used interdental cleaner stick in the trash basket.

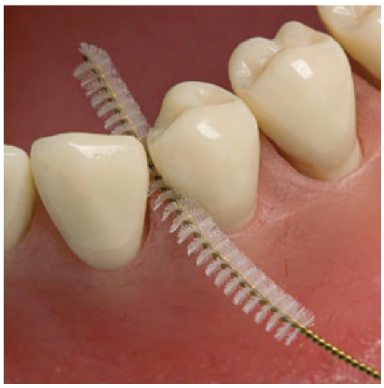
Do not be alarmed if your gums bleed a little at first – this bleeding does not mean that you have injured yourself but is a sign of inflammation of the gums. It will therefore disappear after regular use. So, do not give up!

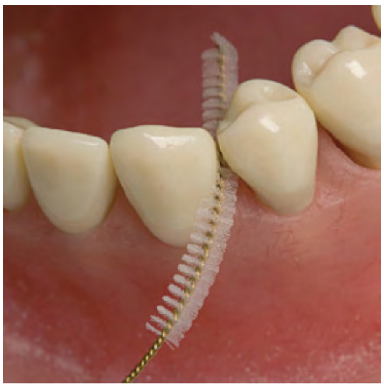
Box 28-6 Instructions for use of interproximal brushes.

Interdental brushes can be purchased in a variety of sizes, ranging from small (1.9 mm) to very large (14 mm). It is important to choose the correct diameter of the bristle part of the brush. The size of the space between the teeth determines the size of the diameter of the bristles on the brush. Dental professionals can precisely identify which sizes you need and also demonstrate their proper use. A brush that is too small will not completely clean the interdental spaces, and a brush that is too large can injure the gums. The wire of an interdental brush must be thin and the bristles as fine and as long as possible. With such dimensions, the interdental brush will fill the entire space between the teeth quite softly and gently. Tooth spacing varies, so it is often necessary to use a different size of brush within one mouth for optimal cleansing. To remove dental plaque effectively, there should be a slight degree of resistance when the brush is moved back and forth between the teeth.









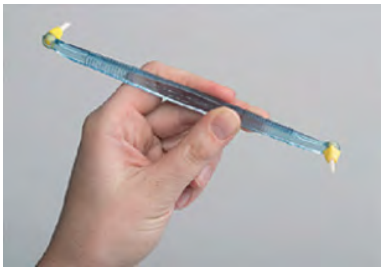
Instructions

- Always use the interdental brush *without* toothpaste.
- Hold the interdental brush just behind the bristles between the thumb and forefinger. Support can be achieved when necessary by placing your other fingers on your chin. From the outer side of the space, push the interdental brush carefully between the teeth, taking care that the brush remains at a right angle to the teeth.
- You may bend the interdental brush slightly to improve accessibility to the posterior interdental spaces.
- Avoid scraping the center (metal spiral part) of the brush against the teeth.
- Slide the brush in and out of the space using the full length of the bristle part of the brush. This action will remove the dental plaque.
- The area of contact between the brush and the teeth can be somewhat increased by using differing angles of insertion.
- Do not push interdental brushes between the teeth with force. Slight pressure of the brush against the gums should be used, as it will allow the bristles to penetrate slightly underneath the gum margin.
- By slightly closing the mouth, it will be easier to manipulate the brush as the tension in the cheeks is lessened. It might also be helpful to bend the brush slightly to ease insertion.
- Cleanse all areas between the teeth where an interdental brush will fit. Rinse interdental brushes thoroughly after use and allow them to dry out. It is often a good idea to combine the use of interdental brushes and woodsticks.

Do not be alarmed if the gums bleed initially. This bleeding does not mean that you have an injury but inflammation, which is caused by concealed, old plaque. This reaction is fairly normal during the first week. Using the interdental brush will soon cure this inflammation, and the bleeding will stop. As the inflammation subsides, the interdental spaces will become slightly larger, and you will most likely need a larger interdental brush. Ask your dental professional.

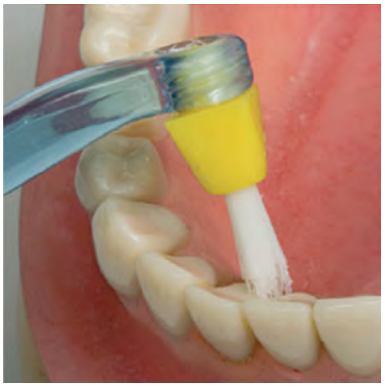
Box 28-7 Instructions for use of single-tufted/end-tufted brushes.

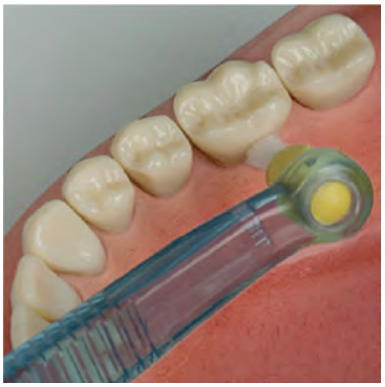
The single-tufted toothbrush is a small brush with a small, single tuft of short bristles attached to the end. The end-tufted brush has a number of small tufts attached in a similar manner. These brushes are an option for cleansing areas of the dentition that cannot be reached with other oral hygiene aids, for example, a lone-standing tooth, the back surface of the last molar or a tooth in the arches, wires and locks of orthodontic braces, grooves or the entrances to areas where the roots have split apart.

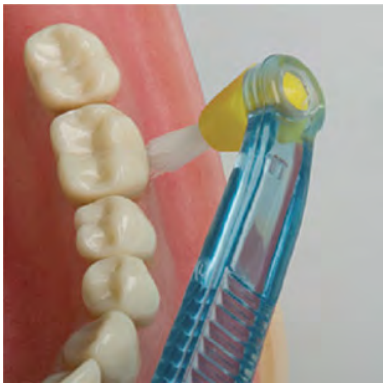


Instructions

- Hold the single-tufted brush as you would hold a pen. This method prevents too much force being applied to the gums.
- Place the single-tufted brush at an angle directed toward the gums (approximately 45°) – this angle allows the bristles to reach just under the gum margin.
- Use small, rotational pencil movements.
- The bristles of the brush will then rotate under and along the gum margin. The brush should then be slowly moved along the tooth surface to cover all areas.







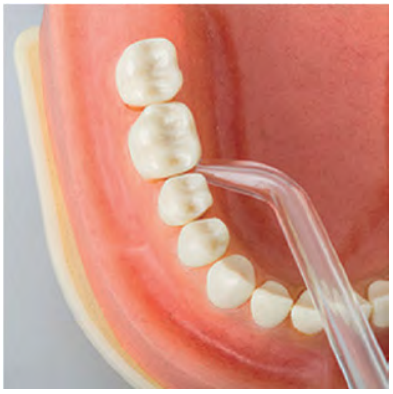
Box 28-8 Instructions for use of oral irrigators.

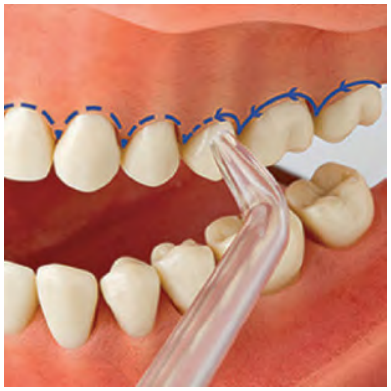
There are various brands of oral irrigators. Before starting to use a product, it is advisable to read the manufacturer's instructions carefully and to be sure you understand how an oral irrigator works.

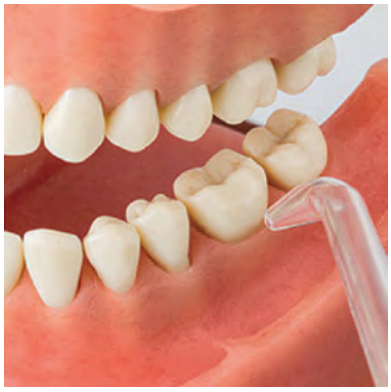
Instructions

- Fill the water reservoir with lukewarm water and plug the power cord into the wall outlet. You can use a cup to fill the reservoir. If the unit has removable tips, press the appropriate tip firmly into the irrigator handle. The tip should snap into place because it works under pressure and may shoot away otherwise.
- Test the oral irrigator before use.
- Breathe calmly through your nose. Lean over the sink, and close your lips enough to prevent splashing, while still allowing water to fall from the mouth into the sink.
- Aim the tip just above and toward the gum line at a 90° angle, and press the switch that allows the water to flow.
- *Do not* attempt to watch yourself in the mirror. You will make a mess!
- Starting with the back teeth (where your molars are located), follow the gum line. Take your time to get in between teeth. Continue to work slowly forward until all areas around and between teeth have been cleaned.
- Use the same sequence each time you use the irrigator so that you do not miss any teeth.
- At difficult to reach areas you can adjust the angle of the nozzle, for example while cleaning the brackets of an orthodontic appliance or at root furrows.
- Spit out excess water as needed.
- Empty any water remaining in the reservoir after use. Dry thoroughly to avoid bacterial growth. Make sure to unplug the unit before cleaning it.

Irrigating is a technique that relies on your sense of touch. At first, it might take a little longer until you develop a routine and become more comfortable with the oral irrigator. Depending on the power level, you might need to refill the water reservoir. Antiseptics can be added if that has been advised by your dental care professional. If so, a mouth rinse or another antiseptic is added to the water in the reservoir.

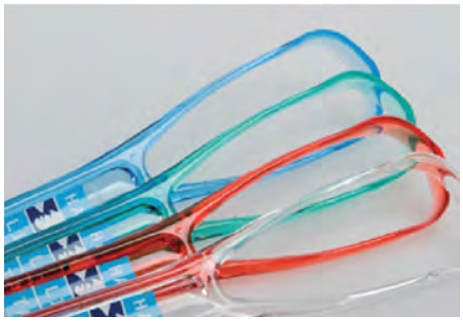


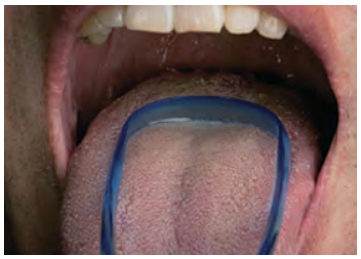




Box 28-9 Instructions for use of tongue cleaners.

Tongue cleaning is a useful addition to the daily oral hygiene routine. Many bacteria can be found within the grooves on the back of the tongue, which can cause bad breath. By brushing or scraping the tongue, this problem can be markedly helped or prevented entirely. One of the problems associated with tongue cleaning is that it can stimulate a gag reflex, especially when first applying this procedure. This reflex occurs more frequently with brushing than when using a scraper. Some people find it less of a problem if they clean their tongue in the evening.





Instructions

- There are various types of tongue cleaners: the most effective seems to one having the form of a loop.
- Extend the tongue as far as possible out of your mouth.
- Breathe calmly through your nose.
- Place the tongue cleaner as far back as possible on the tongue and press lightly with it so that the tongue becomes flattened.
- Ensure full contact of the tongue cleaner with the tongue.
- Pull the tongue cleaner slowly forward.
- Clean the middle part of the tongue, first using the raised edge on one side of the instrument.
- Use the smooth surface of the tongue cleaner on the sides of the tongue.
- Repeat these scraping movements a number of times.
- Rinse the mouth several times.

Remember to clean the tongue cleaner thoroughly after each use.

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Chapter 29

Chemical Dental Biofilm Control

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Rationale for supragingival biofilm control

Bacteria present in oral biofilms are responsible for the most prevalent diseases of mankind: caries and periodontal diseases. Therefore, control of oral biofilms becomes essential for the prevention of these diseases.

In the prevention of periodontal diseases, three levels can be distinguished (Baehni & Takeuchi 2003):

- *Primary prevention*: to protect individuals from pathogens, by means of barriers between the pathogens and the host; trying to keep the population in health; avoiding the development of the disease.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

- *Secondary prevention*: to limit the progression of the disease, once the pathogen has contacted the host; trying to recover health, without damage to the host tissues.
- *Tertiary prevention*: to limit the progression of the disease; trying to restore the host tissues, but with some degree of functional damage.

Primary prevention for periodontal diseases is based on supragingival biofilm control, by means of mechanical and/or chemical oral hygiene products, that are able to limit gingivitis development (Baehni & Takeuchi 2003). Primary prevention of periodontitis assumes that healthy gums (without gingivitis) will not develop periodontitis. Programs for the general population should be implemented, to control dental plaque levels and prevent gingivitis, considering different factors (Sheiham & Netuveli 2002):

- Toothbrushing must be part of daily personal hygiene habits.
- Behavioural factors should be considered.
- Cleaning methods should be socially accepted.
- The proposed methods should be easy to comply with in daily life.
- The hygiene procedures should be simple to perform.
- Quality control methods should be part of the program to assure adequate quality.

Secondary and tertiary prevention of periodontal diseases, once disease progression is arrested after proper active periodontal therapy, are achieved by means of supportive periodontal are programs that include both individual biofilm control and periodic re-evaluation with professional plaque control (Hugoson *et al*. 1998; Saxer & Yankell 1997; Baehni & Takeuchi 2003).

Oral hygiene products

Thus, supragingival biofilm control becomes essential in primary, secondary, and tertiary prevention of periodontal diseases. In order to control biofilms in the oral cavity, different oral hygiene products have been developed and marketed. Oral hygiene products refer to "mechanical devices and chemical formulations designed to provide oral health and cosmetic benefits to the user" (Addy & Moran 1997). Thus, oral hygiene products include both mechanical devices, but also chemical formulations.

Mechanical biofilm control

Physical disruption and elimination of dental biofilms can be accomplished by means of manual toothbrushes, different devices for interdental cleaning, powered toothbrushes, etc. (van der Weijden & Slot 2011).

The manual toothbrush is the most widely used method of plaque control (Saxer and Yankell, 1997; Hugoson *et al*. 1998), and it has demonstrated efficacy in biofilm control and gingivitis prevention (Hancock 1996; van der Weijden & Hioe 2005). Some powered toothbrushes have also demonstrated efficacy (van der Weijden *et al*. 1998).

Devices for interdental cleaning have also demonstrated efficacy in reducing plaque and gingival indices (Kinane 1998). However, their use is not common, because of a lack of proper instruction in their use, difficulties in performance, limited time of use, and awareness of potential adverse effects. Among the available devices, flossing is most commonly used, but interdental brushes are better accepted.

Limitations of mechanical biofilm control

Mechanical devices have demonstrated their efficacy in biofilm and gingivitis control, but different studies (Rugg-Gunn & MacGregor 1978; Lavstedt *et al*. 1982; Addy 1986; Addy *et al*. 1986; Albandar and Buischi 1995; Hugoson *et al*. 1998; Hugoson & Jordan 2004) and systematic reviews (van der Weijden & Hioe 2005) have shown that mechanical control alone may not be enough in a wide proportion of the population for the prevention of the onset or the reactivation of periodontal diseases. Different explanations for this can be found:

- Limited time of usage: the normal mean brushing time does not exceed 37 seconds (Beals *et al*. 2000).
- Devices for interdental cleaning are used daily by <10% of the population (Ronis *et al*. 1994) and only 2–10% flossed daily (Lang *et al*. 1995; Stewart *et al*. 1997; MacGregor *et al*. 1998).
- Even patients instructed in oral hygiene habits tended, with time, to come back to baseline plaque levels (Stewart *et al*. 1997). In most of the studies on mechanical biofilm control, the Hawthorne effect will be present and it may be a relevant hypothesis to test if those patients, included in a study, will maintain their oral hygiene habits after the end of the study (Johansen *et al*. 1975; Emilson & Fornell 1976; Löe *et al*. 1976; Lindhe *et al*. 1993; Yates *et al*. 1993;Claydon *et al*. 1996; Rosling *et al*. 1997b).
- Lack of control of other oral biofilms, besides dental plaque, because of a lack of adequate instructions on cleaning (tongue dorsum, cheek mucosal surfaces) or to a lack of access (tonsils) (Greenstein 2002, 2004; Quirynen *et al*. 1995)

In addition, there are circumstances in which adequate mechanical plaque control is not possible: after oral or periodontal surgery, in patients with intermaxillary fixations, in acute mucosal or gingival infections where pain precludes mechanical hygiene, in mentally or physically handicapped patients, etc. (Storhaug 1977; Nash & Addy 1979; Shaw *et al*. 1984; Zambon *et al*. 1989; Hartnett & Shiloah 1991; Laspisa *et al*. 1994; Eley 1999).

Chemical biofilm control

Chemical dental plaque control may be necessary in those subjects who are unable to properly control supragingival biofilm with mechanical devices. The use of chemical products should be adjunctive to that of mechanical devices. Mechanical biofilm control will reduce the amount of biofilm and disrupt its structure, allowing the chemical formulations to be more effective (FDI Commission 2002b). Adjunctive use may be more relevant than sole use, because most chemical agents are only able to act against the most external parts of the biofilm. However, some agents have shown some capacity for penetration, such as chlorhexidine (CHX) (Netuschil *et al*. 1995) and essential oils (Pan *et al*. 1999;Pan *et al*. 2000; Fine *et al*. 2001).

The use of chemical formulations (especially antiseptics) to control plaque and gingivitis levels has been widely evaluated, and efficacy for some formulations has been observed in different systematic reviews (Hioe & van der Weijden 2005; Gunsolley 2006; Paraskevas & van der Weijden 2006; Addy *et al*. 2007; Stoeken *et al*. 2007; Gunsolley 2010; Sahrmann *et al*. 2010; Afennich *et al*. 2011; Hossainian *et al*. 2011; Escribano *et al*. 2016; Serrano *et al*. 2015; Figuero *et al*. 2019, 2020).

Mechanism of action

Chemical plaque control may be achieved by different mechanisms of action (Fig. 29-1), with a quantitative (reduction of the number of microorganisms) and/or qualitative (altering the vitality of the biofilm) effect (FDI Commission 2002b):

- By preventing bacterial adhesion
- By avoiding bacterial growth and/or co-aggregation
- By the elimination of an already established biofilm
- By altering the pathogenicity of the biofilm.

Categories of formulations

Formulations for chemical biofilm control can be classified according to their effects (Lang & Newman 1997):

- *Antimicrobial agents*: bacteriostatic or bactericidal effects *in vitro*.
- *Plaque-reducing/inhibitory agents*: quantitative or qualitative effect over the plaque that may or may not be enough to affect gingivitis and/or caries.
- *Antiplaque agents*: affect the plaque sufficient to show a benefit in terms of gingivitis and/or caries control.
- *Antigingivitis*: reduce gingival inflammation without, necessarily, affecting dental plaque, including anti-inflammatory drugs.

These definitions are widely accepted in Europe, but in North America the term "antiplaque" refers more often to agents capable of significantly reducing plaque levels and "antigingivitis" to agents capable of significantly reducing gingivitis levels.

Ideal features

The features of the ideal chemical agent for plaque control have been proposed by different authors (Loesche 1976; van der Ouderaa 1991; Baker 1993; Fischman 1994):

- *Specificity*. Agents and formulations for chemical plaque control should demonstrate a wide spectrum of action, including bacteria, viruses, and yeasts. More specific products, such as antibiotics, must not be used in the prevention of periodontal diseases, and their use should be limited for the prevention of bacteraemia, at-risk patients, and for the treatment of some periodontal conditions (Herrera *et al*. 2008).
- *Efficacy*. Antimicrobial capacity must be demonstrated against microorganisms implicated in gingivitis and periodontitis, both in *in vitro* and *in vivo* studies. Although bactericidal effects may be only achieved at high dosages, antimicrobial effect should also be present at lower dosages (FDI Commission 2002b).
- *Substantivity*. The effects of the chemical formulations do not depend only on the antimicrobial activity *in vitro*. Other factors will influence the *in vivo* activity, among which substantivity may be one of the most relevant. Substantivity has been defined as the duration of the antimicrobial action *in vivo* (FDI Commission 2002b) and as a measurement of the contact time between the agent and the substrate in a defined medium. This time may be longer than expected with simple mechanical deposition (von Abbé 1974) (Fig. 29-2). According to their substantivity, agents have been divided (Kornman 1986a) into three distinct generations: (1) first generation agents show very limited substantivity, with limited time of action, and include phenolic derivatives, plant extracts, fluorides, quaternary ammonium compounds and oxygenating agents; (2) second generation agents, demonstrated a good substantivity and CHX is the best example; (3) third generation agents include those which interfere or prevent bacterial or biofilm adhesion.
- *Safety*. This must be demonstrated in animal models, before its use in humans. Because of the chronicity of the conditions to be prevented and the foreseeable long-term use, the secondary effects must be minimal.
- *Stability*. Agents must be stable at room temperature for an extended period of time. Care should be taken when mixing different ingredients in a formulation to avoid interference between molecules.

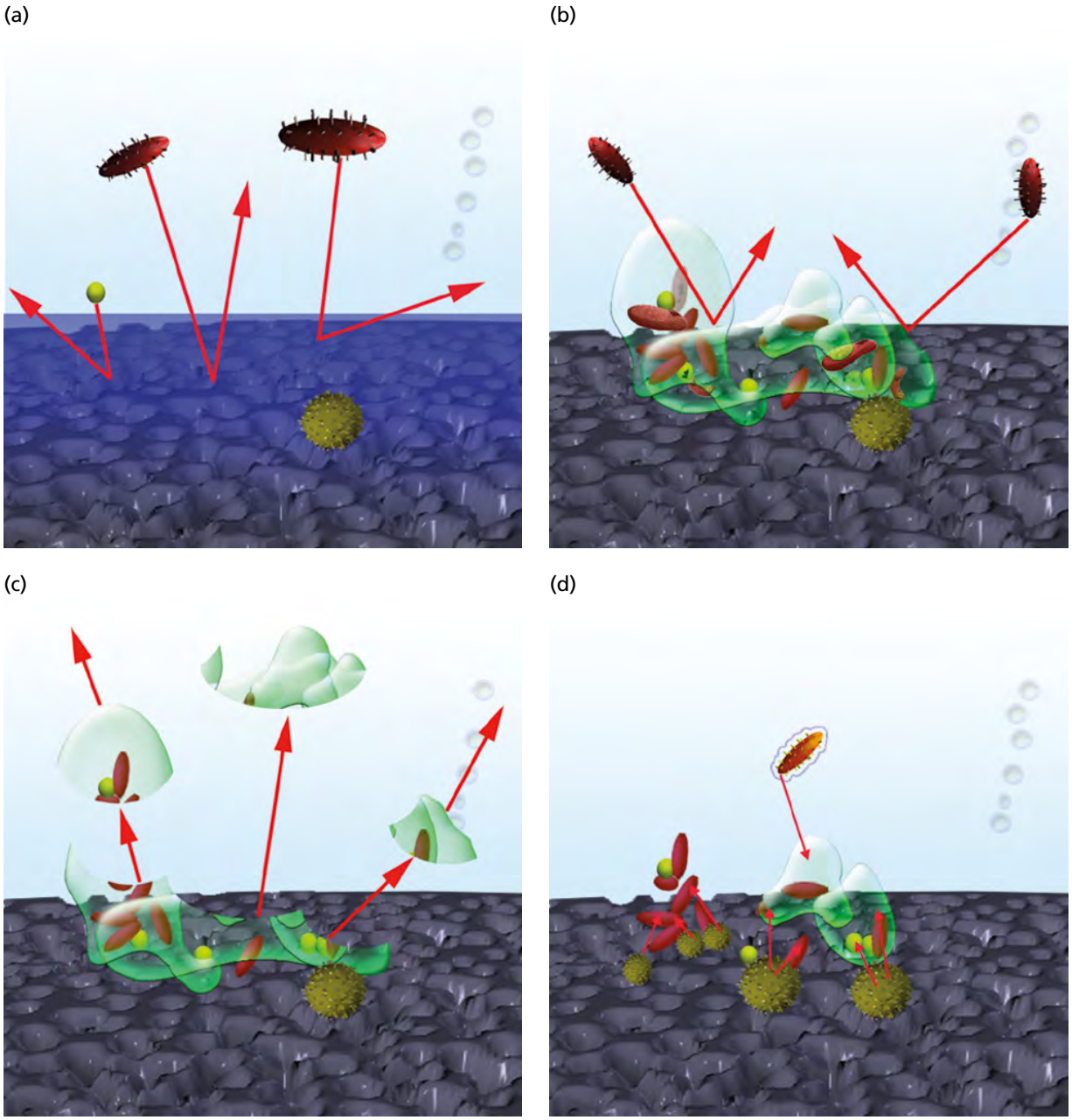

Fig. 29-1 Mechanisms of effect of antiplaque agents on bacterial biofilms (in green). (a) Prevention of bacterial adhesion to tooth surfaces: the active agent forms a pellicle (blue film) over the tooth surface, interfering with bacterial adhesion (red arrows), thus avoiding bacterial colonization. (b) Bactericidal or bacteriostatic effect, avoiding bacterial proliferation and co-aggregation: interference with bacterial division (damaged bacterial cells depicted in red) leads to interference in biofilm formation. In addition, biofilm maturation is also avoided, as co-aggregation of new species (red arrows) is impeded, due to the non-favorable environmental conditions. (c) Biofilm disruption from tooth surfaces: "chemical brushing". The agent induces a detachment and/or biofilm elimination from the tooth surface, by means of the chemical of the links between the surface and the biofilms, and in the biofilm structure disruption (red arrows). (d) Alteration of biofilm pathogenicity or enhancing host immune systems by different mechanisms: enhanced host defence systems, allowing for a more effective biofilm control by the host (short red arrows); or the presence of defined bacterial species that may influence biofilm development and maturation, by means of the release of different products, such as bacteriocins, or by competition for nutrients (long red arrow).

Evaluation of activity of agents for chemical biofilm control

In order to assess the plaque inhibitory and antiplaque activity of chemical compounds, different consecutive phases have been proposed, with the last stage being randomized clinical trials of home use with at least 6-months' duration (Addy & Moran 1997).

In vitro studies

Bacterial tests evaluate the antimicrobial activity of a product, by providing the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) against different bacterial species. The information provided is limited (antibacterial activity, spectrum of action), because many other

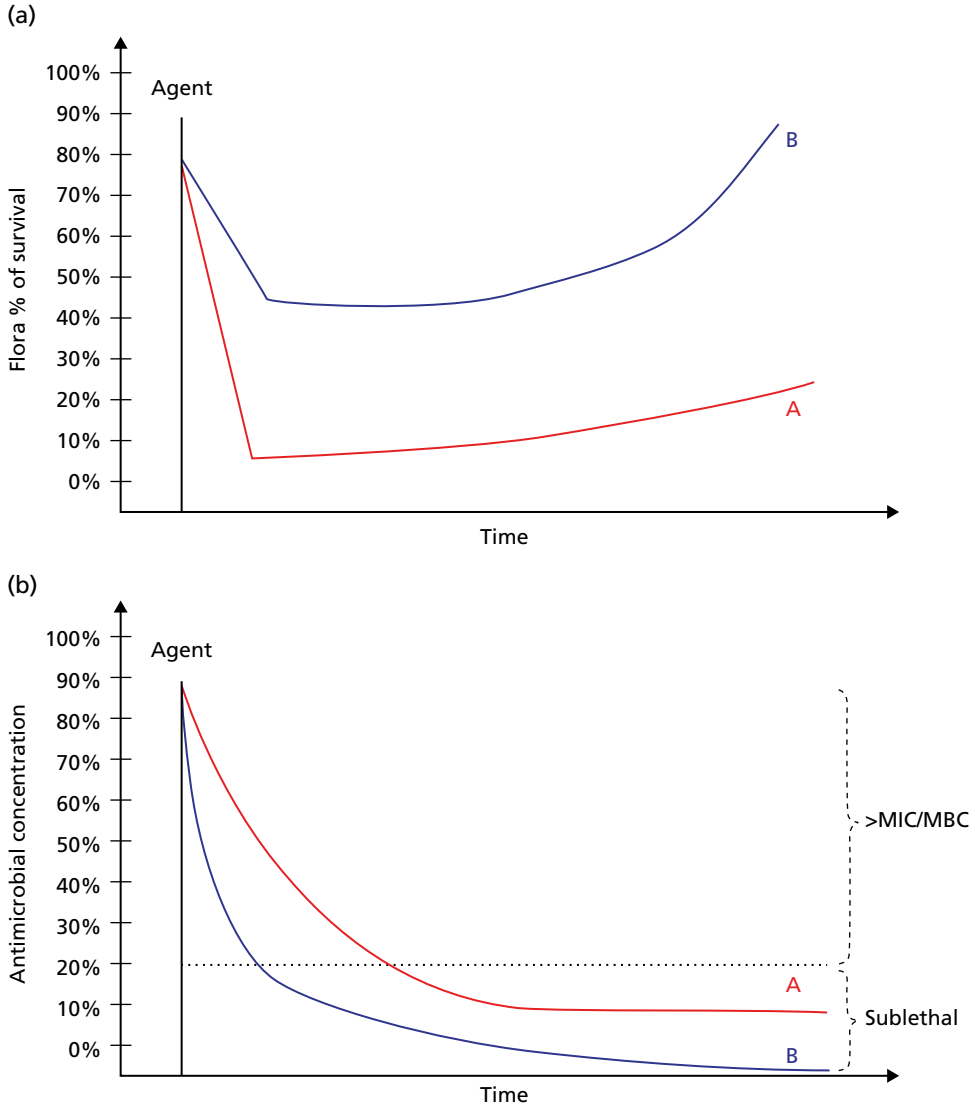

Fig. 29-2 Substantivity. (a, b) Two agents with different substantivity (measurement of the contact time between the agent and the substrate in a defined medium): with time, the concentration of the product decreases and the bacterial concentration increases. Product A has better substantivity than Product B. (a) Time after contact versus percentage of bacterial survival. (b) Time after contact versus concentration of the antibacterial agent. MIC, minimum inhibitory concentration: MBC, minimum bactericidal concentration.

factors will influence the effects *in vivo*, and the bacterial species are tested as planktonic cells, whereas in the mouth they are organized as sessile biofilm cells. However, antibacterial tests are useful for initial screening of products or for evaluation of the effects of the addition of new agents in a formulation.

Uptake studies are *in vitro* studies that assess the adsorption of products on different surfaces, such as hydroxyapatite, enamel, dentine, and acrylic.

Bioavailability and activity can be assessed by different chemical methodologies, such as spectrophotometry, or by indirect methods, such staining.

Biofilm models allowed formulations to be tested *in vitro* against sessile biofilm bacterial cells, which may better simulate real life conditions (Xu *et al*. 2000; Shapiro *et al*. 2002; Socransky & Haffajee 2002). However, a standardized and accepted model is already available, and conversely, several attempts of different *in vitro* biofilm models have been proposed (Sanchez *et al*. 2011). In addition to information on antimicrobial activity, other relevant information, such as the penetration of the agent in the biofilm, can be obtained. Both CHX and essential oils have demonstrated capacity to both penetrate and have a bactericidal action in the biofilm (Arweiler *et al*. 2001, 2003; Shapiro *et al*. 2002; Ouhayoun 2003; Corbin *et al*. 2011; Guggenheim & Meier 2011; Otten *et al*. 2011) (Fig. 29-3).

In vivo study models

Depot studies assess the retention of an agent in the mouth after a single use, by measuring the agent level in saliva or in dental plaque. These studies do not provide information on the activity of the product (Rolla *et al*. 1971; Bonesvoll *et al*. 1974a, b; Gjermo *et al*. 1974, 1975; Bonesvoll 1978; Bonesvoll & Gjermo 1978).

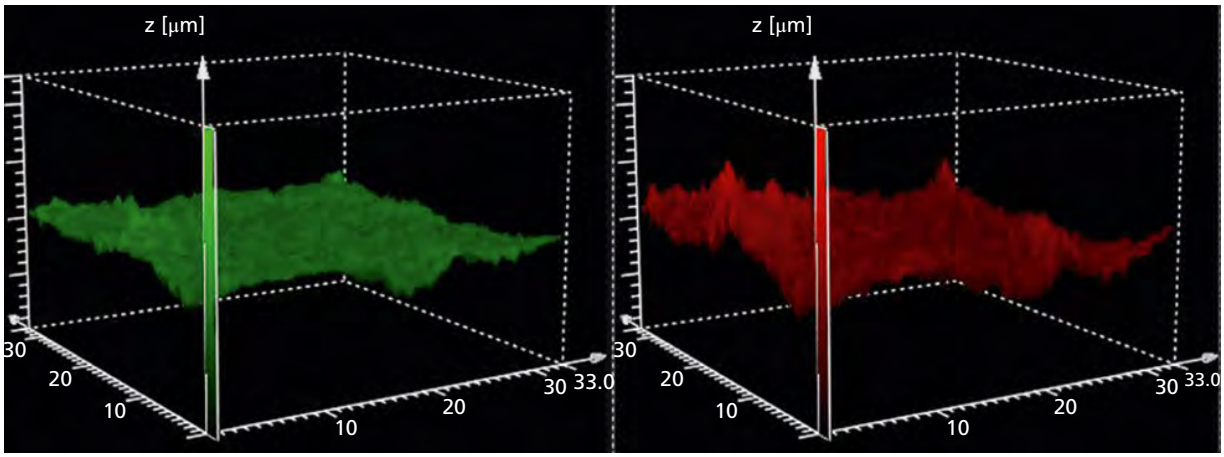

Fig. 29-3 Three-dimensional assessment of cell vitality in a biofilm, with a confocal microscope. Cells in green show vitality and cells with damaged cytoplasmatic membrane appear in red. This tool allows for the assessment of the capacity biofilm penetration by an antiseptic and its bactericidal activity.

In vivo biofilm study models assess the effects of different formulations on disks of enamel, dentine, or other materials, inserted into the mouth of patients (with different prosthetic devices) and retrieved for the evaluation of the biofilms formed under the presence of different products (cross-over designs) (Pan *et al*. 2000; Sreenivasan *et al*. 2004).

Antimicrobial tests *in vivo* are designed as cross-over studies (with a placebo and a positive control), with the amount of bacteria in saliva measured before and after (for several hours and at different times) a single use of a tested formulation (either as a mouth rinse, a dentifrice, or rinsing with a dentifrice in an aqueous slurry). This study design has been extensively used since its first use with CHX (Schiott *et al*. 1970) and provides information on antimicrobial capacity and duration of the effect.

Plaque regrowth models are also designed as cross-over studies (with a placebo and a positive control), in which plaque regrowth after professional prophylaxis is measured for a period of time (normally 3–4 days), and only use of the tested formulation is allowed for oral hygiene (no mechanical hygiene). Information on the plaque inhibitory capacity of the formulation is obtained (Harrap 1974; Addy *et al*. 1983; Moran *et al*. 1992; Arweiler *et al*. 2002; Pizzo *et al*. 2008).

Experimental gingivitis models follow the same design as plaque regrowth models but for longer periods of time (typically 12–28 days), allowing for the evaluation as an outcome variable of gingivitis indices (Löe 1965; Löe & Schiott 1970). No mechanical hygiene is permitted. Parallel studies can also be designed because of the longer duration of the study periods.

Home-use clinical trials

It is a general consensus that plaque inhibitory and antiplaque activities have to be shown in long-term (at least 6 months), home-use, randomized clinical trials, and concomitantly show safety, based on the lack of relevant side effects. In these studies, the use of the tested formulations is adjunctive to mechanical plaque control. The characteristics of these trials, in order for their conclusion to be valid, have been proposed (Council on Dental Therapeutics 1986):

- Double blind (patients and examiner).
- Controlled (negative and/or positive controls). It is not valid to compare the effects of the tested formulation against the baseline values, because of the Hawthorne effect (improvement of the oral hygiene habits of patients because of their awareness of their presence in the study) and to the performance of a professional prophylaxis at the beginning of these studies (Overholser 1988).
- Minimum of 6 months of duration. This period permits a number of advantages: 6 months is the typical period of time between two consecutive supportive periodontal therapy visits; it permits for an adequate evaluation of long-term adverse events, including microbiological effects; and it may compensate for part of the Hawthorne effect, because its effect will slowly disappear as the study progress (Overholser 1988).
- Microbiological evaluation to assess the overgrowth of pathogenic, opportunist, or resistant strains.
- Microbiological sampling and evaluation of plaque and gingival indices should be carried out at least at baseline, at the final evaluation, and at an intermediate point (e.g. 3 months).

In addition, other factors with regards to the quality of these studies should be considered, such as the selection of a representative population, with homogeneous study groups for different factors (age, smoking, gender, general, oral and periodontal health, etc.). Clinical trials must be clear, comparable, and with internal and external validity (Koch & Paquette 1997).

Based on the availability of at least two independent investigations with 6-month duration showing significant differences, as compared with the

negative control, in terms of plaque and gingivitis, different products have received a "seal of approval" for plaque inhibitory and/or antiplaque activity, by the American Dental Association (ADA) and the Food and Drug Administration (FDA).

In the following section, the scientific evidence supporting the use of the most common agents is reviewed, and special attention paid to 6-month, home-use, clinical trials and to systematic reviews with meta-analysis of 6-month studies.

Active agents

Antibiotics

- *Specific agents*. Penicillins, tetracyclines, metronidazole, vancomycin, kanamycin, and spiramycin.
- *Characteristics*. When systemically taken, their effects are stronger, because of the stable serum levels (also in the gingival crevicular fluid) maintained; when topically or locally applied, the effects are smaller, because of the limited time of action.
- *Evaluation*. Different groups of antibiotics have shown an effect on dental biofilms.
- *Limitations*. Use against dental plaque is not recommended because of the poor benefit-to-risk ratio, including adverse effects and an increase in bacterial resistance (Genco 1981; Kornman 1986; Slots & Rams 1990; Herrera *et al*. 2000; van Winkelhoff *et al*. 2000).
- *Usefulness, marketed*. Should not be used for chemical plaque control.

Enzymes: disruption of the biofilm

- *Specific agents*. Dextranase, mutanase, proteases, and lipases.
- *Characteristics*. Very limited substantivity and frequent side effects (Addy *et al*. 1986).
- *Evaluation*. Use *in vivo* is limited because of side effects. Other enzymes and combinations of enzymes have been evaluated, but only *in vitro* data are available (Johansen *et al*. 1997; Donlan & Costerton 2002).
- *Limitations*. Frequent side effects (Hull 1980; Addy *et al*. 1986).
- *Usefulness, marketed*. No.

Enzymes: enhancement of the host defences

- *Specific agents*. Glucose oxidase and amyloglucosidase.
- *Characteristics*. Mechanisms of action rely on the catalysation of thyocianate into hypothyocianate, through the salivary lactoperoxydase system.
- *Evaluation*. Evaluation of their *in vivo* effect on gingivitis has shown contradictory results, and no long-term studies are available (Addy *et al*. 1986; Moran *et al*. 1989; Kirstila *et al*. 1994; Hatti *et al*. 2007).
- *Limitations*. Limited scientific evidence available.
- *Usefulness, marketed*. Marketed as Zendium® by Opus Health Care AB (Malmö, Sweden) as a mouth rinse with amyloglucosidase, glucosidase and lactoperoxidase, sodium fluoride, xylitol and zinc, and no alcohol; and, also, in toothpaste. Another commercialized toothpaste is Bioxtra® (Bio-X Healthcare, Namur, Belgium), with lactoferrin, lysozyme, and lactoperoxidase.

Amine alcohols

- *Specific agents*. Delmopinol (Fig. 29-4) and octapinol.
- *Characteristics*. Mechanism of action is not fully understood, but they are not antimicrobials and the effect is achieved by the inhibition of the biofilm matrix formation or by the disruption of the biofilm matrix. Delmopinol also inhibits glucane synthesis by *Streptococcus mutans* (Rundegren *et al*. 1992; Elworthy *et al*. 1995) and reduces acid synthesis by bacteria (Simonsson *et al*. 1991).
- *Evaluation*. Delmopinol has been formulated and clinically evaluated as a mouth rinse at 0.1% and 0.2% (Collaert *et al*. 1992; Moran *et al*. 1992; Abbott *et al*. 1994; Claydon *et al*. 1996; Zee *et al*. 1997) and has demonstrated efficacy as an antiplaque agent as concluded in a systematic review (Addy *et al*. 2007). It was approved by FDA in 2005 as a medical device as a 0.2% mouth rinse indicated in the treatment of gingivitis (Imrey *et al*. 1994).
- *Limitations*. Most relevant side effects are dental staining, a temporary feeling of numbness in the mucosa (e.g. tongue), and burning sensation.
- *Usefulness, marketed*. Delmopinol has been marketed in several countries by Sinclair Pharma (Paris, France), under the name of Decapinol®, both as a 0.2% delmopinol mouth rinse with 1.5% of alcohol, and as a toothpaste with 0.2% delmopinol and 0.11% sodium fluoride.

Detergents

- *Specific agents*. The most important and frequently used detergent or surfactant (active-surface compounds) is sodium lauryl sulphate (SLS).
- *Characteristics*. SLS has demonstrated substantivity of 5–7 hours. The foaming properties of detergents may help in removing plaque, although there is not enough evidence to support this statement.
- *Evaluation*. SLS has a limited antimicrobial and plaque-inhibitory effect (Addy *et al*. 1983; Moran *et al*. 1988b).
- *Limitations*. SLS has been associated with oral hypersensitive reactions, including cheilitis, stomatitis or aphthous ulcers, burning sensation, and desquamation (Herlofson & Barkvoll 1996; Chahine *et al*. 1997; Plonait & Reichart 1999).
- *Usefulness, marketed*. SLS is present in many dentifrice and mouth rinse formulations, but it has not been formulated as a single active agent product.

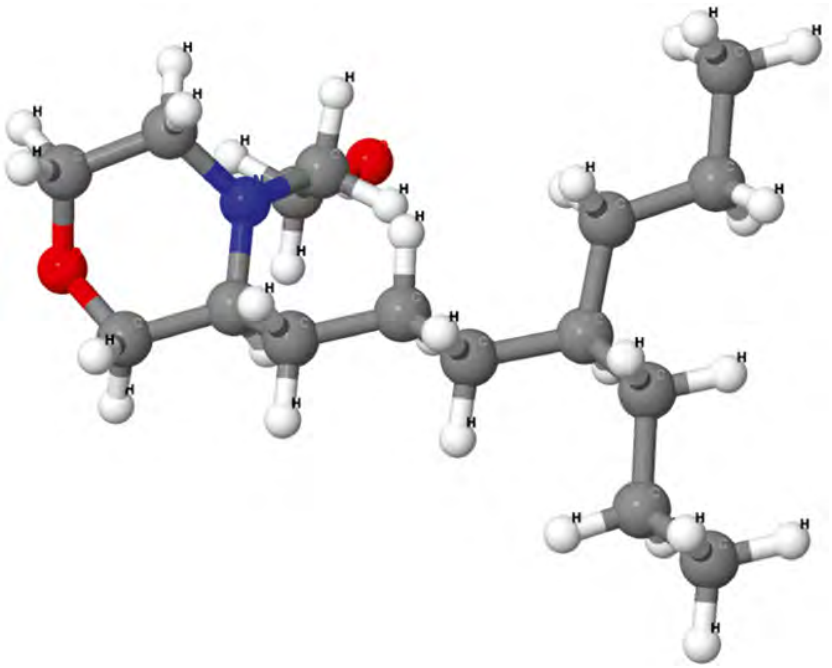

Fig. 29-4 Chemical structure of delmopinol (prepared with Jmol; www.jmol.org/)

Oxygenating agents

- *Specific agents*. Sodium peroxyborate and peroxycarbonate, and hydrogen peroxide.
- *Characteristics*. Exert antimicrobial effects through the release of oxygen.
- *Evaluation*. Peroxyborate and peroxycarbonate have demonstrated some antimicrobial and plaque inhibitory capacity (Moran *et al*. 1995). Hydrogen peroxide was evaluated in a systematic review (Hossainian *et al*. 2011) of 10 publications, three of which (one with a 6 month follow up) had a low risk of bias. No effect was observed in the short term, but the 6-month study showed significant benefits in the modified gingival index (Hasturk *et al*. 2004).
- *Limitations*. No long-term data are available for peroxyborate and peroxycarbonate, and only one study for hydrogen peroxide has been published. At low concentrations (i.e. <1.5% for hydrogen peroxide), adverse events are not common, but at higher concentrations a painful sensation in the mouth and ulcers may be frequent (Rees & Orth 1986).
- *Usefulness, marketed*. Peroxyborate (Bocasan®, Amosan®) and peroxycarbonate (Kavosan®) were marketed by Procter and Gamble (Cincinnati, OH, USA), but they are only available now in some countries; hydrogen peroxide is available in North America as Rembrant® (Dent-Mat Corp., Santa Maria, CA, USA).

Metal salts: zinc salts

- *Specific agents*. Zinc lactate, zinc citrate, zinc sulphate, and zinc chloride.
- *Characteristics*. At low concentrations, no adverse effects are present.
- *Evaluation*. As sole agents they have limited effects on plaque, but used in combination with other active agents there is an improvement in substantivity and action. More recently, 6-month, home-use studies, assessing dentifrices with zinc salts, have reported a therapeutic effect in patients with a diagnosis of gingivitis in whom statistically significant reductions in gingival and plaque indices were observed (Zhong *et al*. 2015; Delgado *et al*. 2018).
- *Limitations*. Limited data for individual agents are available.
- *Usefulness, marketed*. In combination with CHX, cetylpyridinium chloride, triclosan, hexetidine, etc. Combination products have been evaluated for plaque control (zinc lactate with CHX, zinc citrate with triclosan), but some combinations have also been evaluated for halitosis control (zinc lactate with CHX and cetylpyridinium chloride), tartar control (zinc chloride with essential oils), or ulcer healing (zinc sulphate with triclosan).

Metal salts: stannous fluoride

- *Specific agents*. Stannous fluoride has been included in dentifrices, mouth rinses, and gels since 1940. Several formulations have been tested, but the two most commonly evaluated are the combination of stannous fluoride with amine fluoride (addressed in the following section), and different formulations with 0.454% stannous fluoride dentifrice, combined with sodium hexametaphosphate (SHMP) in the most recent formulation.
- *Characteristics*. Combination of tin and fluoride (SnF_2); difficult to formulate in oral hygiene products because of limited stability for hydrolysis in the presence of water (Miller *et al*. 1969). Specifically, it is not frequently used in mouth rinse due to its limited stability in aqueous solutions.

- *Evaluation*. Several 6-month studies have been published, evaluating gel or dentifrice products, more frequently (six investigations) with the 0.454% stannous fluoride formulation (Beiswanger *et al*. 1995; Perlich *et al*. 1995; Mankodi *et al*. 1997; McClanahan *et al*. 1997; Williams *et al*. 1997), but also with stannous fluoride plus SHMP (Mankodi *et al*. 2005a; Mallatt *et al*. 2007; Boneta *et al*. 2010) and older formulations (Wolff *et al*. 1989; Boyd & Chun 1994). Less frequently, mouth rinse products were assessed (Leverett *et al*. 1984, 1986). In a systematic review, the 0.454% stannous fluoride formulation provided significant benefits in terms of gingivitis (weighted mean difference [WMD] 0.441, P <0.001, with significant heterogeneity $P = 0.010$) (Gunsolley 2006). In another systematic review (Paraskevas & van der Weijden 2006), the meta-analysis was limited because of the availability of data, and data pooling was performed at the final study visit, assuming that no differences were found at baseline. In addition, the results combined different stannous fluoride formulations, including the combination with amine fluoride. The results demonstrated significant differences at the final visit (and no differences at baseline) in terms of gingival index (WMD −0.15), modified gingival index (WMD −0.21). and plaque index (WMD −0.31), always with significant heterogeneity.
- *Limitations*. Main limiting factor is dental staining (Brecx *et al*. 1993; Paraskevas & van der Weijden 2006).
- *Usefulness, marketed*. Most recently marketed formulation is Crest Pro-Health® (Procter & Gamble, Mason, OH, USA), with 0.454% stannous fluoride with SHMP, zinc lactate, and SLS, approved by the ADA. The previous formulation with 0.454% stabilized stannous fluoride was marketed as Crest Gum Care or Crest Plus Gum Care (Procter & Gamble, Mason, OH, USA).

Metal salts: stannous fluoride with amine fluoride

- *Specific agents*. Amine fluoride was developed in the 1950s at the University of Zurich.
- *Characteristics*. Stannous fluoride and amine fluoride have demonstrated bactericidal activity against bacteria, and activity is increased if they are combined. Amine fluoride exerts its antimicrobial action by antiglycolytic activities. The activity of stannous/amine fluoride seems to be greater as dentifrice, with 8 hours of action after use (Weiland *et al*. 2008).
- *Evaluation*. Six-month studies are available, assessing stannous/amine fluoride as dentifrice (Sgan-Cohen *et al*. 1996; Shapira *et al*. 1999), mouth rinse (Zimmermann *et al*. 1993), or both (Mengel *et al*. 1996; Paraskevas *et al*. 2005), revealing no significant benefit of the dentifrice alone, whereas the mouth rinse achieved significant plaque and gingivitis reductions. If both products were used in combination, either no significant effects (Mengel *et al*. 1996) or significant effects on plaque, but not on gingivitis (Paraskevas *et al*. 2005), were reported.
- *Limitations*. Tooth staining is the most common adverse effect (Paraskevas *et al*. 2005).
- *Usefulness, marketed*. Both the dentifrice and the mouth rinse are marketed as Meridol® (GABA International AG, Therwil, Switzerland).

Other fluorides

- *Specific agents*. Sodium fluoride and sodium monofluorophosphate.
- *Characteristics*. Usefulness has been shown in reducing caries incidence (Petersson 1993).
- *Evaluation*. Fluoride ion has not demonstrated plaque-inhibitory nor antiplaque properties.
- *Limitations*. Not been evaluated as individual agents.
- *Usefulness, marketed*. Present in most dentifrices.

Natural products

- *Specific agents*. Sanguinarine extract and other herbal ingredients (camomile, echinacea, sage, myrrh, rhatany, peppermint oil).
- *Characteristics*. Sanguinarine is an alkaloid obtained from the plant *Sanguinaria canadensis*.
- *Evaluation*. Sanguinarine extract has demonstrated low bactericidal capacity in an *in vitro* biofilm model (Shapiro *et al*. 2002), whereas the clinical evaluation reported contradictory results (Moran *et al*. 1988a; Scherer *et al*. 1998; Quirynen *et al*. 1990). At least six home-use, 6-month oral hygiene trials were performed in the 1980s and early 1990s, assessing sanguinarine extract with zinc chloride, as dentifrice (Lobene *et al*. 1986; Mauriello & Bader, 1988), as mouth rinse (Grossman *et al*. 1989), or the combined use (Hannah *et al*. 1989; Harper *et al*. 1990; Kopczyk *et al*. 1991). Significant reductions in terms of plaque and gingivitis were reported with combined use.
- *Limitations*. Use of formulations with sanguinarine was associated to oral leukoplakia (Mascarenhas *et al*. 2002).
- *Usefulness, marketed*. Viadent® (Colgate, Piscataway, NJ, USA), with sanguinarine extract is no longer available. Paradontax® (GlaxoSmithKline, Middlesex, UK) contains other active components.

Essential oils

- *Specific agents*. Mouth rinse with eucalyptol (0.092%), menthol (0.042%), methyl salicylate (0.060%), and thymol (0.064%) with alcohol (26.9%, in the original formulation) (Fig. 29-5).
- *Characteristics*. Multiple mechanisms of action have been proposed, such as cell wall disruption, inhibition of bacterial enzymes, extraction of endotoxins derived from lipopolysaccharide (LPS) of Gram-negative bacteria (Fine *et al*. 1985), and anti-inflammatory action based on antioxidant activity (Firatli *et al*. 1994; Sekino & Ramberg 2005).

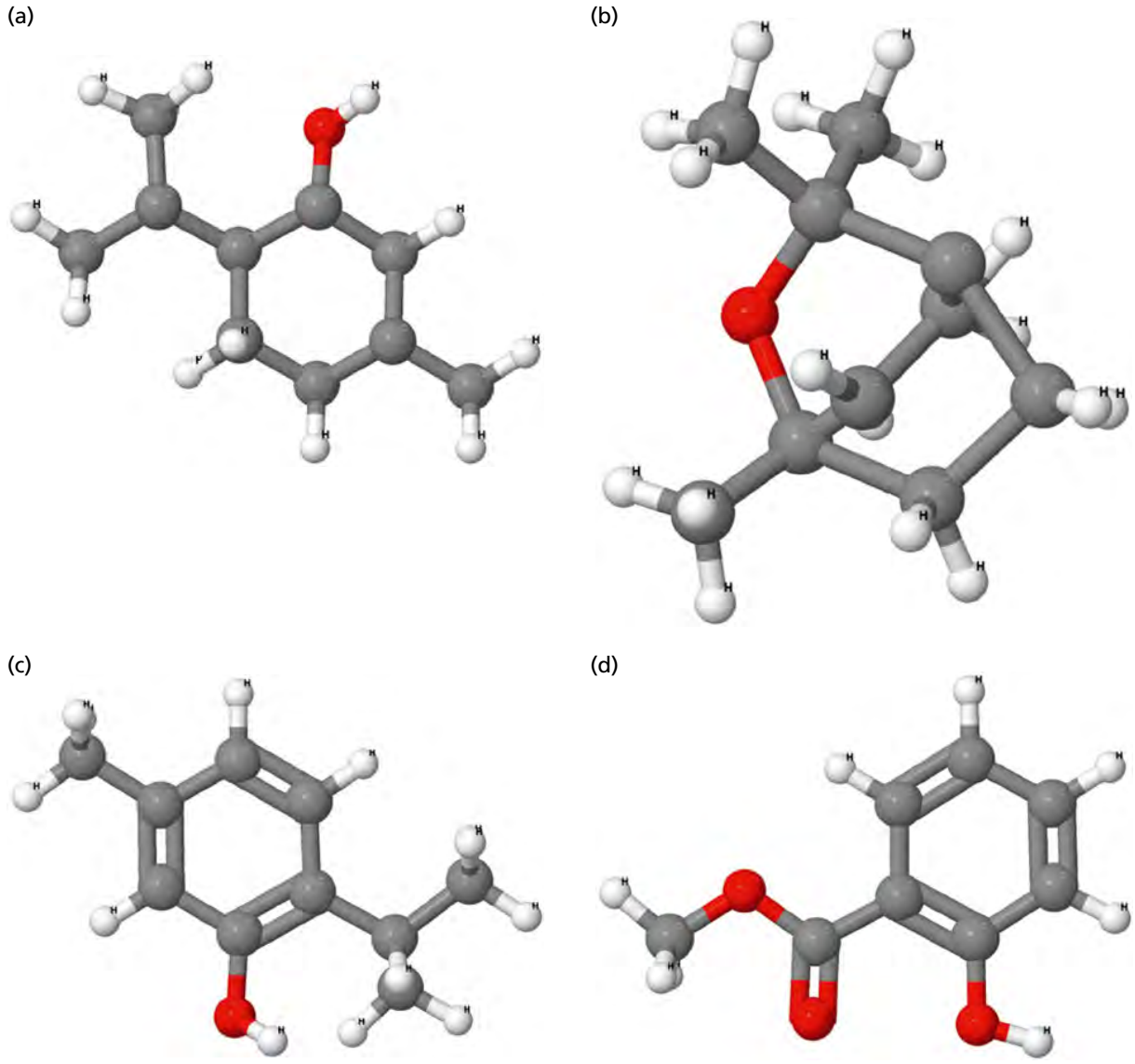

Fig. 29-5 Chemical structure of essential oils: (a) Menthol. (b) Eucalyptol. (c) Thymol. (d) Methyl salicylate (prepared with Jmol).

- *Evaluation*. A mouth rinse with essential oils has demonstrated antimicrobial activity in biofilm models *in vitro* (Fine *et al*. 2001; Shapiro *et al*. 2002), and plaque inhibitory and antiplaque effects in different home-use, 6-month oral hygiene studies (Lamster, 1983; Gordon *et al*. 1985; DePaola *et al*. 1989; Grossman *et al*. 1989; Overholser *et al*. 1990; Beiswanger *et al*. 1997; Charles *et al*. 2001, 2004; Sharma *et al*. 2002, 2004; Bauroth *et al*. 2003). In a systematic review (Stoeken *et al*. 2007), including investigations of 6 months or more, 11 papers were included and statistically significant differences in the meta-analysis were found for both plaque (WMD −0.83, P <0.00001; with significant heterogeneity, P <0.00001) and gingivitis index (WMD −0.32, P <0.00001; with significant heterogeneity P <0.00001).
- *Limitations*. Secondary effects include a burning sensation and tooth staining. There is some controversy concerning alcohol-containing mouth rinses (including Listerine®) and oral cancer (Blot *et al*. 1983). However, critical assessment of the literature does not support those statements (Claffey 2003; Ciancio 1993).
- *Usefulness, marketed*. There are different formulations of Listerine® antiseptic (Johnson & Johnson Healthcare Products, Skillman, NJ, USA).

Triclosan

- *Specific agents*. Triclosan [5-chloro-2-(2,4 dichlorophenoxy) phenol] is a non-ionic bisfenolic, broad spectrum antibacterial agent (Ciancio 2000) (Fig. 29-6).
- *Characteristics*. Formulated both in mouth rinses and in dentifrices. In mouth rinses, at 0.2%, there is a limited bactericidal activity (Shapiro *et al*. 2002; Arweiler *et al*. 2003) and a substantivity of approximately 5 hours (Jenkins *et al*. 1991a). As a dentifrice, it can be detected for up to 8 hours in dental plaque (Gilbert & Williams 1987) and it has been normally formulated in combination with

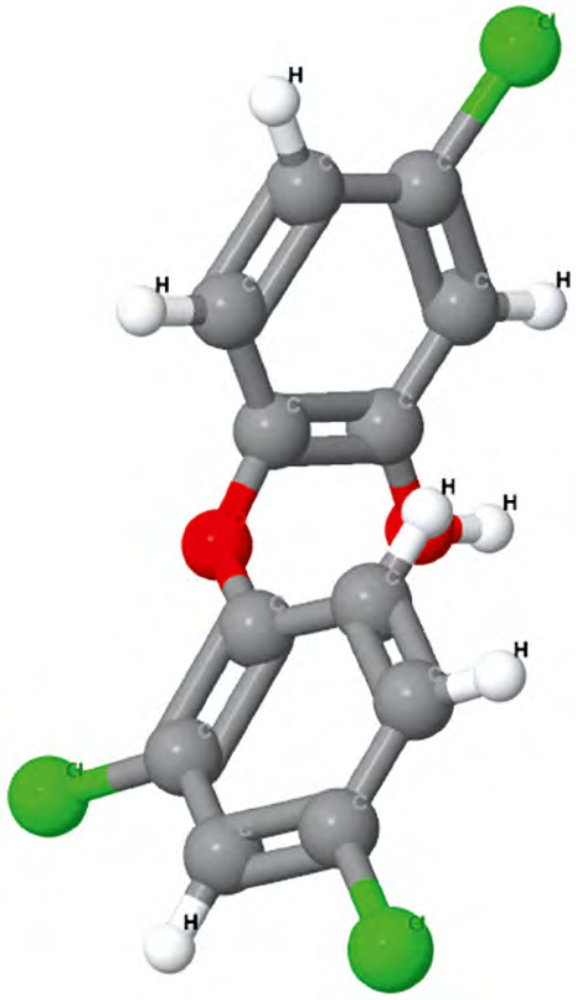

Fig. 29-6 Chemical structure of triclosan (prepared with Jmol).

polyvinyl-methyl ether maleic acid copolymer, zinc citrate or pyrophosphate, in order to improve the substantivity and/or the antimicrobial activity. Triclosan may also induce anti-inflammatory effects (Barkvoll & Rolla, 1994; Gaffar *et al*. 1995; Kjaerheim *et al*. 1996) through inhibition of the cyclooxygenase and lipoxygenase pathways which induces the reduction in the synthesis of prostaglandins and leukotrienes.

- *Evaluation*. Home-use, 6-month, oral hygiene studies are available for three distinct triclosan dentifrice formulations (triclosan with copolymer, triclosan with zinc citrate, triclosan with pyrophosphate), and a mouth rinse with triclosan and copolymer.
  - A *dentifrice with triclosan and zinc citrate* was extensively evaluated in the 1990s (Svatun *et al*. 1989, 1990, 1993a, b; Stephen *et al*. 1990; Palomo *et al*. 1994; Renvert & Birkhed 1995). Conflicting results were reported, and a limited meta-analysis conducted (performed with end of trial values, rather than with the changes), demonstrating a limited but significant effect on plaque (WMD –0.07, P <0.00001) and a more important effect on bleeding (WMD –10.81%, P <0.00001) (Hioe & van der Weijden 2005). Conversely, no significant differences were observed in another systematic review over baseline-final changes (Gunsolley 2006).
  - A *dentifrice with triclosan and copolymer* has also been extensively evaluated in 6-month studies (Garcia-Godoy *et al*. 1990; Cubells *et al*. 1991; Deasy *et al*. 1991; Bolden *et al*. 1992; Denepitiya *et al*. 1992; Mankodi *et al*. 1992; Lindhe *et al*. 1993; Svatun *et al*. 1993b; Palomo *et al*. 1994; Kanchanakamol *et al*. 1995; Triratana *et al*. 1995; Hu *et al*. 1997; McClanahan *et al*. 1997; Charles *et al*. 2001; Allen *et al*. 2002; Winston *et al*. 2002). In a limited meta-analysis over final visit values, a significant effect was observed for the Turesky modification of the plaque index (WMD –0.48, P <0.0001) and for the Talbott modification of the gingival index (WMD –0.24, P <0.0001), in both cases with significant heterogeneity (Hioe & van der Weijden 2005). In another meta-analysis, evaluating changes between baseline and final visit, a significant effect on plaque was observed (WMD 0.823), with significant differences in 14 out of the 18 included arms; and for gingivitis (WMD 0.858), in both cases with significant heterogeneity (Gunsolley 2006).
  - A *dentifrice with triclosan and pyrophosphate* has been evaluated less frequently (Palomo *et al*. 1994; Renvert & Birkhed 1995; Grossman *et al*. 2002; Winston *et al*. 2002), and the results showed significant heterogeneity and conflicting results (Gunsolley 2006).
  - A *mouth rinse with triclosan and copolymer* was evaluated in the 1990s in at least four 6-month trials (Worthington *et al*. 1993; Ayad *et al*. 1995; Triratana *et al*. 1995; Schaeken *et al*. 1996), demonstrating statistically significant differences both in plaque and gingival indices. The formulation of triclosan and copolymer in mouth rinse has also been tested as a prebrushing agent; a meta-analysis of two 6-month studies resulted in a WMD of 0.269 (P <0.0001) (Angelillo *et al*. 2002).
- *Limitations*. There are no relevant side effects, but a risk of formation of a carcinogenic product (chloroform) has been suggested in an *in vitro* study testing the combination of triclosan and free chlorine present in water (Rule *et al*. 2005). Also, environmental problems have been suggested: the presence of triclosan in the food chain (Park *et al*. 2017); triclosan accumulation in the bristles of dental toothbrushes, with delayed release (Han *et al*. 2017); possible action as an endocrine disruptor (Veldhoen *et al*. 2006).
- *Usefulness, marketed*. Triclosan (0.30%) with copolymer and sodium fluoride (0.24%) is marketed as Colgate Total® (Colgate-Palmolive Co.). This formulation is no longer available in some markets. The formulation of triclosan and co-polymer as mouth rinse has been marketed as Plax®, although different products under this name have been marketed, including formulations with sodium benzoate.

Bisbiguanides

- *Specific agents*. CHX digluconate, alexidine dihydrochloride, and octenidine dihydrochloride.
- *Characteristics*. Symmetric molecules, with two chlorophenolic rings and two biguanides groups connected by a central bridge of hexametilene (Fig. 29-7).
- *Evaluation*. Excellent plaque inhibitor and antiplaque agent. CHX is the reference, since the other bisbiguanides show similar or inferior activity (Shapiro *et al*. 2002).
- *Limitations*. Similar among all bisbiguanides, but there are more studies for CHX.
- *Usefulness, marketed*. Many CHX formulations are available on the market.

Chlorhexidine

CHX is the most widely evaluated and the most efficacious agent against oral biofilms. Its activity was first investigated more than 50 years ago (Schroeder 1969).

CHX is most often formulated in mouth rinses with a concentration 0.1–0.2% (Löe *et al*. 1976; Segreto *et al*. 1986; Grossman *et al*. 1989; Flemmig *et al*. 1990; Lang *et al*. 1998). These concentrations achieve the ideal CHX dosage of 18–20 mg/use. Clinical activity is observed with dosages of 5–6 mg twice per day. Higher dosages do not increase the effect (but do increase adverse effects) (Cancro *et al*. 1974). To obtain a 20-mg of dosage with a 0.2% formulation, rinsing with 1 mL should last for 30 seconds; with a 0.12% formulation, 15 mL should last for 60 seconds.

More recently, formulations with lower concentrations (e.g. 0.05%) have been marketed, aiming to decrease adverse effects. The resulting dosages are approximately 5 mg per use, which is at the lower limit of clinical activity; therefore, the complete formulation is crucial and combination with other active agents (triclosan, cetylpyridinium chloride, zinc salts) has been proposed (Joyston-Bechal & Hernaman 1993; Marsh & Bradshaw 1995; Claydon *et al*. 2001; Shapiro *et al*. 2002).

Characteristics

CHX is active against Gram-positive and Gram-negative bacteria, against yeast, and also against viruses, including human immunodeficiency virus and hepatitis B virus (Wade & Addy 1989).

- *Antimicrobial effect*. Depending on the concentration, CHX may show different antimicrobial effects. At low concentrations, it increases the permeability of the plasmatic membrane, leading to a bacteriostatic effect (Hugo & Longworth 1964, 1965). At higher concentrations, it induces precipitation of cytoplasm proteins and cell death, thus having a bactericidal effect (Hugo & Longworth 1966; Fine 1988). However, bacterial cells arranged in biofilms will show higher resistance against antimicrobials. Against biofilms, CHX has demonstrated the capacity to penetrate and to actively act inside the biofilm, both altering biofilm formation or having a bactericidal effect (Arweiler *et al*. 2001; Shapiro *et al*. 2002).
- *Plaque inhibitory effect*. In addition to the antimicrobial effect, CHX molecules adhere to the tooth surface and interact with bacterial cells that are also trying to adhere to the tooth surface; therefore, CHX interferes with bacterial adhesion (Rolla & Melsen 1975; Wolff 1985; Fine 1988; Jenkins *et al*. 1988, 1989). CHX also interacts with salivary glycoproteins, thus leading to the reduced salivary pellicle formation. In addition, it has been suggested that CHX affects the activity of bacterial enzymes involved in glucan production (glycosiltranferase C) (Vacca-Smith & Bowen 1996).

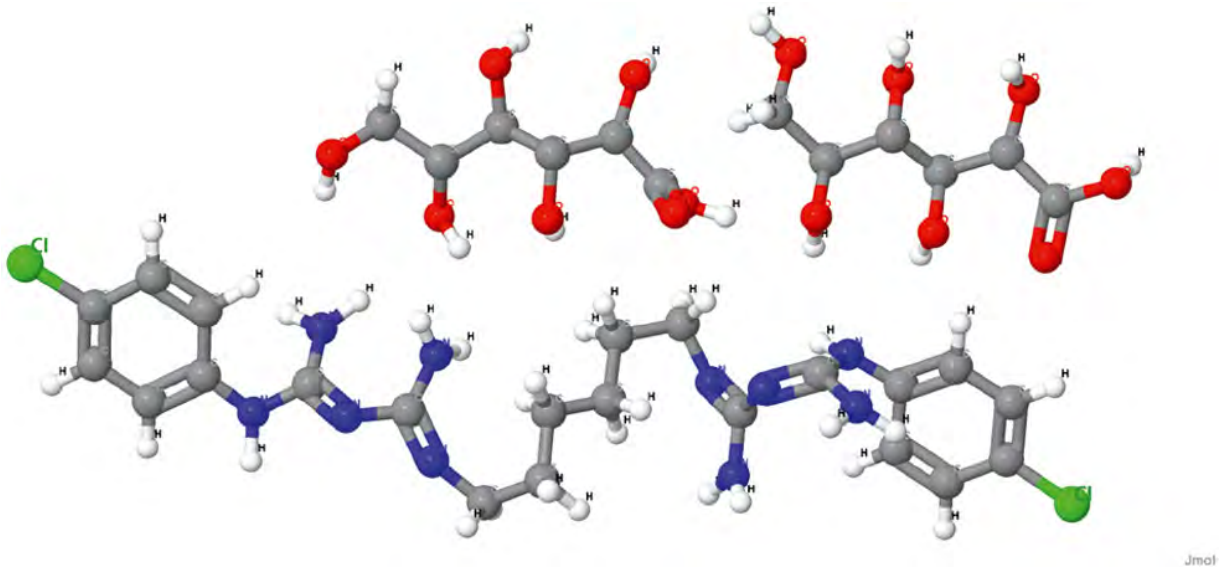

Fig. 29-7 Chemical structure of chlorhexidine digluconate (prepared with Jmol).

- *Substantivity*. CHX molecules bind reversibly to oral tissues, with a slow release (Bonesvoll *et al*. 1974a, b) that allows for sustained antimicrobial effects for up to 12 hours (Schiott *et al*. 1970).

Evaluation of chlorhexidine in clinical studies

Six-month studies are available both for mouth rinses and for dentifrices.

Two 6-month studies evaluating CHX containing *dentifrices* have been published. The difficulties in formulating CHX in dentifrices are well known because of the high risk of inactivation. However, a 1% CHX dentifrice (Yates *et al*. 1993) and a 0.4% CHX dentifrice with zinc (Sanz *et al*. 1994) both demonstrated significant benefits in terms of plaque and, for the 1% CHX dentifrice, also in gingival inflammation.

Different 0.12% and 0.2% *mouth rinse* formulations have been evaluated in 6-month studies (Grossman *et al*. 1986, 1989; Flemmig *et al*. 1990; Overholser *et al*. 1990; Sanz *et al*. 1994; Hase *et al*. 1998; Lang *et al*. 1998; Charles *et al*. 2004; Stookey 2004), and each independent study revealed statistically significant benefits in terms of both plaque and gingival indexes, with one exception. In a systematic review with 0.12% formulations (six studies, one unpublished), the WMD for plaque was 1.040 (P <0.001) and for the gingival index was 0.563 (P <0.001, significant heterogeneity P = 0.013) (Gunsolley 2006).

A systematic review comparing *0.12% and 0.2% formulations* (Berchier *et al*. 2010) included eight papers (with a study duration of 3–14 days, except for one paper reporting 3-month results). For the Quigley and Hein Plaque Index (Quigley & Hein 1962), meta-analyses of seven papers calculated a significant difference (WMD: 0.10; P = 0.008), although the difference was not considered to be clinically relevant and none of the individual studies showed significant differences. For gingival inflammation, no difference was observed in a meta-analysis of three papers.

CHX and essential oils mouth rinses have been compared. In a systematic review (van Leeuwen *et al*. 2011) of 19 papers, meta-analyses were carried out on studies with a follow up of 4 weeks or more. Significant differences (favoring the CHX groups) were found at the final visit for plaque (four studies, WMD 0.19; P = 0.0009), but no significant difference in gingival inflammation (three studies, WMD 0.03; P = 0.58). Significantly more staining was observed in the CHX groups (WMD: 0.42; P <0.000001). It must be highlighted that the meta-analyses considered final visit values, rather than the changes between the baseline and final visit. In addition, different CHX concentrations and formulations were pooled, as well as different follow-up times. Another meta-analysis only included 6-month studies (Gunsolley 2006) and pooled data from four studies (Grossman *et al*. 1989; Overholser *et al*. 1990; Segreto & Collins 1993; Charles *et al*. 2004). A significant difference (P = 0.02) in plaque was reported, favoring 0.12% CHX formulations, with two individual studies demonstrating significant differences. For the gingival index, one study reported significant differences, and the pooled results showed a tendency to significant differences (P = 0.068). The authors highlighted that the essential oils mouth rinse showed 60% of the effect of CHX mouth rinses for both parameters.

Limitations of chlorhexidine use, safety and adverse effect

CHX safety has been extensively studied. Only heating for long periods of time can induce the formation of 4-chloroanilinine, which has been shown to be cancerogenic and mutagenic. Despite the low risk of formation of 4-chloroanilinine, CHX formulations are marketed in dark bottles, and should be kept at room temperatures, out of direct sunlight. No adverse microbiological changes, including the overgrowth of opportunistic strains, are induced after long-term use (Schiott *et al*. 1970, 1976a, b).

Reported adverse events include the following:

- Hypersensitivity reaction (Beaudouin *et al*. 2004).
- Neurosensory deafness if the product is placed in the middle ear (Aursnes 1982).
- Taste alterations (Marinone & Savoldi 2000; Breslin & Tharp 2001), particularly affecting salty and bitter taste; they are reversible and disappear soon after discontinuation of product usage.
- Uni- or bi-lateral parotid tumefaction (Flotra *et al*. 1971; van der Weijden *et al*. 2010).
- Staining, either of teeth, mucosa, tongue dorsum or restorations (Flotra *et al*. 1971).
- Mucosal erosion (Almqvist & Luthman 1988).
- Healing process alterations. *In vitro* studies have suggested some inhibition of fibroblast proliferation in culture. However, *in vivo* studies, using CHX mouth rinses after periodontal surgery, have not found interference with the healing process; indeed, a better resolution of inflammation was observed (Sanz *et al*. 1989).
- Increase in calculus formation (Yates *et al*. 1993).

Tooth and tongue staining is the most common adverse effect (Fig. 29-8) and different mechanisms have been proposed to explain staining associated with CHX usage (Watts & Addy, 2001):

- Degradation of the CHX molecule to para-chloraniline
- Catalysis of Maillard reactions
- Protein denaturation, with formation of metal sulfide
- Precipitation of anionic dietary chromogens.

Among the suggested mechanisms, precipitation of anionic dietary chromogens onto adsorped cations has been considered as the most suitable (Addy & Moran 1995; Watts & Addy 2001). The intensity of staining seems correlate with the frequency of intake

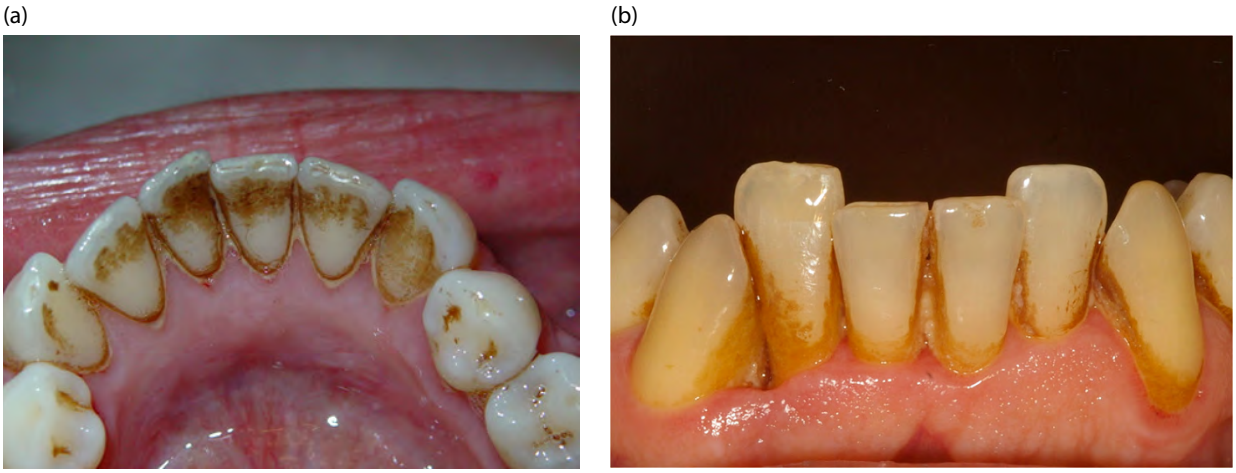

Fig. 29-8 Tooth staining after chlorhexidine use. (a) Lingual aspect. (b) Buccal aspect.

of chromogenic products, such as coffee, tea, wine, and tobacco; and also with the concentration of CHX in commercial formulations. In addition, a direct correlation has been observed between staining and antimicrobial effect (Addy *et al*. 1989; Claydon *et al*. 2001).

Usefulness and availability

The first CHX formulations in Europe were 0.2% mouth rinses in a hydroalcohol vehicle, and the first studies demonstrating antiseptic activity also evaluated 0.2% products (Löe *et al*. 1976). However, the CHX formulation that obtained the ADA seal was Peridex® (Zila Pharmaceuticals, Phoenix, AZ, USA), and was formulated at 0.12%. Since then, many CHX formulations have been marketed. However, it has been demonstrated that the mere presence of CHX in a product does not assure clinical activity (Harper *et al*. 1995; Herrera *et al*. 2003). Therefore, study models and/or clinical trials are needed to confirm that the activity of a new formulation is similar to that of the reference products already evaluated. In addition, concerns for adverse effects and the presence of alcohol in mouth rinses have led to new formulations without alcohol, with lower CHX concentration, and/or combined with other active agents.

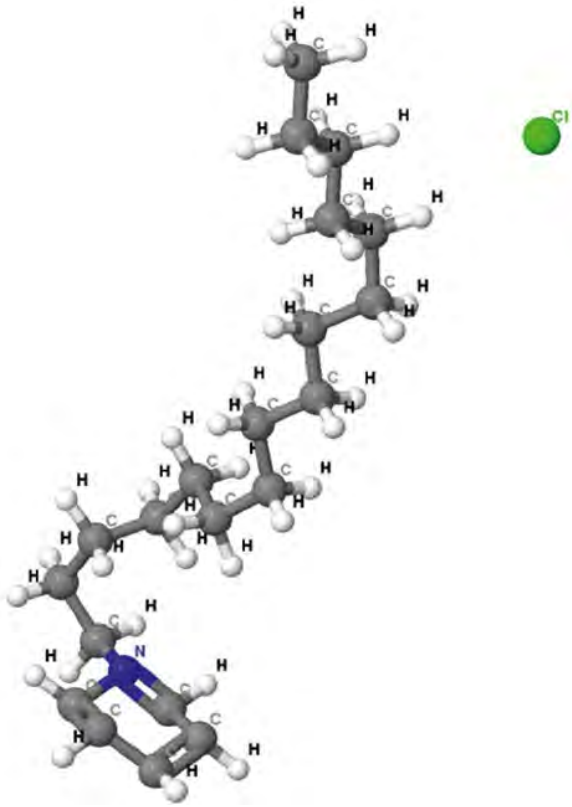

Fig. 29-9 Chemical structure of cetylpyridinium chloride (prepared with Jmol).

Quaternary ammonium compounds

- *Specific agents*. Benzylconium chloride and cetylpyridinium chloride (CPC) (Fig. 29-9).
- *Characteristics*. Monocationic agents that rapidly adsorb to oral surfaces (Bonesvoll & Gjermo 1978). Substantivity approaches 3–5 hours (Roberts & Addy 1981), due to rapid desorption, loss of activity, less retention or neutralization (Bonesvoll & Gjermo 1978). The mechanism of action relies on the hydrophilic part of the CPC molecule interacting with the cell membrane, leading to the loss of cell components, disruption of cell metabolism, inhibition of cell growth, and finally cell death (Merianos 1991; Smith *et al*. 1991). Because of the positive charge of this active hydrophilic part, other products in the formulation may easily inactivate the agent, making it crucial that a CPC formulation is evaluated for bioavailability.
- *Evaluation*. Three 6-month trials have been published, one for a 0.05% formulation (Allen *et al*. 1998) and two with 0.07% formulations (Mankodi *et al*. 2005b; Stookey *et al*. 2005). With the addition of four unpublished studies, a meta-analysis demonstrated significant benefits in terms of plaque (seven studies, three published; $P < 0.001$) and gingivitis (five studies, two published; $P = 0.003$), although high heterogeneity and variability were observed, including the evaluation of different formulations

(Gunsolley 2006). In another systematic review, the meta-analysis of the three 6-months studies revealed a WMD of 0.42 (P <0.00001; heterogeneity P = 0.06) for the Quigley and Hein plaque index at the final visit (Haps *et al*. 2008).

- *Limitations*. The safety of CPC formulations, marketed since 1940, have been demonstrated for concentrations 0.045–0.1% (Nelson & Lyster 1946; Margarone *et al*. 1984; Lin *et al*. 1991; Segreto 2004; Stookey 2004; Federal Register 2004). Adverse effects are less frequent than with CHX formulations, and include tooth and tongue staining, transient gingival irritation and aphthous ulcers in some individuals (Lobene *et al*. 1979). In addition, no significant changes in the oral microbiota or overgrowth of opportunistic species have been observed (Ciancio *et al*. 1975).
- *Usefulness, marketed*. with 0.05% CPC (Cepacol Combe, White Plains, NY, USA), with 0.045% CPC (Scope, Procter & Gamble, Cincinnati, OH, USA), and with 0.07% CPC (Crest ProHealth, Procter & Gamble, Cincinnati, OH, USA).

Hexetidine

- *Specific agents*. Hexetidine is a pyrimidine derivative.
- *Characteristics*. Shows antimicrobial properties against Gram-positive and Gram-negative bacteria and yeast (*Candida albicans*) (Menghini & Sapelli 1980; Jones *et al*. 1997). However, oral retention seems to be limited and antimicrobial activity may not last more than 90 minutes (McCoy *et al*. 2000).
- *Evaluation. In vitro* results suggest some bactericidal activity, even in biofilm models (Shapiro *et al*. 2002), but with a wide variability. In a systematic review (Afennich *et al*. 2011), six randomized controlled trials (RCTs) were identified, but the longest follow-up was 6 weeks; the results demonstrated heterogeneity and therefore, *in vivo* results have not demonstrated plaque inhibitory or antiplaque activity for hexetidine products.
- *Limitations*. Tooth staining, mucosal erosion, and parotid gland swelling, but with low frequency (Addy & Moran 1984; Yusof 1990; van der Weijden *et al*. 2010).
- *Usefulness, marketed*. Normally formulated at 0.1%, with many different brand names (Bactidol, Hexalen, Hexoral, Hextril, Oraldene, Oraldine, Oraseptic).

Povidone iodine

- *Specific agents*. Iodine is a recognized antibacterial agent, which is combined with a synthetic polymer, povidone.
- *Characteristics*. At 1% it has demonstrated substantivity of only 1 hour.
- *Evaluation*. Limited substantivity leads to a very limited plaque inhibitory action (Addy *et al*. 1977; Addy & Wright 1978). It has been evaluated combined with 1.5% of hydrogen peroxide (5% of povidone iodine), both short term (Maruniak *et al*. 1992) and for 6 months (Clark *et al*. 1989), combining rinsing and subgingival irrigation, with clear reductions of gingivitis (Greenstein 1999). Povidone iodine has also been used in the treatment of necrotizing gingivitis (Addy & Llewelyn 1978) and as an adjunct to scaling and root planing, which significantly decreased pocket depth but with only small clinical significance (Sahrmann *et al*. 2010).
- *Limitations*. No relevant side effects, but it may affect thyroid function.
- *Usefulness, marketed*. Betadine® (10% povidone iodine; still available), Perimed® (1.5% hydrogen peroxide with 5% of povidone iodine; no longer available).

Other evaluated products

- *Acidified sodium chlorite*. Suggested to have similar activity to CHX (Fernandes-Naglik *et al*. 2001), but with the potential to erode enamel (Pontefract *et al*. 2001).
- *Chlorine dioxide*. Frequently used against oral halitosis, its plaque-inhibitory and antiplaque effects have still to be assessed (Paraskevas *et al*. 2008; Shinada *et al*. 2010).
- *Salifluor*. 5n-octanoyl-3′-trifluormethylsalicylanilide was tested in the late 1990s with acceptable results (Furuichi *et al*. 1996; Nabi *et al*. 1996).
- *Polyhexamethylene biguanide hydrochloride*. Evaluated in study models in the early 2000s, at concentrations of 0.04–0.2%, demonstrating the capacity to inhibit plaque regrowth (Rosin *et al*. 2002; Welk *et al*. 2005).
- *Herbal products*. Herbal extracts of tea tree oil (*Melaleuca alternifolia*) have been evaluated, with conflicting results (Arweiler *et al*. 2000). Also, green tea extracts have been formulated in mouth rinse, but there is limited evidence available assessing their activity (Venkateswara *et al*. 2011).
- *Ethyl lauroyl arginate (LAE)*. LAE hydrochloride is a cationic surfactant, active against bacteria, algae, and fungi, by modifying the permeability of membranes. It is widely used in the food industry both as an antimicrobial agent and as a food preservative (E243) (Aznar *et al*. 2013). In humans, it is metabolized in lauric acid and arginine, and both are naturally present in food (Hawkins *et al*. 2009). In the oral cavity, LAE may create a barrier to prevent bacterial adhesion on tooth surfaces. Initial findings from short-term clinical studies have shown conflicting results: reductions in plaque levels and gingival inflammation after 4 weeks (Gallob *et al*. 2015); in periodontitis patients, after 3 months, similar reductions to those seen for the use of 0.12% CHX for bleeding and plaque (Pilloni *et al*. 2018); in experimental gingivitis, significant impact on plaque, but not enough to prevent the onset of gingival inflammation (Valor *et al*. 2018).

Future approaches

Future approaches for chemical biofilm control should be based on non-antimicrobial actions because of the problems associated with the excessive use of antimicrobials and the risk of an increase in the emergence of resistant strains.

- *Molecular signaling*. Because signaling molecules (such as acyl homoserine lactones) are involved in biofilm architecture and detachment, future treatment approaches may focus on quorum-sensing systems (Donlan & Costerton 2002). In addition, inhibitors of quorum-sensing processes may reduce the virulence of certain pathogens (Rasch *et al*. 2007; Harjai *et al*. 2010).
- *Inhibition of transcription genes*. If the genes that are activated or repressed during initial biofilm formation are identified and selectively targeted, this may inhibit biofilms formation (Donlan & Costerton 2002).
- *Probiotics and prebiotics*. The use of probiotic products (with putative beneficial bacterial species, such as *Streptococcus salivarius, Lactobacillus reuteri, Lactobacillus salivarius*), may have an effect on biofilm composition, either by competition or by release of bacteriocins. Some studies have reported a decrease in pathogenic species (Mayanagi *et al*. 2009) and some improvement in the levels of plaque and gingival inflammation (Krasse *et al*. 2006; Shimauchi *et al*. 2008; Harini & Anegundi 2010; Teughels *et al*. 2011; Iniesta *et al*. 2012; Montero *et al*. 2017). In addition, the use of prebiotic products, or the combination of prebiotic and probiotic formulations, may be relevant in influencing less pathogenic biofilms (Rosier *et al*. 2018).
- *Molecules interfering with bacterial adhesion*. LAE hydrochloride is an example of this mode of action.
- *Molecules interfering with the biofilm matrix*. Delmopinol is an example of this mode of action.

Delivery formats

Different formats are available to deliver agents for chemical plaque control: mouth rinses, gels, dentifrices, chewing gums, aerosols, varnishes, sustained release devices, lozenges, and irrigators (Addy & Renton-Harper 1996).

Mouth rinses

Mouth rinses are formulated with different ingredients, including colorings, flavorings, preservatives (sodium benzoate), stabilizers, and active agents.

Among the stabilizers, one of the most frequently used is alcohol. However, some controversy exists with regards to the inclusion of alcohol in mouth rinse formulations, because of the suggested association between alcohol and oropharyngeal cancer. However, critical assessment of the literature does not support this statement (Ciancio 1993; Claffey 2003), but mouth rinses containing alcohol should not be used by children, former alcoholics, and in patients with different conditions affecting the oral mucosae (e.g. lichen planus, leucoplakia). Other suggested problems associated with the presence of alcohol in mouth rinses are:

- Systemic toxicity in children: cases arising from swallowing alcohol-containing mouth rinses have been reported, but very infrequently (for review see Eley 1999).
- Intra-oral discomfort: probably concentration related (Bolanowski *et al*. 1995).
- Softening of composite hardness: this softening affect can be directly related to the percentage of alcohol in the mouth rinse (McKinney & Wu 1985; Penugonda *et al*. 1994).

Most agents for chemical plaque control have been formulated as mouth rinses, since this vehicle has a number of advantages:

- Favorable pharmacokinetics: easier to reach the effective dosage of the active agent.
- Can be used independently of the ability of the patient to perform tooth brushing.
- Allows access to difficult-to-reach areas, such as the tonsils, which can be reached by gargling.
- Easy to use and well accepted by patients.

Dentifrices

Dentifrices represent the ideal vehicle, especially from a preventive perspective, since they are used as an adjunct to the most frequently employed oral hygiene measure, which is toothbrushing. However, a number of disadvantages can be listed:

- Formulation of some active agents may be difficult.
- Pharmacokinetics are less predictable.
- Not possible to perform toothbrushing in some situations, thus limiting the use of a dentifrice: for example, patients with disabilities, after oral surgery, intermaxillary fixations, etc.
- Does not reach difficult-to-access areas, such as the tonsils or the dorsum of the tongue.

The ingredients in a dentifrice formulation are:

- *Abrasives*. These determine the consistency of the dentifrice and ease dental plaque and staining removal. However, higher dentifrice abrasivity does not seem to contribute to increased plaque removal with a manual toothbrush. It appears that the mechanical action provided by the use of a toothbrush is the main factor in the plaque-removing process (Paraskevas *et al*. 2006). The most common abrasives are calcium carbonate, alumina, dicalcium phosphate, and silica.

- *Detergent*. The most widely use is SLS, which provides some antimicrobial action (Jenkins *et al*. 1991a, b), although no evidence is available to support its effectiveness in plaque removal.
- *Thickeners*. These include silica and gums, and they influence the viscosity of the toothpaste.
- *Sweeteners*, such as sodium saccharin.
- *Humectants*. These prevent the toothpaste from drying up; glycerine and sorbitol are the most commonly used.
- *Flavorings*, such as mint, strawberry.
- *Coloring agents*.
- *Active agents*, including fluorides, triclosan, CHX (with some difficulties in the formulation, due to the interference with anionic detergents and with flavorings), CPC, and other active agents (anticalculus agents, whitening products, desensitizing agents).

Gels

Gels do not include abrasives or detergents. Active agents are formulated more easily in gels than in dentifrice, but disadvantages are similar: less predictable pharmacokinetics, impossible to use in some clinical situations, and lack of access to some difficult-to-reach areas.

CHX gels are available with different concentrations, including 0.1%, 0.12%, 0.2%, 0.5%, and 1%, to be used with toothbrushing or applied in trays. For tooth brushing, the amount of CHX delivered is not predictable (Saxen *et al*. 1976). When a gel is applied in a dental tray, a reduction in the levels of plaque and inflammation has been reported (Francis *et al*. 1987b; Pannuti *et al*. 2003; Slot *et al*. 2010), although the acceptance by patients with disabilities and therapy providers was not high (Francis *et al*. 1987a).

CHX gels may also be used for other purposes, such as the prevention of alveolitis after tooth extraction (Hita-Iglesias *et al*. 2008; Minguez-Serra *et al*. 2009). Its use has also been suggested as part of the protocol for full-mouth disinfection, including tongue brushing with a 1% CHX gel for 1 minute and subgingival irrigation of pockets with 1% CHX gel (Bollen *et al*. 1996, 1998). More recently, it has been evaluated in peri-implant mucositis therapy (Heitz-Mayfield *et al*. 2011), with limited effects.

Gels containing 0.4% stannous fluoride have also been evaluated, reporting reductions in gingival inflammation and in bleeding on probing (Tinanoff *et al*. 1989; Boyd & Chun 1994).

Chewing gums

CHX has been formulated in chewing gums for use as an adjunct to or even short-term replacement for mechanical plaque control. A reduction in the levels of plaque and gingival inflammation has been reported (Ainamo & Etemadzadeh 1987; Smith *et al*. 1996; Simons *et al*. 2001; Kolahi *et al*. 2008).

Varnishes

CHX varnishes have been used in the prevention of root caries (Clavero *et al*. 2006; Baca *et al*. 2009), although no solid evidence is available to support their use (Bader *et al*. 2001; Zhang *et al*. 2006).

Lozenges

Both CPC and CHX have been formulated as lozenges. For CPC lozenges, interactions with other ingredients of the formulation have been observed (Richards *et al*. 1996). Clinical use is associated with a reduction in levels of plaque and gingival inflammation, although smaller than those achieved with a CHX mouth rinse (Vandekerckhove *et al*. 1995). Reductions in plaque and gingivitis levels have also been reported for CHX lozenges. The mean plaque score was reduced by 62.8% (from 2.38 to 0.89; P <0.0001), after 1 week of usage (Kaufman *et al*. 1989).

Irrigators

The use of irrigators has been suggested to remove food debris from teeth and dental restorations. It may help to improve oral health in subjects not using interdental devices (Frascella *et al*. 2000). The use of irrigators is not associated with an improvement in plaque levels, but it may have some effect on gingival inflammation (Husseini *et al*. 2008). Different agents can be used with irrigators, and good results have been reported for CHX (Lang & Raber 1981).

Sprays

The advantage of aerosols is that the agent is used exactly where it is needed. However, the dosage is not predictable. Aerosols with 0.2% CHX have been used in patients with disabilities to prevent biofilm formation (Francis *et al*. 1987b; Kalaga *et al*. 1989b). Their use on all dental surfaces is associated with a reduction in plaque levels similar to that obtained with mouth rinsing, but the adverse effects are also the same (Francis *et al*. 1987b; Kalaga *et al*. 1989a). Recent evidence suggests that oral sprays are an acceptable delivery method for antiseptic agents (Zhang *et al*. 2019).

Sustained-release devices

CHX is also present in sustained release devices, designed with a therapeutic purpose, and includes chips, gels, and xanthan gels. A review of their effects can be found in Chapter 37.

Selection of delivery format

The most frequently used delivery formats for chemical biofilm control are dentifrices and mouth rinses, either alone or simultaneously. The obvious benefit

of dentifrice delivery is that no other delivery format is needed; a dentifrice is used by the majority of patients. However, mouth rinse delivery offers better distribution around the mouth (Serrano *et al*. 2015) and better pharmacokinetic properties (Cummins & Creeth 1992).

In clinical studies, mouth rinses normally show greater benefits in terms of plaque and gingival indices: in the systematic review by Serrano *et al*. (2015), the WMDs in the Turesky plaque index were 0.425 for dentifrices and 0.522 for mouth rinses, whereas for the modified gingival index (MGI) WMDs were 0.355 and 0.439, respectively. In the review by Figuero *et al*. (2020), the results in changes in plaque indices showed, again, a larger impact for mouth rinses ($n = 43$; standardized-WMD = −1.231; 95% CI [−1.490; −0.973]; $P < 0.001$) than for dentifrices ($n = 45$; standardized-WMD = −0.803; 95% CI [−1.054; −0.552]; $P < 0.001$), with the meta-regression showing a tendency towards statistically significant differences between dentifrices and mouth rinses (coefficient = 0.423; 95% CI [−0.169; 0.864]; $P = 0.059$). In addition, when plaque levels were assessed as percentage of sites with plaque, mouth rinses offered better results than dentifrices (27.70% versus 14.00%, respectively), with statistically significant differences in the meta-regression (coefficient = 13.80%; 95% CI [2.40%; 25.10%]; $P = 0.020$).

Therefore, some evidence suggests that the adjunctive use of mouth rinses may provide better outcomes than that of dentifrices (Figuero *et al*. 2020). However, the evidence is conflictive and statistically significant differences were only observed for secondary outcomes. In addition, direct comparisons between similar agents/formulations, delivered either as dentifrices or mouth rinses, are not available.

It has been suggested (Serrano *et al*. 2015), based on the reported findings, that mouth rinses may be the delivery format of choice for periodontitis patients, while dentifrices may be more suitable for less susceptible subjects, in which the added effect of chemical biofilm control is less relevant, and the lower cost of using only one product (namely, dentifrice) may be justified.

Clinical indications for chemical plaque control: selection of agents

As has been reviewed, different agents (alone or in combination) in different delivery formats and formulations are available for clinical use. In addition, many different indications have been proposed. Therefore, it may be challenging for the clinician to decide whether or not to prescribe a chemical oral hygiene product and, if the evaluation favors a prescription, which one should be prescribed, as well as which formulation, in which delivery format, at which dosage, and for how long. In this section, some recommendations are provided, based on the scientific evidence available. However, due to the limitations of the evidence, all suggestions should be viewed with caution and each clinical case considered individually.

Different clinical scenarios, depending on the duration of product usage and the main objective of the intervention, are considered: single use, short-term use (either with a preventive or a therapeutic aim), and long-term use (either for a preventive or a therapeutic aim).

Single use

Different objectives may be considered for a single use.

To decrease the bacterial load

CHX has been shown to reduce the presence of bacteria in aerosols generated during different oral interventions (e.g. instrumentation with sonic or ultrasonic devices), decreasing the risk of cross contamination in a dental setting (Stirrups, 1987; Worrall *et al*. 1987; Logothetis & Martinez-Welles 1995). Also, a single rinsing with essential oils has been shown to affect bacterial presence in aerosols (Fine *et al*. 1993).

To decrease the risk of bacteremia

Different studies have assessed the effect of CHX usage on the risk of bacteremia associated with dental interventions (scaling, tooth extraction), both by means of rinsing (Jokinen 1978; Rahn *et al*. 1995; Lockhart 1996; Brown *et al*. 1998; Tomas *et al*. 2007) or subgingival irrigation (MacFarlane *et al*. 1984). Other active agents have also been evaluated: essentials oils (Fine *et al*. 1993; DePaola *et al*. 1996; Fine *et al*. 2010) or povidone iodine, both as mouth rinse (Jokinen 1978) or subgingival irrigation (Rahn *et al*. 1995). However, after the evaluation of the available evidence, a recent consensus report concluded that CHX, used as an oral rinse, does not significantly reduce the level of bacteremia following dental procedures (Centre for Clinical Practice (NICE) 2008). In addition, the American Heart Association concluded: "topical antiseptic rinses do not penetrate beyond 3 mm into the periodontal pocket and, therefore, do not reach areas of ulcerated tissue where bacteria most often gain entrance to the circulation. On the basis of these data, it is unlikely that topical antiseptics are effective in significantly reducing the frequency, magnitude, and duration of bacteremia associated with a dental procedure" (Wilson *et al*. 2007).

To decrease the risk of infection of the surgical area

CHX has been evaluated as a preoperative measure before oral surgery, to decrease bacterial load and decrease the risk of postoperative infection (Worrall *et al*. 1987).

Summary: The general aim of single use is to reduce the bacterial load in the oral cavity before

an intervention. The highest bactericidal action is desirable and is demonstrated by CHX formulations both *in vitro* and *in vivo*. Because of the single use, side effects are not common and if present, they will rapidly disappear. In case of intolerance, other active agents may be considered, such as CPC (Pitten & Kramer 2001), essentials oils (Fine *et al*. 1993, 2010; DePaola *et al*. 1996), or povidone iodine (Jokinen 1978; Rahn *et al*. 1995).

Short-term use for the prevention of dental biofilm formation

In clinical situations in which mechanical control may be limited due to discomfort or postoperative instructions to avoid mechanical contact with a treated area, the use of chemical plaque control may have a preventive objective in a short-term basis. The most widely use agent for preventive indications (aiming to compensate for the limitations of mechanical biofilm control) is CHX, because side effects will be limited due to the short-term usage.

After subgingival instrumentation or periodontal surgery

When mechanical control may be limited due to discomfort or to postoperative instructions to avoid mechanical contact with the treated area (e.g. regenerative or mucogingival surgery), both CHX mouth rinses (Sanz *et al*. 1989; Christie *et al*. 1998; Eley 1999) and essential oils mouth rinses (Zambon *et al*. 1989; Laspisa *et al*. 1994) have demonstrated benefits. Use of antiseptic products should be maintained until mechanical biofilm control is again adequate.

The European Federation of Periodontology (EFP) S3 Level Clinical Practice Guideline (CPG), for the treatment of stage I–III periodontitis, included a recommendation of the adjunctive use (to subgingival instrumentation) of chlorhexidine mouth rinses in step 2 of periodontal therapy, which reads "adjunctive antiseptics may be considered, specifically chlorhexidine mouth rinses for a limited period of time, in periodontitis therapy, as adjuncts to mechanical debridement, in specific cases" (Sanz *et al*. 2020). The recommendation was based on a previously published systematic review (da Costa *et al*. 2017).

Prevention of postsurgical infection

When CHX rinses were used during postsurgical care, a lower infection rate (17 infections in 900 procedures, 1.89%) was observed, compared with procedures with no CHX as part of the postsurgical care (five infections in 153 procedures, 3.27%) (Powell *et al*. 2005). In addition, a lower incidence of post-extraction alveolitis has been reported with the use of a 0.2% CHX gel (Hita-Iglesias *et al*. 2008; Minguez-Serra *et al*. 2009) or with a 0.2% CHX rinse (Tjernberg 1979).

Patients with intermaxillary fixations

After bone fractures or after orthognathic or cosmetic maxillary surgeries, when no mechanical hygiene is possible, CHX mouth rinses have shown to be useful in biofilm formation prevention (Nash & Addy 1979).

Patients with mucosal or gingival acute infections

In these patients, pain precludes mechanical hygiene, and CHX mouth rinses may be useful in biofilm formation prevention (Eley 1999).

Short-term use for therapy

Other clinical situations may require the short-term use of antiseptic products with a therapeutic aim. The most widely used agent for therapeutic indications (aiming to control the pathogenic microorganisms) is CHX, since the risk of side effects of CHX usage will be limited due to the short-term usage. Side effects, if they appear, are easily reversible.

Gingivitis therapy

Chemical agents may have limited antimicrobial activity against an organized biofilm, because of the difficulties of penetration and action. Therefore, chemical agents should be used in conjunction with mechanical debridement. The recommended agent is a CHX mouth rinse (Hartnett & Shiloah 1991). Other agents have been evaluated in necrotizing gingivitis, such as oxygenating agents and iodine povidone (Wade *et al*. 1966; Addy & Llewelyn 1978).

Candidiasis therapy

CHX mouth rinses have been proposed as an alternative in candidiasis treatment (Ellepola & Samaranayake 2001; Torres *et al*. 2007). However, as sole therapy, complete resolution is not achieved, and it is more effective in combination with specific antifungal agents (e.g. itraconazole) (Simonetti *et al*. 1988). However, a possible interaction between CHX and nystatin has been proposed, due to the formation of a less soluble salt (Barkvoll & Attramadal 1989). Also, as part of candidiasis therapy, the immersion of the dental prosthesis in 0.2% CHX is effective in eliminating *Candida* spp. from the prosthesis (Olsen 1975; Uludamar *et al*. 2011). In cases of intolerance to CHX, CPC mouth rinses have been proposed as an alternative (Pitten & Kramer 2001).

Peri-implant mucositis therapy

Treatment strategies have been developed based on mechanical or chemical plaque control, alone or in combination, and some of them have been evaluated in RCTs. No additive effect (over mechanical

control) from the application of a CHX gel was observed (Thone-Muhling *et al*. 2010; Heitz-Mayfield *et al*. 2011), as was also true for irrigation of the sulcus (Porras *et al*. 2002). In one study, CHX irrigation provided better results that CHX rinsing (Felo *et al*. 1997). In home-use studies, an essential oil mouth rinse (Ciancio *et al*. 1995), a triclosan/copolymer dentifrice (Ramberg *et al*. 2009), and a 0.03% CHX and 0.05% CPC mouth rinse (Pulcini *et al*. 2019) have demonstrated better clinical results than the negative control.

Peri-implantitis therapy

Adjunctive CHX application in the treatment of peri-implantitis lesions has been shown to have only limited effects on clinical and microbiological parameters (Renvert *et al*. 2008).

In periodontitis therapy

The adjunctive use of antiseptics (especially CHX mouth rinses) has been evaluated, most frequently in the full-mouth disinfection approach (Quirynen *et al*. 1995, 2000; Greenstein 2002, 2004). The use of different CHX formulations (including mouth rinse, spray, irrigation, gel for the tongue dorsum) in addition to subgingival instrumentation within 24 hours showed additional benefits in some studies (Quirynen *et al*. 2000). However, systematic reviews have not confirmed these results, although modest benefits favoring full-mouth approaches were observed (Eberhard *et al*. 2008a, b; Lang *et al*. 2008). The use of CHX mouth rinse during the step 2 periodontal therapy may help in controlling the dental biofilm, resulting in additional benefits in terms of clinical and microbiological parameters (Faveri *et al*. 2006; Feres *et al*. 2009).

Long-term use for the prevention of dental biofilm formation

Patients carrying fixed or removable orthodontic appliances

The presence of these appliances makes mechanical control more difficult, facilitates plaque retention, and thus promotes gingivitis development (Ristic *et al*. 2007; Levin *et al*. 2008). Additionally, many orthodontic patients, especially children and adolescents, fail to floss because they find this procedure time-consuming and tedious in the presence of orthodontic arch wires (Alexander 1993). A common strategy to improve mechanical plaque removal in these patients is the addition, as part of the oral hygiene regimen, of a chemotherapeutic antimicrobial agent (Ainamo 1977). The efficacy of different active ingredients, such as CHX (Brightman *et al*. 1991; Anderson *et al*. 1997; Chin *et al*. 2006; Olympio *et al*. 2006), essential oils (Tufekci *et al*. 2008), amine/stannous fluoride (Ogaard *et al*. 2006), CPC (Herrera *et al*. 2018), or sanguinarine (Hannah *et al*. 1989) in the form of mouth rinses, toothpastes or gels, has been evaluated in clinical studies. Most of these clinical studies have reported significant benefits from the adjunctive use of these products, although the magnitude of the reported benefits might not have clear clinical relevance. In addition, the use of some of the formulations was associated with adverse effects (such as staining with the use of CHX).

Patients with disabilities

In patients with physical or mental disabilities, the use of CHX improves plaque and gingival health (Storhaug 1977). In these patients, a spray (0.2% CHX) is preferred (Francis *et al*. 1987a, b; Kalaga *et al*. 1989b; Clavero *et al*. 2003).

Patients with gingival overgrowth or enlargement

In these patients, mechanical control is more difficult and CHX mouth rinse may be helpful (O'Neil & Figures 1982; Saravia *et al*. 1990; Francetti *et al*. 1991).

Periodontitis patients

Together with an adequate professional supportive periodontal therapy program, chemical agents may be recommended to improve biofilm control and to decrease the risk of disease progression. A careful consideration of the risk-to-benefit ratio should be made, because these patients will be in supportive therapy for life. Lower dosage CHX mouth rinses have been evaluated and a formulation with 0.05% CHX and 0.05% CPC reported beneficial effects with limited adverse events (Soers *et al*. 2003; Santos *et al*. 2004; Quirynen *et al*. 2005; Escribano *et al*. 2010). Also, a dentifrice with triclosan and copolymer, evaluated for 2 years, demonstrated a significant reduction in the detection of deep pockets and sites with clinical attachment loss and bone loss (Rosling *et al*. 1997a, b; Bruhn *et al*. 2002).

In a systematic review (Figuero *et al*. 2020), the impact of chemical plaque control was compared between periodontitis patients with gingival inflammation and gingivitis patients. Changes in gingival indices tended to be greater in periodontitis patients ($n = 16$; standardized-WMD = −1.564; 95% CI [−2.197; −0.931]; $P < 0.001$) versus gingivitis patients (= 44; standardized-WMD = −1.289, 95% CI [−1.560; −1.018]; $P < 0.001$), but meta-regression did not find statistically significant differences between them (coefficient = −0.266; 95% CI [−1.027; 0.495]; $P = 0.487$).

The EFP S3 Level CPG, for the treatment of stage I–III periodontitis, included different recommendations on the adjunctive use (to mechanical supragingival biofilm control) of mouth rinses and dentifrices for gingival inflammation control, as part of the step

Supportive Periodontal Care. It was highlighted that "adjunctive measures, including antiseptic, may be considered in specific cases, as part of a personalized treatment approach" (Sanz *et al*. 2020). Among the recommended agents, CHX, essential oils, and cetylpyridinium chloride were listed for mouth rinse formulations, and CHX, triclosan-copolymer, and stannous fluoride-sodium hexametaphosphate, for dentifrice formulations.

Patients with dental implants

The use of different agents (CHX, triclosan, stannous fluoride, essentials oils) has been suggested to favor biofilm control and decrease the risk of peri-implant diseases (Ciancio *et al*. 1995; Di Carlo *et al*. 2008; Sreenivasan *et al*. 2011). In RCTs, triclosan/copolymer significantly improved clinical and microbiological variables, as compared with a fluoride dentifrice, after 6 months (Sreenivasan *et al*. 2011). A toothpaste containing 0.3% triclosan was more effective than a toothpaste without triclosan in maintaining a healthy peri-implant environment around treated implants and implants with no history of peri-implantitis during a 2-year maintenance program (Stewart *et al*. 2018); conversely, no influence in implant survival and clinical variables was observed for the use of 0.12% CHX mouth rinses in a 5-year study (Truhlar *et al*. 2000).

General population

The main aim is to allow for the presence of a biofilm in equilibrium with the host response to maintain periodontal health. Different agents have demonstrated an antiplaque effect in 6-month trials, including mouth rinses with CHX (Gunsolley 2006), with essentials oils (Stoeken *et al*. 2007), with delmopinol (Addy *et al*. 2007), with CPC (Gunsolley 2006), or with dentifrices with triclosan and copolymer (Hioe and van der Weijden 2005; Gunsolley 2006), and with stannous fluoride (Gunsolley 2006; Paraskevas & van der Weijden 2006).

The benefit of the daily usage of antiseptic products in a general population is a subject of controversy. However, the results of available studies reflect clinical benefits beyond those obtained with improvement in mechanical oral hygiene due to oral hygiene instructions. As suggested by the systematic review by Gunsolley (2006), reductions observed in the placebo groups in plaque (15.7, standard deviation SD = 18.7) and gingivitis (18.5, SD = 15.6) are associated with the Hawthorne effect and to oral hygiene instructions, and should mimic efficacy of oral hygiene instructions provided in clinical practice. The added benefit of the addition of CHX or essentials oils mouth rinses were evident and significant (for CHX 40.4, SD = 11.5 in plaque and 28.7, SD = 6.5 in gingivitis; for essentials oils, 27.0, SD = 11.0 and 18.2, SD = 9.0, respectively).

Another relevant question is which product for chemical biofilm control is the most efficacious. As discussed before, the answer should be different for dentifrices and for mouth rinses, and it is based on the results of two systematic reviews with conventional meta-analysis (Serrano *et al*. 2015; Figuero *et al*. 2020) and two with network meta-analyses (Escribano *et al*. 2016; Figuero *et al*. 2019).

For mouth rinses, in the systematic review by Figuero *et al*. (2020), 11 different mouth rinse formulations were included, with a large variability in the number of studies testing each formulation. The studies showing the largest impact on gingival inflammation indices, providing that more than one study was available, were essential oils (standardized-WMD = 2.248, $n = 10$), cetylpyridinium chloride (standardized-WMD = 1.499, $n = 5$), and CHX at high concentration (standardized-WMD = 1.144, $n = 5$). In network meta-analyses, CHX and essential oil mouth rinses were ranked as the most efficacious agents in terms of changes in plaque and gingival indices (Escribano *et al*. 2016; Figuero *et al*. 2019).

For dentifrices, in the systematic review by Figuero *et al*. (2020), 14 different dentifrice formulations were considered, also with a large variability in the number of available studies. The formulations showing the largest impact on gingival inflammation indices, providing that more than one study was available, were stannous fluoride with sodium hexametaphosphate (standardized-WMD = 1.503, $n = 2$), triclosan and copolymer (standardized-WMD = 1.313, n–18), and CHX (standardized-WMD = 1.278, $n = 2$). In network meta-analyses, CHX and triclosan and copolymer were the most effective agents for plaque reduction, but no clear differences were observed for gingival index control (Escribano *et al*. 2016; Figuero *et al*. 2019).

Long-term use for the prevention of other oral conditions

Predisposed patients, with high risk of suffering oral infections

In patients with blood dyscrasia who are immunesuppressed, the use of CHX mouth rinses may help to prevent oral or systemic complications, but they may not be useful once the infection appears (Eley 1999). In patients with mechanical ventilation, reduction of aerobic pathogens in the oropharyngeal tract was observed in patients using a CHX gel (Fourrier *et al*. 2005). Studies with CHX have demonstrated its capacity to prevent oral complications, such as the occurrence of chronic or opportunistic infections, including *Candida* spp. infections in high-risk patients (irradiated patients, patients in chemotherapy, or bone marrow transplant recipients) (for review, see Addy & Moran 1997).

Oral mucositis prevention (associated with radiation or chemotherapy in head and neck cancer patients)

CHX rinses have proposed as part of combined treatments to prevent or treat oral mucositis. CHX mouth rinses in the prevention of oral mucositis have been evaluated in numerous RCTs (Ferretti *et al*. 1990; Spijkervet *et al*. 1990; Epstein *et al*. 1992; Foote *et al*. 1994; Dodd *et al*. 1996; Pitten *et al*. 2003; Lanzos *et al*. 2010, 2011), but the outcomes were quite different. Seven studies were included in a meta-analysis (Stokman *et al*. 2006) that showed no effect of CHX in the prevention of mucositis in chemotherapy and radiotherapy patients (odds ratio 0.7; 95% CI 0.43–1.12).

Caries prevention

CHX use has been shown to reduce counts of *Streptococcus mutans* in at-risk patients (Ullsfoss *et al*. 1994; Quirynen *et al*. 2005). The best vehicle was varnish, followed by gel and mouth rinse (Emilson & Fornell 1976; Emilson 1994). Also, a reduction in caries incidence was reported in dentifrice with sodium fluoride (Dolles & Gjermo 1980; FDI Commission 2002a). Based on the previous findings, the use of CHX and fluoride together was suggested, but different studies reported poorer results for CHX formulations with sodium fluoride (Shapiro *et al*. 2002; Herrera *et al*. 2003). Essential oil mouth rinses have also been shown to reduce *S. mutans* levels (Fine *et al*. 2000; Agarwal & Nagesh 2011), but no studies on caries incidence are available. Dentifrices with triclosan and copolymer or a zinc salt, have demonstrated superior anticaries activity than fluoride dentifrices (Panagakos *et al*. 2005), even in long-term studies (Mann *et al*. 2001). In high-risk patients, amine and stannous fluoride may also be recommended, based on their proven remineralization and anticaries action (Tinanoff *et al*. 1980; Paraskevas *et al*. 2004).

Candidiasis prevention

CHX has been evaluated with regards to candidiasis prevention in patients with systemic diseases and in patients with a dental prosthesis (Ferretti *et al*. 1987, 1988; Toth *et al*. 1990; Barasch *et al*. 2004; Elad *et al*. 2006).

Prevention of recurrent aphthous ulcers

CHX use may reduce the incidence, duration, and severity of ulcers, including in patients with fixed orthodontic appliances (Shaw *et al*. 1984). Triclosan formulations may also decrease the incidence of oral ulcers (Skaare *et al*. 1996).

Halitosis therapy and secondary prevention

Different chemical agents and formulations have been evaluated, with two main aims: antibacterial and interference with volatilization of odoriferous compounds. Among the most evaluated agents, the following may be highlighted: essential oils mouth rinses (Pitts *et al*. 1983; Kozlovsky *et al*. 1996); triclosan with zinc or copolymer (van Steenberghe 1997; Sharma *et al*. 1999; Niles *et al*. 2003; Hu *et al*. 2005); or CHX, especially if combined with zinc salts and CPC (Roldan *et al*. 2003b; Winkel *et al*. 2003; Roldan *et al*. 2004). In order to be effective, these agents need to be used in conjunction with adequate oral hygiene and tongue scrapping or brushing (Roldan *et al*. 2003a). This topic is covered in detail in Chapter 28.

Conclusion

The main aim of supragingival biofilm control would be to allow for the presence of a biofilm in equilibrium with the host response, in order to maintain a health status. Due to the limitations of mechanical biofilm control, chemical control has been extensively evaluated and is widely used.

Although different vehicles are available to deliver the active agents, two of them can be highlighted: mouth rinses, due to the favorable pharmacokinetics and the ease of use, and dentifrices, due the concomitant use with tooth brushing, their pharmacokinetic profiles are less favorable and they are more difficult to formulate.

Most of the agents are antimicrobials, but other mechanisms of action have also been proposed and some marketed effective agents are not antimicrobials (e.g. delmopinol).

In the evaluation of the different agents and formulations, 6-month, home-use, RCTs provide the highest level of evidence, especially when their results are pooled in systematic reviews with meta-analyses. For mouth rinses, those showing the largest impact on gingival inflammation indices were essential oils, cetylpyridinium chloride, and CHX, at high concentrations; CHX and essential oil mouth rinses were the most efficacious agents in terms of changes in plaque and gingival indices (see Table 29-1). For dentifrices, stannous fluoride with sodium hexametaphosphate, triclosan, and copolymer, and CHX were the formulations that showed the largest impact on gingival inflammation indices; CHX and triclosan with copolymer were the most effective agents for plaque reduction, but no clear differences were observed for gingival index control (see Table 29-2).

However, CHX products are not free of adverse effect, especially tooth staining. Therefore, in a clinical situation in which the product is needed for a prolonged period of time, the risk-to-benefit ratio should be evaluated. In some clinical situations, the benefits will compensate for the adverse effects (staining), such as in patients with disabilities or with high systemic risk. In clinical scenarios in which the benefits do not compensate for the adverse effects, other alternatives with less effect but also with fewer adverse events should be considered.

Table 29-1 Summary of meta-analyses of 6-month, home-use, randomized clinical trials: plaque levels.

Active agent (delivery format)	Study	*n*	WMD/ SMD	*P* value	95% CI	Heterogeneity	
						P value, I^2	Method
Chlorhexidine (mouth rinse)	Gunsolley (2006)	6	1.040	*P* <0.001	NA	Low, I^2 <25%[a]	Fixed??
	Serrano *et al*. (2015)	3	0.640	*P* = 0.000	0.75–0.52	*P* = 0.149, I^2 = 47.4%	Fixed
	Escribano *et al*. (2016)	4	0.70	*P* = 0.000	0.88–0.54	I^2 = 58.1%	Random
	James *et al*. (2017)	11	1.43	*P* <0.00001	1.76–1.10	*P* <0.00001, I^2 = 88%	Random
	Jassoma *et al*. (2019)	18	1.79	*P* <0.00001	1.39–2.19	I^2 = 82%	Random
	Figuero *et al*. (2020)	6	1.45[SMD]	*P* <0.001	1.80–1.11	*P* <0.046, I^2 = 55.8%	Random
Essential oils (mouth rinse)	Gunsolley (2006)	20	0.852	*P* <0.0001	NA	Positive, I^2 >25%[a]	NA
	Stoeken *et al*. (2007)	7	0.83	*P* <0.00001	0.53–1.13	*P* <0.00001, I^2 = 96.1%	Random
	van Leeuwen *et al*. (2014)	4	0.39	*P* <0.00001	0.30–0.47	*P* = 041, I^2 = 0%	Random
	Serrano *et al*. (2015)	9	0.827	*P* = 0.000	1.05–0.60	*P* = 0.000, I^2 = 97%	Random
	Escribano *et al*. (2016)	9	0.83	*P* = 0.000	1.05–0.60	I^2 = 97%	Random
	Figuero *et al*. (2020)	10	1.94[SMD]	*P* <0.001	2.69–1.19	*P* <0.001, I^2 = 97.8%	Random
Cetylpyridinium chloride (mouth rinse)	Haps *et al*. (2008)	3	0.42	*P* <0.00001	0.53–0.31	*P* = 0.06, I^2 = 58.8%	Random
	Serrano *et al*. (2015)	10	0.392	*P* = 0.000	0.54–0.24	*P* = 0.000, I^2 = 93.9%	Random
	Escribano *et al*. (2016)	6	0.48	*P* = 0.000	0.68–0.29	I^2 = 90.9%	Random
	Figuero *et al*. (2020)	7	1.08[SMD]	*P* <0.001	1.41–0.75	*P* <0.001, I^2 = 80.6%	Random
Delmopinol (mouth rinse)	Addy *et al*. (2007)	8	0.34	*P* <0.00001	0.29–0.39	Low, I^2 <25%[a]	Fixed
	Serrano *et al*. (2015)	3	0.144	*P* = 0.001	0.23–0.05	*P* = 0.492, I^2 = 0%	Random
	Escribano *et al*. (2016)	2	0.15	*P* = 0.01	0.25–0.05	I^2 = 0%	Random
	Figuero *et al*. (2020)	3	0.26[SMD]	*P* <0.001	0.41–0.10	*P* <0.52, I^2 = 0%	Random
Triclosan and copolymer (dentifrice)	Davies *et al*. (2004)	17	0.823	*P* <0.0001	NA	High, I^2 >75%	Random
	Gunsolley (2006)	9	0.48	*P* <0.0001	0.24–0.73	*P* <0.00001, I^2 = 97.2%	Random
	Hioe & vdW. (2005)	11	0.48	*P* <0.00001	0.32–0.64	*P* <0.00001, I^2 = 95.7%	Random
	Riley & Lamont (2013)	20	0.47	*P* <0.00001	0.60–0.34	*P* <0.00001, I^2 = 94%	Random
	Serrano *et al*. (2015)	18	0.447	*P* = 0.000	0.59–0.30	*P* = 0.000, I^2 = 95.4%	Random
	Escribano *et al*. (2016)	16	0.49	*P* = 0.000	0.60–0.28	I^2 = 94.2%	Random
	Figuero et al. (2020)	23	1.16[SMD]	*P* <0.001	1.54–0.78	*P* <0.001, I^2 = 95.3%	Random
Triclosan and zinc citrate (dentifrice)	Gunsolley (2006)	6	0.07	*P* <0.00001	0.05–0.10	*P* = 0.53, I^2 = 0%	Random
	Hioe and vdW. (2005)	?	NA	NA	NA	NA	NA
	Serrano *et al*. (2015)	1	0.120	NS	-	-	-
	Escribano *et al*. (2016)	1	0.12	NS	-	-	-
	Figuero *et al*. (2020)	6	0.37[SMD]	*P* = 0.008	0.64–0.09	*P* = 0.01, I^2 = 67.1%	Random
Stannous fluoride (dentifrice)	Gunsolley (2006)	5	0.168	Significant	NA	Low, I^2 <25%[a]	NA Random
	Paraskevas & vdW. (2006)	4	0.31	*P* = 0.01	0.07–0.54	*P* <0.0001, I^2 = 91.7%	Fixed
	Serrano *et al*. (2015)	3	0.112	*P* = 0.002	0.18–0.04	*P* = 0.062, I^2 = 61.4%	Random
	Escribano *et al*. (2016)	5	0.28	*P* = 0.01	0.49–0.07	I^2 = 90.7%	
Stannous fluoride and SHMP (dentifrice)	Figuero *et al*. (2020)	1	0.55[SMD]	*P* = 0.002	0.90–0.19	-	-
Chlorhexidine (dentifrice)	Serrano *et al*. (2015)	4	0.687	*P* = 0.000	1.31–0.05	*P* = 0.000, I^2 = 97.4%	Random
	Figuero *et al*. (2020)	3	1.51[SMD]	*P* = 0.01	2.65–0.36	*P* <0.001, I^2 = 96%	Random

n, number of studies included in each meta-analysis; [a]Estimated; WMD, weighted mean difference, between test and control groups; SMD, standardized weighted mean difference, between test and control groups; CI, confidence interval; NA, not available, SHMP, sodium hexametaphosphate; vdW, van der Weijden.

Table 29-2 Summary of meta-analyses of 6-month home-use randomized clinical trials: gingivitis levels.

Active agent (delivery format)	Reference	*n*	WMD/ SMD	*P* value	95% CI	Heterogeneity	
						P value, I^2	Method
Chlorhexidine (mouth rinse)	Gunsolley (2006)	6	0.563	*P* <0.001	NA	*P* = 0.013	NA
	Serrano *et al*. (2015)	6	0.166	*P* = 0.000	0.25–0.08	*P* <0.030, I^2 = 59.5%	Random
	James *et al*. (2017)	13	0.20	*P* = 0.00002	0.30–0.11	*P* <0.00001, I^2 = 96%	Random
	Figuero *et al*. (2019)	3	0.95[SMD]	*P* <0.05	0.70–1.21	I^2 = 0%	Random
	Figuero *et al*. (2020)	5	1.14[SMD]	*P* <0.001	1.37–0.91	*P* <0.442, I^2 = 0%	Random
Essential oils (mouth rinse)	Gunsolley (2006)	8	0.306	*P* = 0.006	NA	*P* < 0.001	NA
	Stoeken *et al*. (2007)	8	0.32	*P* <0.00001	0.19–0.46	*P* <0.00001, I^2 = 96.7%	Random
	van Leeuwen *et al*. (2014)	4	0.36	*P* <0.00001	0.26–0.62	*P* = 0004, I^2 = 92%	Fixed
	Serrano *et al*. (2015)	2	0.133	*P* <0.000	0.19–0.07	*P* = 0.000, I^2 = 45.1%	Fixed
	Figuero *et al*. (2019)	9	1.47[SMD]	*P* <0.05	0.72–2.22	I^2 = 97.7%	Random
	Figuero *et al*. (2020)	10	2.25[SMD]	*P* <0.001	3.24–1.25	*P* <0.001, I^2 = 98.6%	Random
Cetylpyridinium chloride (mouth rinse)	Haps *et al*. (2008)	3	0.15	*P* = 0.00003	0.07–0.23	*P* = 0.0001, I^2 = 87%	Random
	Serrano *et al*. (2015)	4	0.325	*P* = 0.002	0.53–0.11	*P* = 0.000, I^2 = 95.3%	Random
	Figuero *et al*. (2019)	3	0.62[SMD]	*P* <0.05	0.27–0.96	I^2 = 75.2%	Random
	Figuero *et al*. (2020)	5	1.49[SMD]	*P* <0.001	2.33–0.66	*P* <0.001, I^2 = 96.3%	Random
Delmopinol (mouth rinse)	Addy *et al*. (2007)	8	0.10	*P* <0.00001	0.06–0.14	Low, I^2 <25%[a]	Fixed
	Figuero *et al*. (2019)	1	0.06[SMD]	NS	-	-	Random
	Figuero *et al*. (2020)	2	0.06[SMD]	NS	-	-	Random
Triclosa and copolymer (dentifrice)	Davies *et al*. (2004)	16	0.858	*P* <0.001	NA	*P* < 0.001	Random
	Gunsolley (2006)	8	0.24	*P* <0.0001	0.13–0.35	*P* <0.00001, I^2 = 98.3%	Random
	Hioe & vdW. (2005)	14	0.26	*P* <0.00001	0.18–0.34	*P* <0.00001, I^2 = 96.5%	NA
	Riley & Lamont (2013)	20	0.27	*P* <0.00001	0.33–0.21	*P* <0.00001, I^2 = 95%	Random
	Serrano *et al*. (2015)	16	0.241	*P* = 0.000	0.30–0.17	*P* = 0.000, I^2 = 91.2%	Random
	Figuero *et al*. (2019)	17	1.17[SMD]	*P* <0.05	0.80–1.54	I^2 = 94.6%	Random
	Figuero *et al*. (2020)	18	1.31[SMD]	*P* <0.001	1.71–0.91	*P* <0.001, I^2 = 95.1%	Random
Triclosan and zinc citrate (dentifrice)	Gunsolley (2006)	4	10.81%[b]	*P* <0.00001	8.93-12.69	*P* = 0.48, I^2 = 0%	Random
	Hioe & vdW. (2005)	1	NA	NA	NA	NA	NA
Stannous fluoride (dentifrice)	Gunsolley (2006)	6	0.441	*P* <0.001	NA	*P* = 0.010	NA
	Paraskevas & vdW. (2006)	6	0.15	*P* <0.00001	0.11–0.20	*P* <0.00001, I^2= 91.1%	Random
	Serrano *et al*. (2015)	2	0.115	*P* = 0.000	0.16–0.07	*P* = 0.092, I^2 = 64.8%	Fixed
	Figuero *et al*. (2019)	4	0.92[SMD]	*P* <0.05	0.35–1.50	I^2 = 93.7%	Random
	Figuero *et al*. (2020)	2	0.41[SMD]	*P* <0.001	0.58–0.23	*P* <0.252, I^2 =23.8%	Random
Stannous fluoride and SHMP (dentifrice)	Figuero *et al*. (2019)	2	1.37[SMD]	*P* <0.05	0.82–1.91	I^2 = 74.6%	Random
	Figuero *et al*. (2020)	2	1.50[SMD]	*P* <0.001	2.11–0.89	*P* = 0.029, I^2 = 79.1%	Random
Chlorhexidine (dentifrice)	Serrano *et al*. (2015)	4	0.29	*P* =0.000	0.56–0.02	*P* = 0.000, I^2 = 92.8%	Random
	Figuero *et al*. (2019)	2	1.09[SMD]	NS	-	-	
	Figuero *et al*. (2020)	2	1.28[SMD]	NS	-	-	Random

n, number of studies included in each meta-analysis; [a]estimated; [b]effect on bleeding; WMD, weighted mean difference, between test and control groups; SMD, standardized weighted mean difference, between test and control groups; CI, confidence interval; NA, not available, SHMP, sodium hexametaphosphate; vdW, van der Weijden.

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Chapter 30

Non-Surgical Therapy

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Introduction

According to the clinical guidelines for the treatment of patients with periodontitis stages I–III by the European Federation of Periodontology (Sanz *et al*. 2020), treatment should be given according to a pre-established stepwise approach. Hence, whereas *the first step* in the treatment is directed towards motivation and behavioral changes to achieve adequate self-performed oral hygiene practices and the control of local and systemic modifiable risk factors, *the second step* is focused on professional interventions aimed at reducing/eliminating the subgingival biofilm and calculus.

The second step of treatment involves various non-surgical means to control the subgingival infection causing pathologic lesions in the tooth supporting tissues. Pocket/root instrumentation, combined with effective self-performed supragingival plaque control measures, serves this purpose by altering the subgingival ecology through disruption of the microbial biofilm, reduction of the amount of bacteria, and suppression of the inflammation. A variety of instruments and approaches to treatment may be utilized in non-surgical therapy.

This chapter outlines the various means and methods used in non-surgical periodontal therapy and their respective merits, shortcomings, and clinical efficacy. Considerations in relation to the selection of instruments and treatment approach are also addressed, as well as re-evaluation after the initial phase of non-surgical therapy.

Goal of non-surgical pocket/root instrumentation

Periodontitis is strongly associated with the presence of bacterial biofilms and dental calculus on root surfaces. Hence, the ultimate goal of non-surgical pocket/root instrumentation is to render the root free from microbial deposits and calculus. However, several *in vitro* (e.g. Breininger *et al*. 1987; Rateitschak-Pluss *et al*. 1992) and *in vivo* studies (e.g. Waerhaug 1978; Eaton *et al*. 1985; Caffesse *et al*. 1986; Sherman *et al*. 1990; Wylam *et al*. 1993) have shown that complete removal of hard and soft deposits is not a feasible objective of closed pocket/root instrumentation, even with the most meticulous scaling and root planing procedures (SRP). Nevertheless, non-surgically performed

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

SRP is an effective treatment modality for periodontal disease, as demonstrated by the marked reduction in clinical signs and symptoms of the disease following treatment (e.g. van der Weijden & Timmerman 2002; Suvan *et al*. 2020). Taken together, these observations indicate that there may exist an individual threshold level of remaining bacterial load following instrumentation below which the host can cope with the infection, and hence the goal of non-surgical pocket/root debridement is to reach below this threshold level for all pathologic tooth sites. Besides the quantity and quality of the remaining biofilm, host-related and modifiable environmental factors are to be recognized in this respect, for example diabetes, smoking, and stress. Although it is not feasible by probing the root surface to determine if adequate debridement has been achieved (Sherman *et al*. 1990), clinical signs of resolution of the inflammatory lesion (e.g. lack of bleeding on probing, increased tissue resistance to probing or "pocket closure") are indeed useful assessments to indicate sufficient removal of subgingival biofilms and calculus. Nonetheless, from a practical standpoint, if calculus is detected clinically, it should be removed.

Debridement, scaling, and root planing

Kieser (1994) proposed that, in preference to the traditionally practiced combination of scaling and root planing (SRP), pocket/root instrumentation should be performed as three separate stages of treatment – *debridement*, *scaling*, and *root planing* – with objectives pursued in an orderly sequence. According to the author, *debridement* is defined as instrumentation for disruption and removal of microbial biofilms, *scaling* instrumentation for removal of mineralized deposits (calculus), and *root planing* instrumentation to remove "contaminated" cementum and dentin in order to restore the biologic compatibility of periodontally diseased root surfaces. Furthermore, it was advocated that the healing obtained following pocket/root debridement should be clinically assessed before any repeated instrumentation efforts, or proceeding to the next stage of instrumentation. Although the intention of the various stages of instrumentation is different, overlap to some degree is of course inevitable.

Since periodontal diseases are infections caused by bacteria residing in subgingival biofilms, the need to lower the microbial load by disruption/removal of subgingival biofilms is indisputable. Calculus does not in itself induce inflammation, but has a deleterious effect because of its ability to provide an ideal surface for microbial colonization (Waerhaug 1952). In fact, it has been demonstrated that epithelial adherence to subgingival calculus can occur following its disinfection with chlorhexidine (CHX) (Listgarten & Ellegaard 1973). Thus, the rationale for the removal of calculus relates to eliminating, as far as possible, surface irregularities harboring pathogenic bacteria.

The rationale for performing root planing was originally based on the concept that bacterial endotoxins penetrate into the cementum (Hatfield & Baumhammers 1971; Aleo *et al*. 1974), and for this reason it was thought necessary to remove not only biofilms and calculus but also underlying cementum. However, evidence gained from experimental studies demonstrated that endotoxins were only loosely adherent to the surface and did not penetrate into the cementum (Hughes & Smales 1986; Moore *et al*. 1986; Hughes *et al*. 1988; Cadosch *et al*. 2003). Furthermore, animal and human studies revealed similar clinical and histologic healing following treatment of infected root surfaces, previously exposed to the periodontal pocket, in conjunction with flap surgery by polishing only with a low-abrasive paste as following extensive SRP, provided supragingival hygiene was meticulous (Nyman *et al*. 1986, 1988). Hence, aggressive tooth substance removal does not seem warranted and pocket/root instrumentation should preferably be carried out with instruments that cause minimal root substance removal, but are effective in disrupting the biofilm and removing calculus.

Instruments used for non-surgical pocket/root debridement

Non-surgical periodontal treatment may be carried out using various types of instruments, for example hand instruments, sonic and ultrasonic instruments, air polishing, and ablative laser devices.

Hand instruments

The use of traditional hand instruments of steel allows good tactile sensation, but tends to be more time consuming than other methods, and requires correct and frequent instrument sharpening. A hand instrument is composed of three parts: the working part (the blade), the shank, and the handle (Fig. 30-1). The cutting edges of the blade are centered over the long axis of the handle in order to give the instrument proper balance. The blade is made of carbon steel or stainless steel. Instruments with titanium, plastic, or carbon fiber blades are also available and used for bacterial

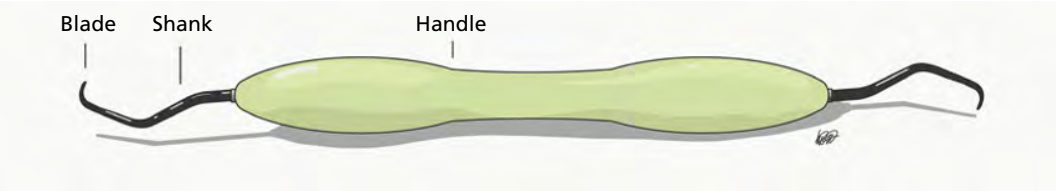


Fig. 30-1 Curette demonstrating the handle, shank, and blade.

biofilm and calculus removal on dental implant surfaces. Hand instruments are categorized based on the design of the blade. The most common categories of hand instruments are sickles and curettes.

A *sickle* has either a curved or a straight blade with a triangular cross-section and two cutting edges (Figs. 30-2, 30-3). The "facial" surface between the two cutting edges is flat in the lateral direction but may be curved in the direction of its long axis. The "facial" surface converges with the two lateral surfaces of the blade. Sickles are mainly used for debridement/scaling supragingivally but may be used also subgingivally at tooth sites with shallow pockets.

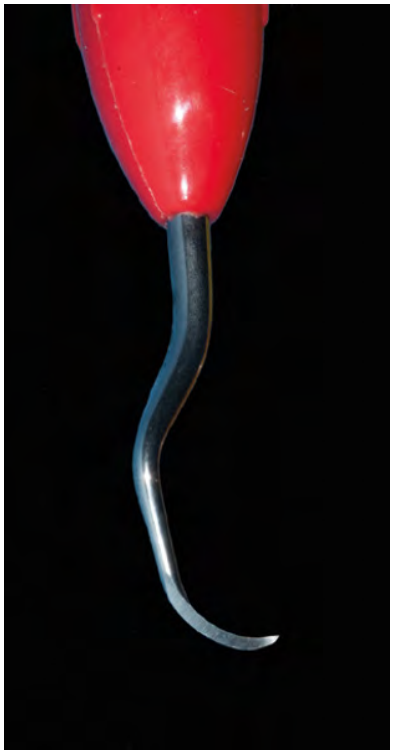


Fig. 30-2 Working end of a sickle, which has a triangular cross-section and two cutting edges.

Curettes are instruments used for debridement and scaling, both supra- and subgingivally (Fig. 30-3). The working part of the curette is the spoon-shaped blade that has two curved cutting edges, united by the rounded toe. The curettes are usually made "double-ended" with mirror-turned blades. The length and angulation of the shank as well as the dimensions of the blade differ between different brands of instruments (Fig. 30-4). Curettes with extended shanks and mini-blades have been designed to improve the efficacy of subgingival instrumentation in deep and narrow pockets. In addition, the availability of double-ended universal curettes with double cutting blades has markedly reduced the number of instruments needed. In fact, with only two types of such curettes (e.g. LM Dual Gracey™ curettes; Syntette™ and Syntette™ Anterior) the entire dentition may be properly reached for subgingival debridement. The tip of these instruments is designed with two elliptical cutting edges that allows for treatment of both mesial and distal tooth surfaces (Fig. 30-3).

Use of curettes for subgingival debridement/scaling

Subgingival instrumentation should preferably be performed under local anesthesia. The root surface of the diseased site is explored with a probe to identify (1) the probing depth, (2) the anatomy of the root surface (irregularities, root furrows, open furcations, etc.), and (3) the location of the calcified deposits.

The type of hand instrument most suitable for subgingival debridement is the curette. The angulation of the cutting edge of the curette to the tooth surface influences the efficiency of debridement. The optimal angle is approximately 80° (Fig. 30-5c). Too obtuse an

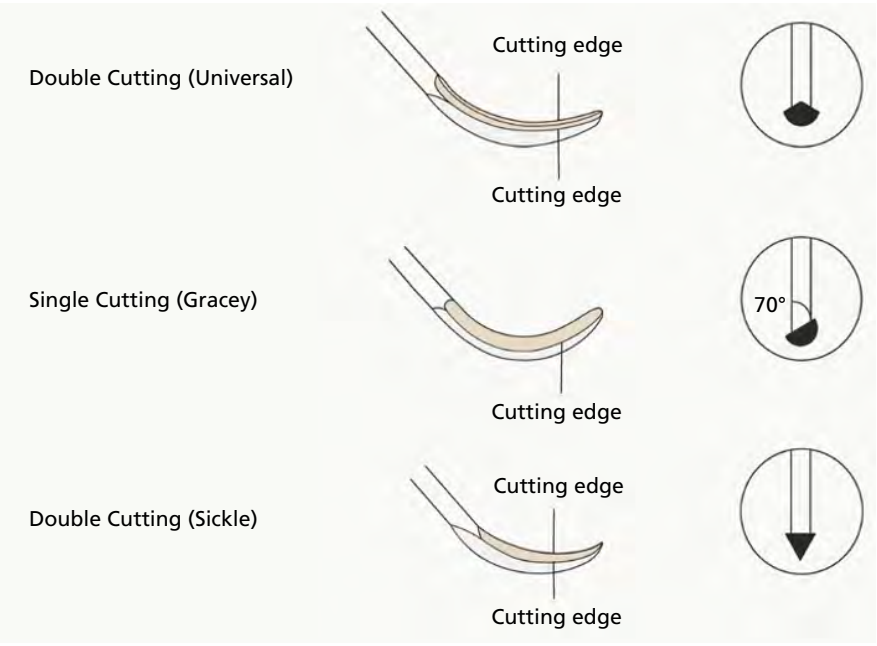


Fig. 30-3 Examples of the working end of instruments and their design with cutting edges.

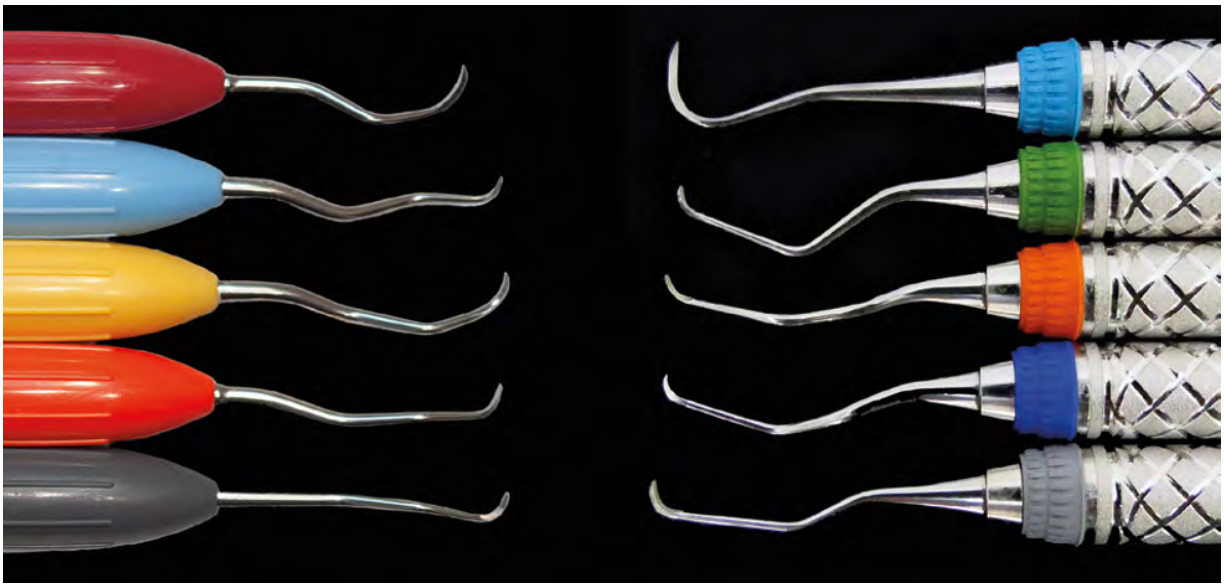


Fig. 30-4 Selection of instruments with varying shank configurations to facilitate debridement of different areas of the dentition.

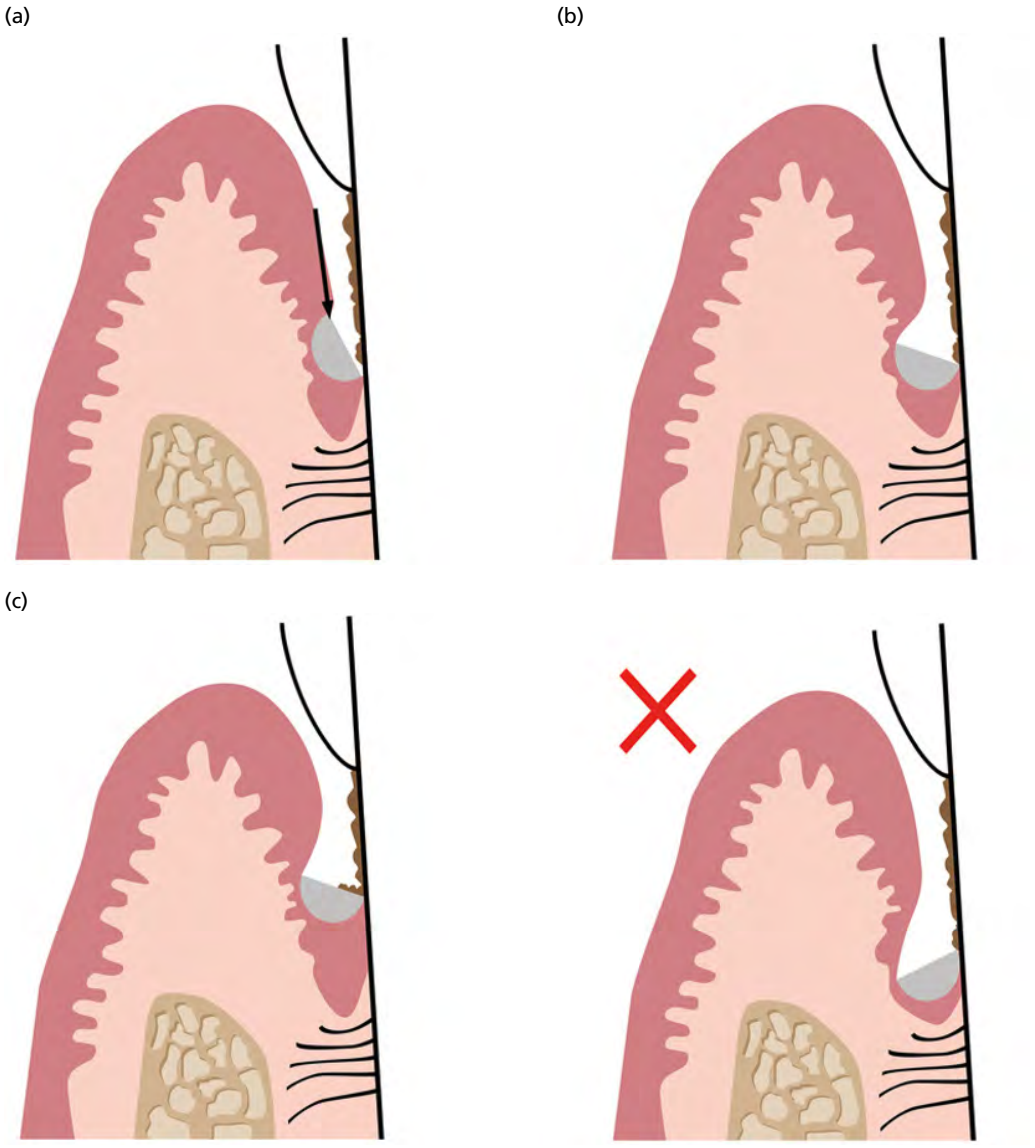


Fig. 30-5 (a) Curette is inserted into the periodontal pocket. Note the near 0° angulation of the face of the curette against the root surface to facilitate access of the pocket. (b) Bottom of the periodontal pocket is identified with the distal edge of the blade of the curette. (c) Curette is turned to a proper cutting position for scaling. Blade is moved along the root surface in a scaling stroke to remove calculus. (X) A too obtuse or acute angulation will result in ineffective calculus removal.

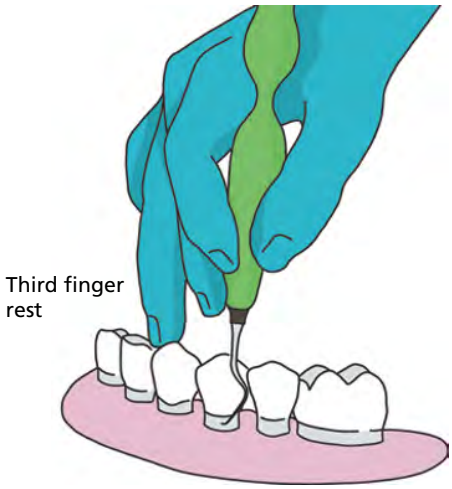


Fig. 30-6 A modified pen grasp and "third finger rest" in the premolar and molar region of the mandible.

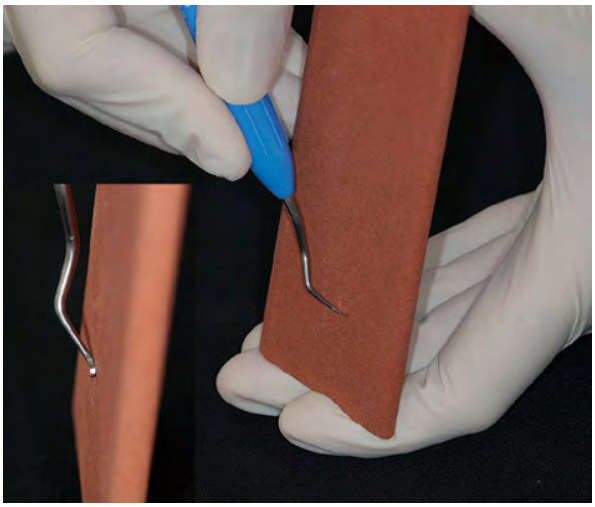


Fig. 30-7 Sharpening of a curette. The original geometry of the cutting edge must be maintained during the sharpening procedure.

angle, as shown in Fig. 30-5X, or too acute an angle will result in ineffective removal and burnishing of subgingival calculus deposits.

The instrument is held in a modified pen grasp and the blade inserted into the periodontal pocket with the face of the blade parallel to and in light contact with the root. It is important that all root surface instrumentation is performed with a proper finger rest. This implies that one finger – the third or the fourth – must act as a fulcrum for the movement of the blade of the instrument (Fig. 30-6). A proper finger rest serves to (1) provide a stable fulcrum, (2) permit optimal angulation of the blade, and (3) enable the use of wrist–forearm motion. The finger rest must be secured as close as possible to the site of instrumentation to facilitate controlled use of the instrument.

After the base of the periodontal pocket has been identified with the lower edge of the blade, the instrument is turned into a proper working position: that is, the shank is parallel to the long axis of the tooth (Fig. 30-5). The grasp of the instrument is tightened somewhat, the force between the cutting edge and the root surface is increased, and the blade is moved in a coronal direction. Strokes must be made in different directions to cover all aspects of the root surface (cross-wise, back and forth) but, as stated previously, strokes should always start from an apical position and be guided in a coronal direction. The probe is inserted into the pocket again and the surface of the root assessed anew for the presence of calculus.

Frequent sharpening of the cutting edge of the instrument is necessary to obtain efficient calculus removal. The angle between the face and the back of curettes must be maintained at approximately 70° during sharpening (Fig. 30-7). A greater angle will result in dulling of the cutting edge, whereas a more acute angle results in a fragile and easily worn cutting edge. A new generation of hand instruments that have sharpen-free blades are now available.

Sonic and ultrasonic instruments

A common alternative to hand instrumentation for non-surgical periodontal therapy is the use of sonic and ultrasonic instruments. Sonic devices use air pressure to create mechanical vibration that in turn causes the instrument tip to vibrate; the frequencies of vibration range from 2000 to 6000 Hz (Gankerseer & Walmsley 1987; Shah *et al*. 1994). Ultrasonic scalers convert electrical current into mechanical energy in the form of high-frequency vibrations at the instrument tip; the vibration frequencies range from 18 000 to 45 000 Hz with an amplitude range of 10–100 µm.

There are two types of ultrasonic scalers: magnetostrictive and piezoelectric. In *piezoelectric scalers* the alternating electrical current causes a dimensional change in the handpiece that is transmitted to the working tip as vibrations. The pattern of vibration at the tip is primarily linear. In *magnetostrictive scalers* the electrical current produces a magnetic field in the handpiece that causes the insert to expand and contract along its length and in turn causes the insert to vibrate. The pattern of vibration at the tip is elliptical. Modified sonic and ultrasonic scaler tips, for example the tiny, thin, periodontal probe type (Fig. 30-8), are available for use in deep pockets.

Wear of the ultrasonic tip will affect the working performance of the ultrasonic instrument and therefore the degree of loss of tip dimension should be checked regularly (Fig. 30-9). A 1 mm wear of the tip will reduce the amplitude of the tip movement by more than half (Lea et al. 2006). The same effect is obtained if too much pressure (50 g) is applied to the instrument. Water is typically used as coolant during instrumentation, but the use of antiseptic solutions such as CHX or povidone-iodine have also been proposed. A potential hazard for the operator with the use of these devices is the production of contaminated aerosol due to the high vibration frequency (Timmerman *et al*. 2004).

Fig. 30-8 Inserts of different length and curvature for piezoelectric (left) and magnetostrictive (right) ultrasonic devices.

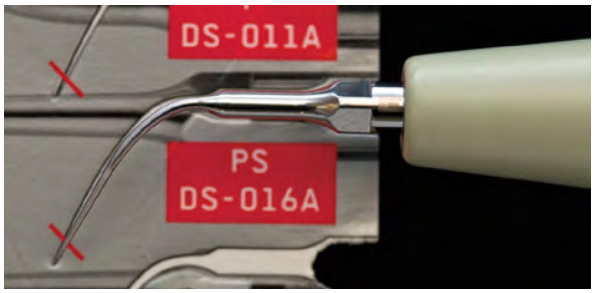


Fig. 30-9 Control of wear of the piezoelectric ultrasonic tip. The red line marks the level of wear when the tip should be discarded because of loss of instrument efficacy.

Another type of ultrasonic instrument is the Vector system (Sculean *et al*. 2004; Guentsch & Preshaw 2008) which uses a working frequency of 25 000 Hz and a coupling at the head of the handpiece to transfer energy indirectly to the working tip, providing an amplitude of movement of 30–35 µm. These instruments are cooled by a water-based medium containing polishing particles of various sizes dependent on the therapeutic indication. The amount of contaminated aerosol is said to be reduced compared to that produced by other ultrasonic or sonic devices.

Air-polishing devices

For removal of soft deposits (plaque and debris) from tooth surfaces, air-polishing devices may be used. These instruments are effective in the supragingival area to remove staining and plaque, with a reduced working time compared to other polishing procedures. The introduction of low-abrasive powders (i.e. glycine and erythritol) and the development of devices with a subgingival nozzle have opened the possibility of using air-polishing in subgingival instrumentation (Fig. 30-10). A specially designed subgingival nozzle delivers the glycine powder/air spray perpendicularly to the root surface, while water is sprayed in the apical direction. In addition, the effective working pressure is reduced compared with that of supragingivally applied air polishing. Bacterial biofilms on root surfaces are effectively removed by glycine powder/air polishing without causing damage to the root surface (Petersilka 2011; Bozbay *et al*. 2018). However, due the inability of glycine powder/air polishing to remove calculus, air-polishing should only be considered as a potentially adjunctive measure to hand or machine-driven instrumentation in the initial phase of periodontal therapy.

Ablative laser devices

A laser is a device that produces coherent electromagnetic radiation. Laser radiation is characterized by a low divergence of the radiation beam and, with few exceptions, a well-defined wavelength. The term laser is well known as the acronym for "light amplification by stimulated emission of radiation".

Ablative laser therapy has bacteriocidal and detoxification effects, is capable of removing bacterial biofilm and calculus with extremely low mechanical stress and no formation of a smear layer on root surfaces, and can remove the epithelium lining and inflamed tissue within the periodontal pocket (Ishikawa *et al*. 2009). However, with regard to the removal of inflamed tissue, studies have shown that curettage of the soft tissue walls has no added benefit over SRP (Lindhe & Nyman 1985).

ErbiumYAG (Er:YAG) lasers are capable of effectively removing calculus from the root surface. To reduce potential damage to the root surface, some Er:YAG laser devices are equipped with a feedback system based on a diode laser that activates the main laser irradiation only if calculus is detected. Er:YAG laser irradiation energy is absorbed by water and organic components of the biologic tissues, which raises the temperature and causes water vapor production, and thus an increase in internal pressure within the calculus deposits. The resulting expansion of the calculus deposits causes their separation from the root surface. Inadvertent irradiation and reflection from shiny metal surfaces may damage a patient's eyes, throat, and oral tissues other than the targeted area. Therefore, care must be taken when using these devices and both patient and operator

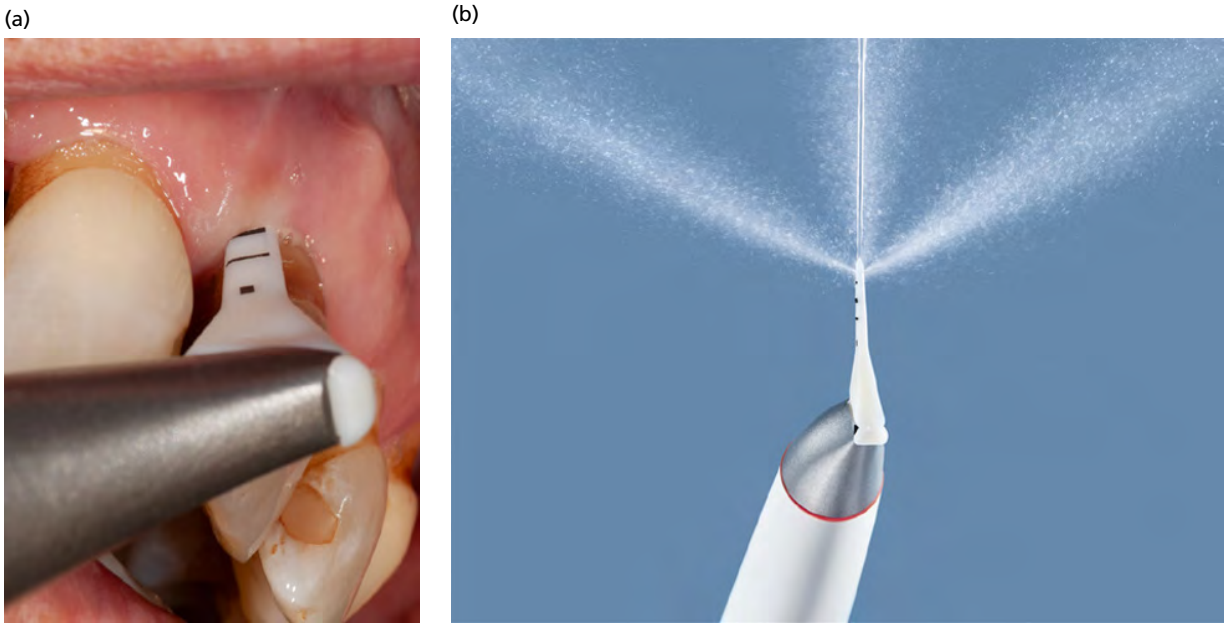


Fig. 30-10 (a) The specially designed subgingival nozzle applied for debridement of periodontal pockets by glycine powder/air spray polishing. (b) Lateral direction of powder/air jet while water jet is apically directed. (Source: Reproduced with permission from EMS, Nyon, Switzerland.)

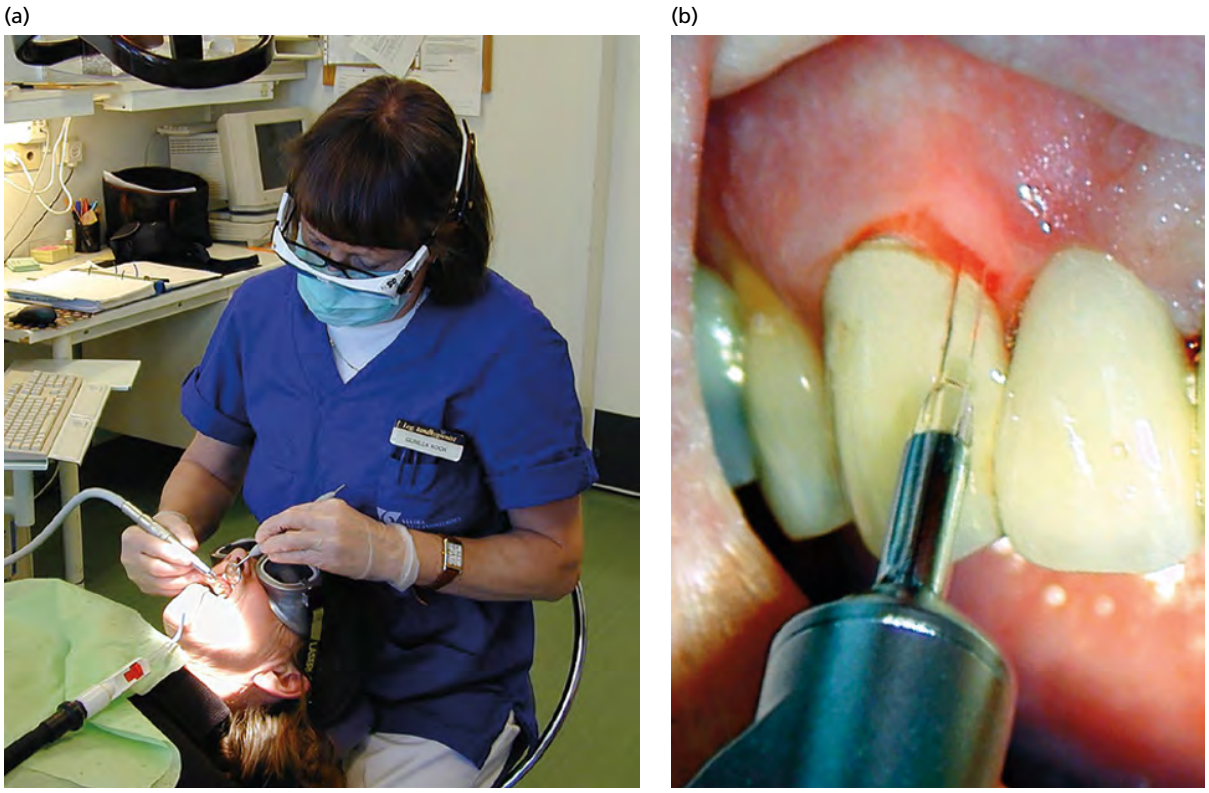


Fig. 30-11 (a) Using a laser in periodontal treatment: patient and operator must wear protective eyeglasses. (b) Er:YAG laser tip inserted into the pocket and activated.

must use protective eyeglasses (Fig. 30-11). There may also be a risk of excessive tissue destruction from direct ablation and thermal side effects.

Other types of lasers such as carbon dioxide lasers, diode lasers, and Nd:YAG lasers are not effective in removing calculus and hence, their use in periodontal therapy has been primarily as an adjunct therapy to SRP. Carbon dioxide lasers, when used with relatively low energy output in a pulsed and/or defocused mode, have root conditioning, detoxification, and bactericidal effects on contaminated root surfaces. Diode lasers of different wavelength have been introduced as an adjunctive measure to mechanical subgingival debridement to detoxify the root surface or

in photodynamic therapy to reduce bacterial load. In photodynamic therapy a photoactive compound such as toluidine blue is placed in the pocket and activated with a laser in order to produce free radical ions that have a bactericidal effect (Ishikawa *et al*. 2009). Another potential application for diode lasers is as low-level laser therapy (LLLT), which may stimulate cell proliferation and promote wound healing (Walsh 1997).

Approaches to subgingival debridement

The traditional modality of non-surgical therapy as an initial periodontal treatment phase is pocket/root instrumentation, including root planing, by jaw quadrant or sextant, depending on the extent and severity of the disease, at a series of appointments (Badersten *et al*. 1984). However, various other treatment protocols have also been proposed in the literature as alternatives to this conventional staged approach of SRP for periodontal infection control. In order to prevent re-infection of treated sites from remaining untreated periodontal pockets, Quirynen *et al*. (1995) advocated the benefit of carrying out the pocket/root instrumentation of the entire dentition within a time frame of 24 hours (*full-mouth SRP*). They also considered the risk of re-infection from other intraoral niches such as the tongue and tonsils and therefore also included tongue cleaning and an extensive antimicrobial regimen with CHX (*full-mouth disinfection protocol*). Other proposed treatment protocols that similarly challenge the traditional approach of non-surgical periodontal therapy restrict the number of and the interval between treatment sessions and the time allocated to instrumentation, and may or may not include the adjunctive use of various antimicrobials.

Full-mouth instrumentation protocols

The first full-mouth instrumentation protocol described by Quirynen *et al*. (1995) comprised two sessions of SRP within 24 hours, each covering half of the dentition. However, the total time used for subgingival instrumentation in this approach did not differ from that of the traditional quadrant-wise approach. As already mentioned, the benefit of this treatment protocol was suggested to be a reduced risk of re-infection of treated sites from the otherwise untreated sites, as well as a potential boost to the immunologic response by inoculation of periodontal bacteria into the local vasculature. From the patient's perspective, a tangible benefit of the full-mouth treatment protocol is that fewer appointments, but not necessarily less chair-time for treatment, are required. Apatzidou and Kinane (2004) described a modified protocol in which the SRP of the entire dentition was completed at two sessions on the same day. Another proposed approach consisted of four sessions of SRP on four consecutive days (Eren *et al*. 2002). In all these protocols the time allocated for SRP was 1 hour per jaw quadrant.

Adhering to the concept of differentiation between debridement, scaling, and root planing in non-surgical periodontal therapy (Kieser 1994), modified approaches to the full-mouth instrumentation protocol have been proposed that involve pocket/root debridement by the use of piezoelectric ultrasonic devices in a single-visit, full-mouth procedure, limited to 45–60 minutes to minimize removal of root substance (Wennström *et al*. 2005; Zanatta *et al*. 2006; Del Peloso Ribeiro *et al*. 2008) or without time limit (Koshy *et al*. 2005). Hence, common features of these modified protocols are that the initial subgingival treatment is reduced to one session only and that markedly less time is devoted to instrumentation than that to SRP in the previously described protocols for full-mouth instrumentation.

Full-mouth disinfection protocols

Several intraoral niches, such as the tongue, mucosa, saliva, and tonsils, may act as reservoirs for Gram-negative strains recognized as periodontal pathogens (Beikler *et al*. 2004), and translocation of these bacteria might result in rapid recolonization of a recently instrumented pocket. Hence, as already mentioned, in order to optimize the treatment outcome of the full-mouth SRP approach, Quirynen *et al*. (1995) proposed adjunctive therapy including tongue cleaning and an extensive antimicrobial regimen with CHX (*full-mouth disinfection protocol*). The CHX regimen in conjunction with each treatment session included (1) brushing the dorsum of the tongue for 1 minute with 1% CHX gel, (2) rinsing twice with 0.2% CHX solution for 1 minute, (3) spraying the tonsils four times with a 0.2% CHX solution, (4) three subgingival irrigations with 1% CHX gel (repeated after 8 days), and (5) instructing the patient to rinse twice daily with a 0.2% CHX solution for 2 weeks. The protocol was later modified by adding the instruction that patients should rinse the mouth and spray the tonsils twice daily with a 0.2% CHX solution for a period of 2 months after the SRP (Mongardini *et al*. 1999).

Other full-mouth instrumentation protocols including adjunctive antimicrobial therapy can be found in the literature, but none is as rigorous as the full-mouth disinfection protocol proposed by the Quirynen group. For example, Koshy *et al*. (2005) included the use of 1% povidone iodine solution as a coolant during the full-mouth ultrasonic debridement session, instruction of patients in careful oral hygiene and brushing of the tongue, as well as mouth rinsing with a 0.05% CHX solution twice daily for 1 month.

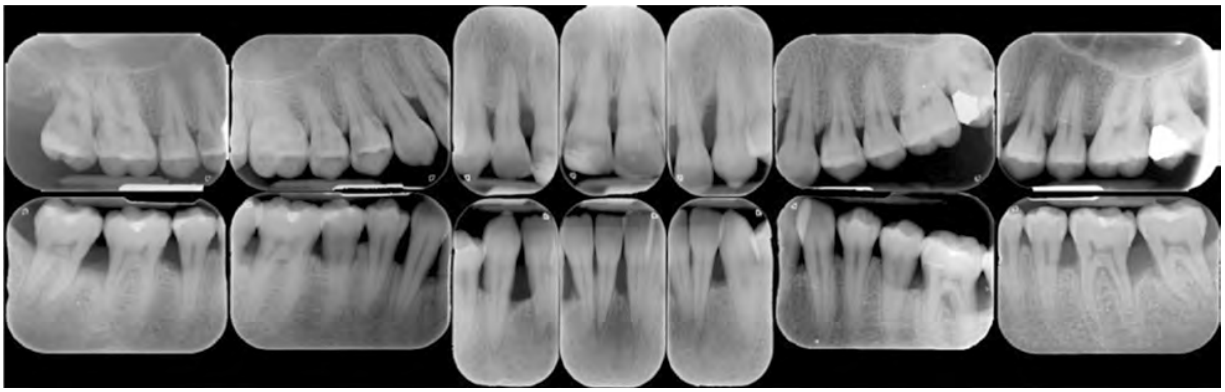
Clinical outcomes following various approaches to pocket/root instrumentation

A number of systematic reviews on the efficacy of mechanical non-surgical periodontal therapy have been published (e.g. van der Weijden &

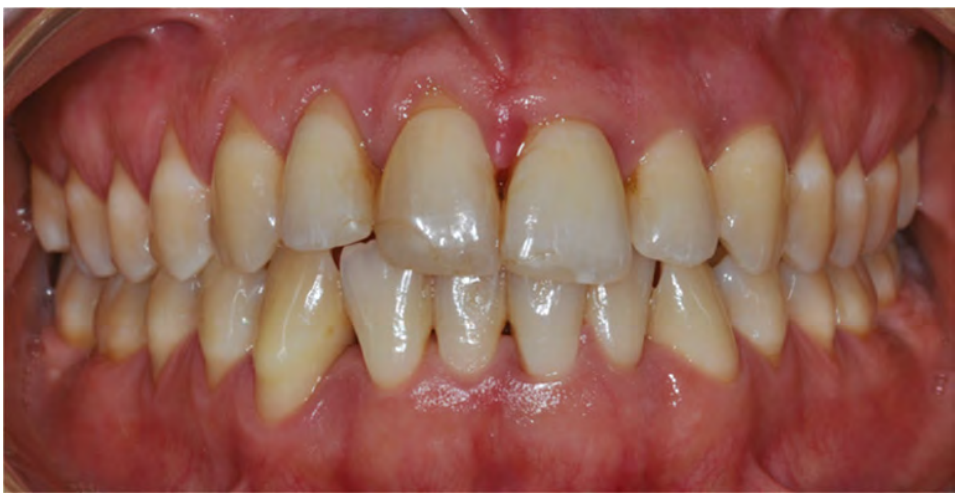
Timmerman 2002; Hallmon & Rees 2003; Lang *et al*. 2008; Eberhard *et al*. 2015; Suvan *et al*. 2020). There is a consensus among these reviews that pocket/root instrumentation combined with proper supragingival plaque control measures is an effective treatment modality in reducing probing pocket depths (PPDs) and improving clinical attachment levels (CALs) (Figs. 30-12, 30-13), and that there is no major difference in the efficacy of pocket/root instrumentation using hand or power-driven instruments (sonic/ultrasonic). Furthermore, it was deliberated that the data available from published clinical studies are too limited to judge whether the adverse effects of the treatment may vary with the type of instrument used.

Both in the Cochrane review by Eberhard *et al*. (2015) and the most recent systematic meta-analyses (Suvan *et al*. 2020) comparing *full-mouth instrumentation* versus quadrant-wise SRP revealed no statistically significant differences with regard to mean PPD reduction or CAL change. Subgroup analyses of initially moderate (5–6 mm) and deep (>6 mm) pockets at single- and multirooted teeth disclosed no significant differences for either between the two treatment approaches.

The comparison between *full-mouth disinfection* and quadrant-wise SRP performed in the Cochrane review (Eberhard *et al*. 2015), based on data from six trials, failed to find a statistically significant difference



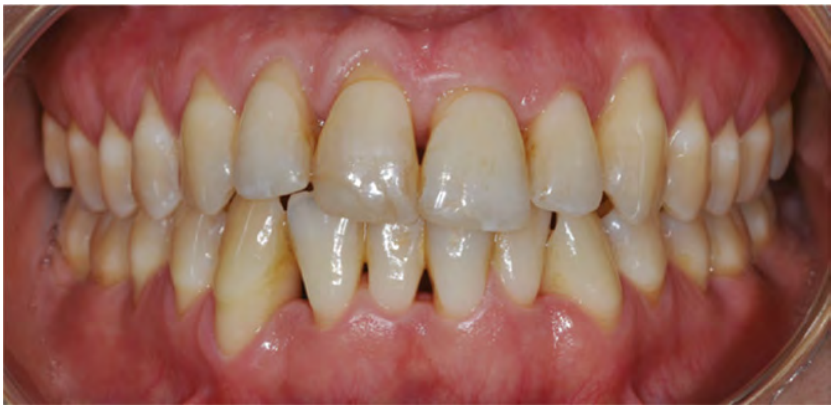
	Tooth	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
PPD	m						6	7		6		9	6				
	b											6					
	d		7							6						9	
	l		4									6				6	
Furc			D1													D1	
	Mobility																



	Tooth	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
PPD	m		6	6			9			6					6	9	
	b															6	
	d		9	9	6		6	6			6			6	10	9	
	l		6	6	6		9							6	6	6	
Furc			L2	L1													
	Mobility																

Fig. 30-12 Radiographs, clinical image, and probing pocket assessments of a 32-year-old female non-smoker with untreated periodontitis, before periodontal therapy.

	Tooth	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
PPD	m							6				5					
	b																
	d		6													9	
	l																
Furc			D1													D1	
	Mobility																



	Tooth	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
PPD	m															4	
	b																
	d		9												4	9	
	l														4		
Furc			L1														
	Mobility																

Fig. 30-13 Clinical image and probing pocket assessments of the same patient as in Fig. 30-12, 6 months following initial non-surgical therapy.

between the two treatment protocols overall regarding probing depth reduction, but found some differences in favor of *full-mouth disinfection* in specific subgroups, such as deep sites at 6 months follow-up for single and multirooted teeth. Corresponding analyses in a systematic review by Lang *et al*. (2008) showed outcomes of similar magnitude in favor of the full-mouth disinfection approach. However, none of the systematic reviews found any significant differences for the clinical outcome variables between full-mouth disinfection and full-mouth instrumentation, not supporting the extensive use of CHX adopted in these protocols.

Conclusion: All three non-surgical treatment approaches to periodontal infection control (conventional staged quadrant-wise SRP, full-mouth instrumentation and full-mouth disinfection) result in marked improvements in clinical conditions, and the decision to select one approach over another has to involve considerations other than just clinical outcomes.

Microbiologic outcomes following various approaches to pocket/root instrumentation

Removal of subgingival plaque and calculus deposits through subgingival debridement in combination with efficient self-performed supragingival infection control alters the ecology of the pockets through reduction in the quantity of microorganisms, resolution of the inflammation, and a decrease in pocket depth, and species that may have flourished in the subgingival environment of the diseased pocket may find the new habitat less hospitable. A decrease in the total bacterial count for sites of >3 mm depth, from 91×10^5 to 23×10^5, has been observed immediately following subgingival debridement (Teles *et al*. 2006). Furthermore, a decrease in the mean counts and number of sites colonized by *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia* (Shiloah & Patters 1994), *Tannerella forsythia*, and *Treponema denticola* (Haffajee *et al*. 1997; Darby *et al*. 2005) and an increase in proportion of streptococci (e.g. *Streptococcus gordonni*, *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguinis*) and *Actinomyces* spp., *Eikenella corrodens*, and *Gemella morbillarum* were observed several weeks following subgingival debridement. An increase in the proportions of Gram-positive aerobic cocci and rods is associated with periodontal health (Cobb 2002). Interestingly, microorganisms do not exist in isolation in the subgingival environment, but rather as members of communities. Socransky *et al*. (1998) identified groups of organisms that were commonly found together and subdivided microorganisms into

complexes accordingly. Members of the "red" and "orange" complexes are most commonly identified at sites displaying signs of periodontitis. Hence, a re-emergence of species of the red and orange complexes 3–12 months post debridement may indicate lack of resolution of the periodontal lesion (Haffajee *et al*. 2006). It is also important to recognize that in the absence of appropriate home care, the re-establishment of the pretreatment microflora will occur in a matter of weeks (Magnusson *et al*. 1984; Loos *et al*. 1988; Sbordone *et al*. 1990).

In a study comparing the microbiologic outcome of *full-mouth instrumentation* and quadrant-wise SRP (Quirynen *et al*. 2000), it was demonstrated by phase-contrast microscopy and culturing techniques that both treatment approaches reduced the total number of facultative and strict anaerobic species, as well as the number of black-pigmented bacteria, spirochetes, and motile rods in subgingival samples, but also that the reductions were more pronounced following the full-mouth instrumentation. Other studies comparing the microbiologic outcomes following the two treatment approaches using polymerase chain reaction (PCR) techniques (Apatzidou *et al*. 2004; Koshy *et al*. 2005; Jervøe-Storm *et al*. 2007) also reported reductions in presumptive periodontal pathogens, but no detectable differences between the approaches. Hence, these studies failed to support the concept that a full-mouth debridement approach may prevent or delay recolonization of instrumented pockets. Besides the different microbiologic techniques employed in these studies compared with the study by Quirynen *et al*. (2000), the fact that the patients in the former studies showed a high standard of oral hygiene before the initiation of the subgingival instrumentation may explain the contradictory findings. It should be noted that the Quirynen study was primarily designed as a "proof of principle" study, and in order to increase the chance for cross-contamination, interproximal cleaning in the quadrant-wise SRP group was prohibited until the last quadrant had been instrumented.

Studies evaluating microbiologic alterations after *full-mouth ultrasonic instrumentation* with a restricted time protocol (45 minutes of ultrasonic debridement) (Zanatta *et al*. 2006; Del Peloso Ribeiro *et al*. 2008) also showed significant reductions in the frequency and amount of presumptive periodontal pathogens, as evaluated by the use of real-time PCR; reductions were similar to those after conventional quadrant-wise SRP.

More favorable microbiologic changes have been reported following *full-mouth disinfection* as compared with quadrant-wise SRP with respect to decreases in the total amount of motile organisms and spirochetes, total number of facultative or strict anaerobic bacteria, black-pigmented bacteria, as well as frequencies and levels of "red" and "orange" microbial complexes detected using differential phase-contrast microscopy, culturing, and DNA–DNA hybridization technique (Quirynen *et al*. 1999, 2000; De Soete *et al*. 2001). By contrast, Koshy *et al*. (2005) could not detect any added microbiologic benefits as recorded by PCR following their modified full-mouth disinfection approach compared with quadrant-wise instrumentation. The question of differences in microbiologic outcomes following full-mouth instrumentation, full-mouth disinfection, and conventional staged quadrant-wise SRP was addressed in a systematic review (Lang *et al*. 2008). Based on the analysis of seven studies, it was concluded that no superior reductions in either bacterial load or specific presumptive periodontal pathogens could be proven for any of the three treatment modalities.

The effect on the microbiome of non-surgical treatment has been confirmed in clinical trials that have adopted metagenomic techniques for analysis, which allow decoding of all the genetic material present in plaque samples (Takahashi 2015; Yang *et al*. 2016; Chen et al. 2018). Such analyses have also revealed that the oral microbiome is far more complex and heterogeneous than previously perceived (Huttenhower *et al*. 2012), and that methabolic pathways and microbial interactions in biofilms are significant factors to consider (Marsh & Zaura 2017).

Considerations in relation to selection of instruments and treatment approach

Selection of instruments

It has been demonstrated that hand, sonic, and ultrasonic instruments produce similar periodontal healing response with respect to PPD, bleeding on probing, and CAL (Badersten *et al*. 1981, 1984; Lindhe & Nyman 1985; Kalkwarf *et al*. 1989; Loos *et al*. 1987; Copulos *et al*. 1993; Obeid *et al*. 2004; Wennström *et al*. 2005; Christgau *et al*. 2006; Suvan *et al*. 2020). With respect to root surface loss, sonic and ultrasonic scalers have been shown to produce less loss than hand instruments (Ritz *et al*. 1991; Busslinger *et al*. 2001; Schmidlin *et al*. 2001; Kawashima *et al*. 2007; Bozbay *et al*. 2018).

In comparison to hand instrumentation, the use of sonic and ultrasonic instruments may provide better access to deep pockets and furcation areas (Kocher *et al*. 1998; Beuchat *et al*. 2001). In addition, the flushing action of water used as coolant during sonic and ultrasonic instrumentation removes, to a certain extent, debris and bacteria from the pocket area, but the use of antiseptic solutions, for example CHX, iodine, and Listerine®, as coolant has shown no greater effects compared with water irrigation (Koshy *et al*. 2005; Del Peloso Ribeiro *et al*. 2006, 2010; Feng *et al*. 2011; Krück *et al*. 2012; Van der Sluijs *et al*. 2016). However, tactile sensation is reduced, contaminated aerosols are produced (Barnes *et al*. 1998; Harrel *et al*. 1998; Rivera-Hidalgo *et al*. 1999; Timmerman *et al*. 2004), and some patients may find the vibration,

sound, and water spray uncomfortable. The use of the Vector ultrasonic system has been shown to result in clinical and microbiologic outcomes comparable to those achieved by manual instrumentation and conventional ultrasonic instruments; however, it may be less efficient in removing large accumulations of calculus (Sculean *et al*. 2004; Christgau *et al*. 2007; Kahl *et al*. 2007; Guentsch & Preshaw 2008).

The effect of air-polishing has been investigated in maintenance patients, and the results indicate that air polishing with glycine powder is a valid treatment approach to subgingival mechanical debridement during SPT in sites with moderate deep (5–6 mm) pockets (e.g. Moëne *et al*. 2010; Wennström *et al*. 2011; Flemmig *et al*. 2012; Zhang *et al*. 2019). However, in the presence of subgingival calculus and in the initial phase of periodontal therapy, hand/machine-driven instrumentation should be selected as the primary approach to root debridement. Whether subgingival air-polishing used as an adjunct to hand/ultrasonic instrumentation may have beneficial effects on the healing of periodontal lesions has not been addressed scientifically.

The use of Er:YAG lasers produces results comparable to those with hand or ultrasonic instrumentation (Schwarz *et al*. 2008; Sgolastra *et al*. 2012; Salvi *et al*. 2020). However, no adjunctive benefit of the use of Er:YAG lasers over mechanical debridement alone has been demonstrated (Schwarz *et al*. 2003; Lopes *et al*. 2010; Rotundo *et al*. 2010; Salvi *et al*. 2020). The use of other types of lasers has not shown treatment effects comparable to mechanical debridement or any adjunctive effect when used in combination with hand or ultrasonic instrumentation (Ambrosini *et al*. 2005; Schwarz *et al*. 2008; Slot *et al*. 2009; Salvi *et al*. 2020). Contradictory findings have been reported with regard to beneficial clinical and microbiologic effects of photodynamic diode laser therapy when used as an adjunct to mechanical debridement (Christodoulides *et al*. 2008; Chondros *et al*. 2009; Lulic *et al*. 2009; Salvi *et al*. 2020). There is no evidence of positive healing effects of LLLT when applied following mechanical pocket/root debridement (Lai *et al*. 2009; Makhlouf *et al*. 2012; Matarese *et al*. 2017). Hence, the European S3 Level Clinical Practice Guidelines in Periodontology, developed by the European Federation of Periodontology (Sanz *et al*. 2020), recommend that these various adjunctive therapies should not be used in clinical practice.

Selection of treatment approach

At the VI European Workshop on Periodontology the effects of full-mouth debridement with and without adjunctive use of antiseptics was addressed. Based on evaluation of the systematic reviews by Lang *et al*. (2008) and Eberhard *et al*. (2015), the consensus of the workshop was that *full-mouth debridement* and *full-mouth disinfection* do not provide clinically relevant advantages over the conventional staged quadrant-wise SRP in the treatment of patients with moderate-to-advanced periodontitis (Sanz & Teughels 2008). Furthermore, the clinical recommendations given were that (1) "all three modalities may be recommended for debridement" and (2) "clinicians should choose the modality of debridement according to the needs and preferences of the patient, their personal skills and experience, the logistic setting of the practice and the cost-effectiveness of the therapy rendered. It should be noted that the performance of optimal oral hygiene practices is an inseparable principle to be observed with any protocol of mechanical debridement". Similar recommendations are provided in the recently published clinical guideline for the treatment of patients with periodontitis stages I–III by the European Federation of Periodontology (Sanz *et al*. 2020).

Considering cost-to-benefit issues, it is of interest to note that piezoelectric ultrasonic debridement performed as a single-visit, full-mouth procedure restricted to 45–60 minutes of pocket/root instrumentation has been shown to result in comparable healing outcomes to those of SRP performed in a quadrant-wise manner at weekly intervals (Wennström *et al*. 2005; Zanatta *et al*. 2006; Del Peloso Ribeiro *et al*. 2008). This finding indicates that sufficient removal of subgingival deposits may be attainable using a shorter treatment time than that traditionally allocated to non-surgical pocket/root instrumentation. Calculating the efficiency of the treatment approaches, in this case the time used for instrumentation in relation to the number of pockets reaching the end point of treatment success (PPD ≤4 mm), it was shown that the full-mouth ultrasonic approach was three times more favorable than the quadrant-wise SRP approach (Wennström *et al*. 2005). Hence, tangible benefits of full-mouth ultrasonic debridement as an initial approach to subgingival infection control would be fewer appointments and less chair-time for treatment. Furthermore, available data regarding patients' experience of discomfort/pain related to the treatment do not indicate differences between full-mouth ultrasonic debridement and the quadrant-wise approach. It has to be recognized, however, that it is the quality of the instrumentation, not the time factor, that is the important issue in pocket/root debridement, and that the goal of the instrumentation is to reduce the bacterial load at all tooth sites below the threshold level at which the individual host can cope with the remaining infection. It is important to point out that the studies referred to should not be interpreted to justify a protocol of a defined time for instrumentation in non-surgical periodontal therapy, but merely illustrate that many, but not all, pockets may respond positively to less aggressive instrumentation, which in fact supports the concept proposed by Kieser (1994) that the clinical healing obtained following initial pocket/root debridement should be assessed before more extensive instrumentation efforts, including root planing, are performed.

Re-evaluation following initial non-surgical periodontal treatment

Although recent studies indicate that the conventional section-wise as well as the full-mouth debridement approach, combined with careful instruction in self-performed plaque control methods, are evidence-based and rational initial approaches to the treatment of patients with chronic periodontitis (Fig. 30-12), it is important to be aware that all lesions may not be resolved (Fig. 30-13). Hence, a critical component in the establishment of periodontal infection control is to follow up the initial non-surgical treatment and to perform a re-evaluation examination with regard to sites with remaining clinical signs of pathology.

An increased resistance of the periodontal tissues to probing and absence of bleeding are signs of resolution of the inflammatory lesion related to a sufficient removal of biofilm/calculus. Thus, clinical end points of treatment success may be defined as (1) no bleeding on pocket probing and (2) "pocket closure", that is a PPD of ≤4 mm. PPD change is a combined result of recession of the gingival margin and decreased probe penetration into the pocket due to resolution of the inflammatory lesion in the bordering soft tissues (Fig. 30-14).

Pocket reduction or "pocket closure" as an important outcome variable is validated by data showing that it demonstrates lower risk for disease progression and tooth loss (Westfelt *et al*. 1988; Badersten *et al*. 1990; Claffey & Egelberg 1995; Lang & Tonetti 2003; Matuliene *et al*. 2008). In a retrospective study including 172 subjects followed for a mean of 11 years after active periodontal therapy, Matuliene *et al*. (2008) reported that, compared with a PPD of ≤3 mm, a remaining PPD of 5 mm represented a risk factor for tooth loss with an odds ratio of 7.7. The corresponding odds ratios for a remaining PPD of 6 mm and ≥7 mm were 11.0 and 64.2, respectively. The long-term influence of the variable "bleeding on probing" on tooth loss was addressed in a 26-year longitudinal study of 565 Norwegian males (Schätzle *et al*. 2004), and revealed that teeth that at all examinations were positive for bleeding on probing had a 46 times higher risk of being lost compared with teeth not showing gingival inflammation. Hence, these data justify the use of "pocket closure" and absence of bleeding on probing as clinical end points of treatment success in the re-evaluation following periodontal treatment.

On average about 35% of initially pathologic pockets may not reach the end point of treatment success at re-evaluation following initial non-surgical periodontal therapy, and this percentage is independent of the type of instruments or approach used for subgingival debridement (Wennström *et al*. 2005; Jervøe-Storm *et al*. 2006; Suvan *et al*. 2020). Generally, clinical improvement is less pronounced at molars, particularly at furcation sites, than at single-rooted teeth (Lindhe *et al*. 1982; Loos *et al*. 1989). However, there are certainly many other factors related to the patient, the tooth, and the tooth site that might influence the treatment response. The use of multilevel statistical modeling allows the simultaneous investigation of factors at different levels. As an example, in Table 30-1 the probability of "pocket closure" (final PPD ≤4 mm) following initial non-surgical therapy could be estimated for pockets of various initial PPD, taking into consideration the factors smoking habit, single- or multirooted tooth, as well as presence/absence of supragingival plaque at the level of the tooth site (Tomasi *et al*. 2007). The marked difference in probability of pocket closure noted between smokers and non-smokers (e.g. 36% versus 63% for 7 mm deep pockets) places the focus on smoking as a significant factor influencing treatment outcome following non-surgical periodontal therapy. Smoking is proven to negatively affect the outcome of all modalities of

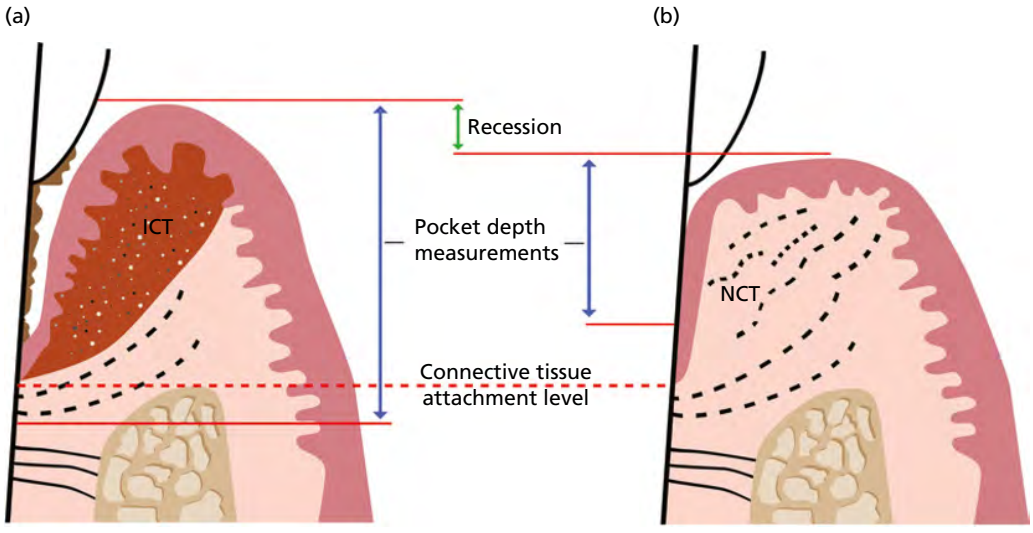


Fig. 30-14 A gingival unit (a) before and (b) after periodontal therapy. Probing depth measurements are shown by the blue lines. The dotted line indicates the "histologic" attachment level. The green line shows degree of recession of the gingival margin. ICT, infiltrated connective tissue; NCT, non-infiltrated connective tissue.

Table 30-1 Predicted probability of pocket closure (probing pocket depth ≤4 mm and no bleeding on probing) for sites with different initial depth.

	Oral hygiene	Tooth-type	Initial pocket depth		
			6 mm	7 mm	8 mm
Non-smoker	No plaque	Single-rooted	84%	63%	36%
	No plaque	Multirooted	70%	43%	19%
	Plaque	Single-rooted	76%	50%	24%
	Plaque	Multirooted	57%	30%	12%
Smoker	No plaque	Single-rooted	64%	36%	16%
	No plaque	Multirooted	43%	20%	7%
	Plaque	Singlerooted	51%	25%	10%
	Plaque	Multirooted	31%	12%	4%

(Source: Adapted from Tomasi *et al*. 2007. Reproduced with permission from John Wiley & Sons.)

periodontal therapy (Labriola *et al*. 2005; Heasman *et al*. 2006) and hence, if the patient is a smoker, inclusion of a smoking cessation program should be considered as an adjunctive measure.

Efficacy of repeated non-surgical pocket/root instrumentation

If the patient fails to maintain an adequate standard of oral hygiene, efforts have to be devoted to improving the patient's motivation. Persisting pathologic pockets, that is with a PPD of ≥5 mm and bleeding on probing, should be subjected to re-instrumentation efforts which now may also include root planing. The patient is then scheduled for a new re-evaluation and a decision regarding potential need for supplementary active treatment options. Whether it will be worthwhile to once again carry out repeated non-surgical instrumentation of a site/tooth that shows poor response to the performed subgingival debridement, or if other treatment modalities (e.g. adjunctive antimicrobial therapy, open-flap debridement, surgical pocket reduction) to achieve the goal of periodontal infection control should be selected, is a delicate decision in which both subject- and site-specific factors, as well as clinical skills and experience, have to be considered. Largely clinical improvements following pocket retreatment by non-surgical SRP are rather limited compared with those following the initial phase of subgingival instrumentation (Badersten *et al*. 1984; Wennström *et al*. 2005). It has been shown that of all sites that respond poorly to initial mechanical debridement, only 11–16% might be brought to a successful treatment end point following mechanical re-instrumentation, and about 50% of the pockets with an initial PPD of ≥7 mm will remain as non-successful sites (Wennström *et al*. 2005). Another study evaluating the outcome of re-instrumentation of periodontal sites showed that the overall probability of achieving "pocket closure" 3 months after retreatment was about 45%, whereas for sites with a PPD of >6 mm, the probability was only 12% (Tomasi *et al*. 2008). The fact that pockets associated with molars, furcation sites, and angular bone defects have been shown to respond less favorably to repeated non-surgical instrumentation (e.g. Axtelius *et al*. 1999; D'Aiuto *et al*. 2005; Tomasi *et al*. 2007) should be considered in the decision-making process regarding selection of retreatment procedure and the potential benefit of repeated non-surgical instrumentation.

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Chapter 31

Treatment of Acute Periodontal and Endo-Periodontal Lesions

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Introduction

Acute lesions affecting the periodontal tissues (see Chapter 19) often require immediate action, with the patient seeking emergency care because of acute pain, which is uncommon in periodontal practice. Moreover, and also in contrast with most chronic periodontal diseases and conditions, rapid onset and destruction of periodontal tissues may occur as a result of acute lesions, making early and swift diagnosis and treatment imperative (Papapanou *et al*. 2018). This chapter focuses on two acute conditions (abscesses in the periodontium and necrotizing periodontal diseases [NPDs]) and on endo-periodontal lesions (EPLs), which can occur in acute or chronic forms.

Treatment of periodontal abscesses

For the management of a periodontal abscess, the first crucial step is a quick and accurate diagnosis (see Chapter 19). Once it has been diagnosed, the type of periodontal abscess that has developed must be clarified (e.g. whether it is in a pre-existing pocket, and the associated etiological factors). The treatment should include two distinct phases: the initial control of the acute condition, in order to arrest tissue destruction and to control the symptoms (e.g. pain), and the management of the pre-existing and/or residual lesion, especially when the patient with a periodontal abscess has periodontitis.

Control of the acute condition

Four therapeutic alternatives have been proposed for periodontal abscesses: (1) tooth extraction, (2) drainage and debridement of the abscess, (3) systemic or local antimicrobials alone or in combination, and (4) surgery.

Tooth extraction

If the periodontal support of the tooth is severely damaged, and its prognosis is hopeless after the additional destruction caused by the abscess, the preferred treatment should be tooth extraction (Smith & Davies 1986). The rapid destruction of periodontal tissues caused by a periodontal abscess may negatively affect the prognosis of the affected tooth, and

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this has been considered the main cause of tooth extraction during periodontal maintenance (Smith & Davies 1986; Chace & Low 1993; McLeod *et al*. 1997; Silva *et al*. 2008). In addition, in periodontal abscesses in non-periodontitis patients with alteration of the root surface, in the category of severe root damage (fissure or fracture, cracked tooth syndrome) tooth extraction may also be the treatment of choice (for details, see the last section of this chapter).

Drainage and abscess debridement

The best treatment for a periodontal abscess, as for other abscesses in the body, should include drainage (through the pocket or through an external incision), compression and debridement of the soft tissue wall, and the application of topical antiseptics after drainage. However, no specific study has directly evaluated this treatment approach. If the abscess is associated with a foreign body impaction, the object must be eliminated through careful debridement (Abrams & Kopczyk 1983), although the foreign body is normally no longer present.

Antimicrobials

Systemic antimicrobials can be used as sole treatment, as initial treatment, or as an adjunctive treatment to drainage. Sole or initial treatment may only be recommended if pre-medication is required, or when the infection cannot be conclusively located and adequate drainage cannot be ascertained (Lewis *et al*. 1986). As an adjunctive treatment to drainage and debridement, systemic antimicrobials may be considered if there is clear systemic involvement (Ahl *et al*. 1986; Lewis *et al*. 1986). The duration and type of antibiotic therapy is also a matter for discussion, including the recommendation of shorter courses of drugs (Lewis *et al*. 1986; Martin *et al*. 1997). The available scientific evidence on the efficacy of these therapies, however, is very limited, with only two prospective case series and one randomized clinical trial (RCT) available. Smith and Davies (1986) evaluated drainage of the abscess, together with adjunctive systemic metronidazole (200 mg, three times a day [t.i.d.], 5 days), followed by delayed periodontal therapy. They followed 22 abscesses for up to 3 years, and most studied teeth (14) were finally extracted. Hafström *et al*. (1994) proposed drainage through the periodontal pocket, irrigation with sterile saline, supragingival scaling, and tetracycline for 2 weeks (1 g per day). Twenty abscesses were included in this study, with 13 of them followed for 180 days, with significant reductions in suppuration, bleeding, and probing depth that lasted, in the latter case, for 6 months. The authors highlighted the importance of drainage and an increased potential for regeneration if deep scaling is not performed at the initial phase of abscess treatment. Herrera *et al*. (2000) compared azithromycin (500 mg, once a day [q.d.], 3 days) versus amoxicillin plus clavulanate (500 plus 125 mg, t.i.d., 8 days), with delayed scaling (after 12 days), in 29 patients with an abscess, followed for 1 month. Both protocols were similarly effective in controlling signs and symptoms of the acute processes, including significant reductions in probing depth (1.6–1.8 mm) or in pain or swelling.

Local antimicrobials have only been tested in a RCT (Eguchi *et al*. 2008) which compared irrigation with sterile physiological saline and 2% minocycline hydrochloride ointment (Periocline®, Sunstar Inc., Osaka, Japan) with irrigation with sterile physiological saline without the local antibiotic in 91 patients for 7 days. At 7 days, microbiological outcomes (frequency of detection of different pathogens) and periodontal pocket depth reduction (test, 0.56 mm versus control, 0.18 mm) were considered better in the test group.

Periodontal surgery

Surgical procedures have also been proposed, mainly for abscesses associated with deep vertical defects (Kareha *et al*. 1981), or in cases after subgingival periodontal instrumentation in which calculus is left after treatment (Dello Russo 1985). A case series evaluating a combination of an access flap with deep scaling and irrigation with doxycycline is also available, reporting "good results", but no clear data were presented in the manuscript (Taani 1996).

Treatment protocol

In summary, the first line of treatment for a periodontal abscess is drainage and debridement, as for all abscesses in the human body. Alternative approaches may be considered in specific clinical scenarios:

- If tooth prognosis is deemed hopeless, tooth extraction should be the treatment of choice.
- If drainage and debridement is not possible because of a lack of access or the abscess is not well-localized, or there is a need to premedicate the patient, a systemic antimicrobial should be prescribed as initial therapy and, when possible, drainage and debridement should be scheduled.
- If the infection is associated with severe systemic involvement and/or the immune system of the patient is affected, an adjunctive systemic antimicrobial should be considered.
- If there is solid evidence that the abscess is caused by a foreign body impaction which is still in place, periodontal surgery may be the only approach to eliminate the foreign body.

When selecting a systemic antimicrobial, there is a choice of drugs and dosages which may be effective. However, metronidazole, 200–250 mg, t.i.d., for the duration of the active lesion (2–3 days) may be the best option, considering the similarity of the microbiological profile of these lesions with that of periodontitis (for details see Chapter 19).

Subgingival mechanical instrumentation must be avoided at this first stage of treatment because it may

cause irreversible damage to healthy periodontal tissues adjacent to the lesion, particularly when the swelling is diffuse or is associated with marked tissue tension. In addition, acute lesions have some potential for regeneration during healing. Therefore, subgingival mechanical instrumentation should only be performed once the acute lesion has been controlled.

Re-evaluation of treatment outcomes

After drainage and debridement, the patient should be recalled 24–48 hours later to evaluate the resolution of the abscess (Fig. 31-1) and, if needed, the duration of the antimicrobial intake. Once the acute phase has resolved, the patient should be scheduled for management of the pre-existing and/or residual lesion.

Management of the pre-existing and/or residual lesion

Periodontal abscesses in periodontitis patients should be treated appropriately depending on the clinical scenario. Periodontal therapy should be recommended for acute exacerbation in untreated patients; for patients in periodontal maintenance or refractory cases, and different treatment options should be considered after evaluation of the possible reasons for active disease onset. In patients already receiving active periodontal therapy, adequate subgingival instrumentation should be performed in those who have already been treated with scaling and root planing or with systemic antimicrobials with no adjunctive instrumentation; in abscesses detected after a periodontal surgery, careful removal of possible foreign bodies may be needed.

No additional treatments are needed for periodontal abscesses in non-periodontitis patients. For cases of impaction, advice should be given to the patient on oral hygiene. For cases associated with orthodontic factors, consultation with the orthodontist may be crucial. For cases of gingival overgrowth, periodontal surgery may be considered. For patients with root damage, the severity and magnitude of the damage will influence both the prognosis and management, once the periodontal abscess has been controlled.

Treatment of necrotizing periodontal diseases

Due to the specific features of NPDs (rapid tissue destruction, acute course/onset, and pain), the diagnosis (see Chapter 19) and treatment of these conditions must be provided as quickly as possible. Conventional periodontal therapies may need adjunctive measures (Johnson & Engel 1986; AAP 2001). Treatment should be organized in successive stages,

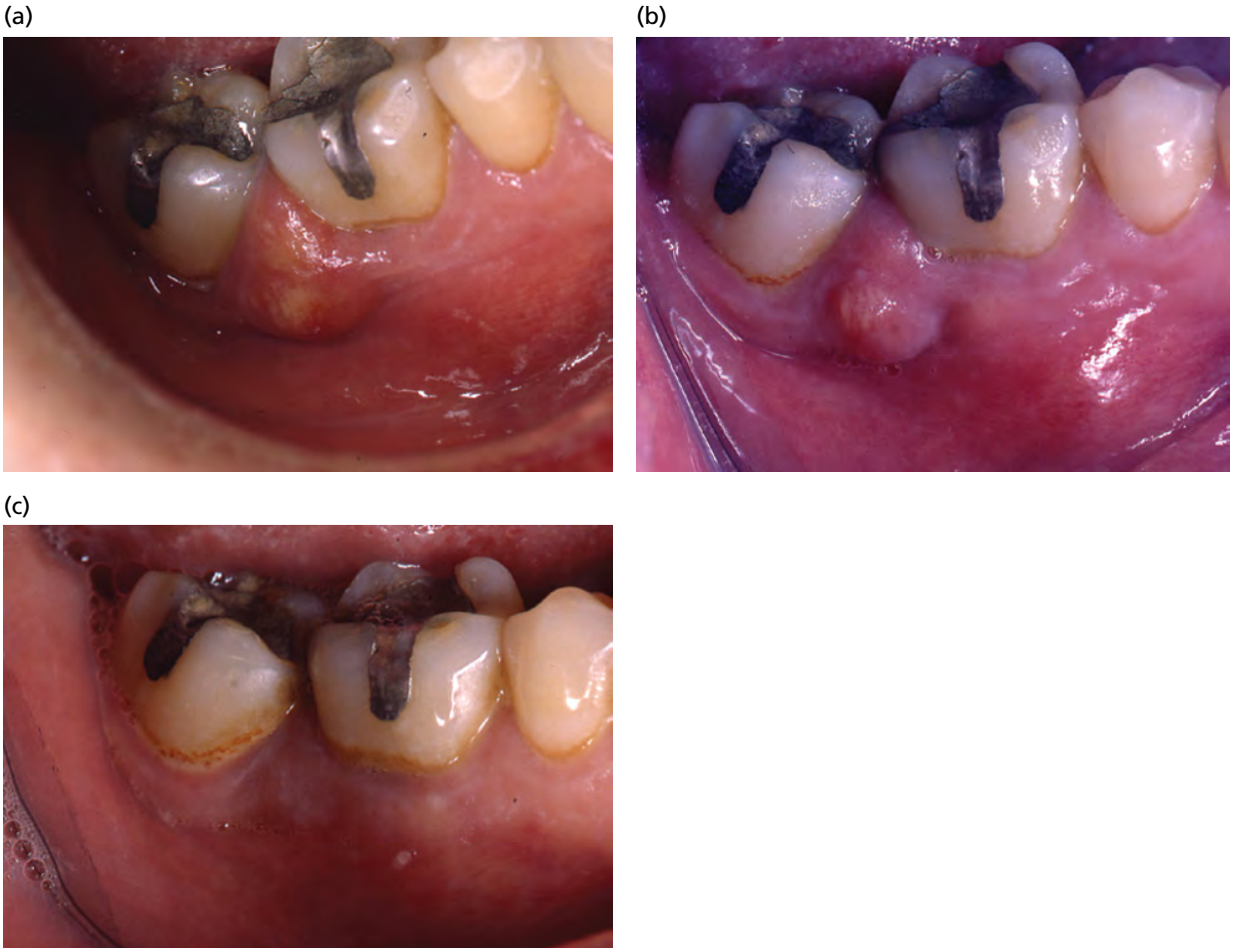

Fig. 31-1 Treatment of a periodontal abscess with systemic antibiotics (azithromycin, 500 mg, q.d., 3 days), without drainage, debridement or instrumentation (a) Baseline situation; (b) 5 days after antibiotic therapy; (c) 12 days after antibiotic therapy, just before the subgingival instrumentation.

including the control of the acute condition and a subsequent treatment phase that should include treatment of the pre-existing condition, corrective treatment of the disease sequelae, and a supportive or maintenance phase. However, different approaches can be applied, depending on the level of compromise in a patient's immune system: moderately and/or short-term immunocompromised patients or continuously and severely immunocompromised patients.

Treatment of necrotizing periodontal diseases in moderately and/or short-term immunocompromised patients

Control of the acute condition

There are two main objectives for treatment in patients who are moderately and/or short-term systemically immunocompromised: to arrest the NPD process and tissue destruction, and to control the patient´s general feeling of discomfort and pain, which may be interfering with nutrition and oral hygiene practices (Holmstrup & Westergaard 2008). The first task should be a careful superficial debridement to remove soft and mineralized deposits. Power-driven devices (e.g. ultrasonic devices) are usually recommended at this stage, exerting minimum pressure over the ulcerated soft tissues, without anesthesia. The debridement should be performed daily, becoming deeper as the tolerance of the patient improves, for as long as the acute phase lasts (normally 2–4 days). To avoid pain, mechanical oral hygiene measures should be limited; in addition, brushing directly on the wounds may impair healing. During this period the patient is advised to use antiseptic agents; chlorhexidine-based mouth rinses (at 0.12–0.2%, twice daily) are recommended. Other products have also been suggested, such as 3% hydrogen peroxide diluted 1:1 in warm water, and other oxygen-releasing agents, which not only contribute to the mechanical cleaning of the lesions, but also provide the antibacterial effect of oxygen against anaerobes (Wennstrom & Lindhe 1979). Other oxygen-based therapies have also been evaluated, such as a local oxygen therapy, which may help to reduce or even eradicate microorganisms, resulting in faster clinical healing with less periodontal destruction (Gaggl *et al*. 2006).

In severe cases with clear systemic involvement (e.g. fever or malaise), or in those patients who show an unsatisfactory response to debridement, the use of systemic antimicrobials may be considered. Metronidazole, at a dose of 250 mg every 8 hours, may represent the first line of treatment, due to its effectiveness against strict anaerobes (Loesche *et al*. 1982). Other systemic drugs have also been proposed, including penicillin, tetracyclines, clindamycin, amoxicillin, or amoxicillin plus clavulanate. Conversely, locally delivered antimicrobials are not recommended because they cannot reach adequate concentrations to be able to treat bacteria present within the tissues.

Re-evaluation of treatment outcomes

Patients must be followed-up very closely, daily if possible, and as symptoms and signs improve, strict mechanical hygiene measures should be enforced. In addition, complete debridement of the lesions should be performed (i.e. complete elimination of calculus and biofilm deposits; see Fig. 31-2).

Management of the pre-existing condition

NPDs normally develop over a pre-existing gingivitis (necrotizing gingivitis) or periodontitis (necrotizing periodontitis). Once the acute phase has been controlled, the treatment of the pre-existing chronic condition should be implemented, including professional mechanical plaque removal (in gingivitis) and/or scaling and root planing (in periodontitis). Oral hygiene instructions and motivation should be enforced. Existing predisposing local factors, such as overhanging restorations, interdental open spaces, and tooth malposition should be carefully evaluated and treated (Horning & Cohen 1995). At this stage, and also during the acute phase of therapy, attention should be paid to the control of the systemic predisposing factors, including smoking, inadequate sleep, psychological stress, or relevant systemic conditions.

Management of the residual lesions/sequalae

The correction of the altered gingival topography caused by the disease should be considered (Fig. 31-3)

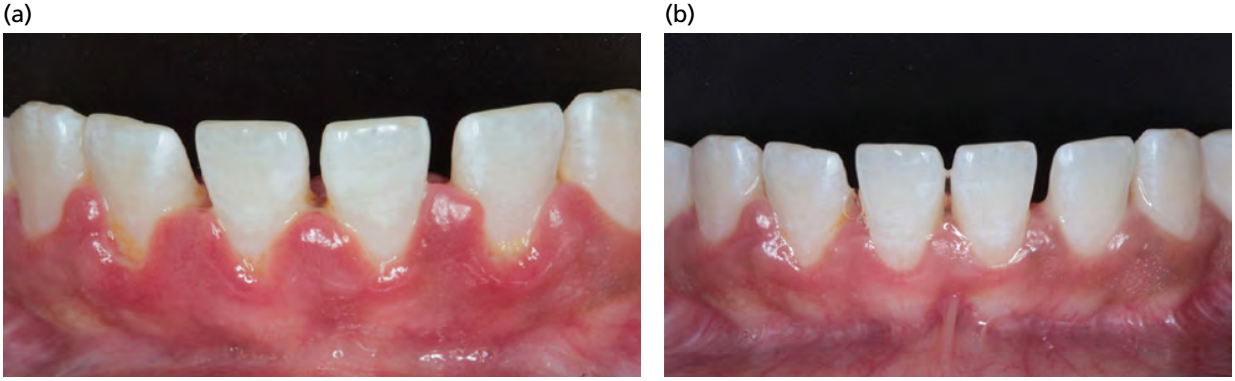

Fig. 31-2 Healing of necrotizing gingivitis lesions, after treatment, in the lower anterior sextant. (a) Lesions with necrosis in the interdental papillae. (b) Complete resolution after 60 days. (Source: Courtesy of Dr. Nidia Castro dos Santos and Mauro Santamaria.)

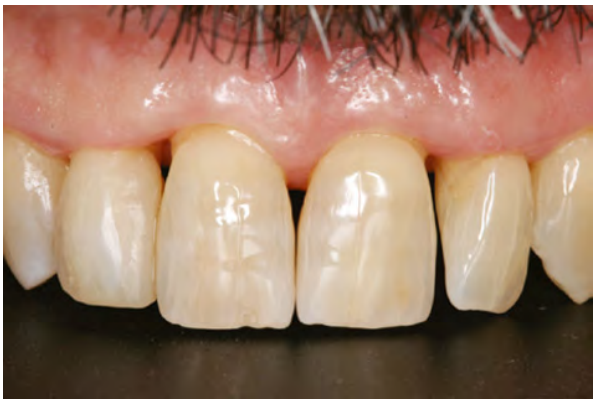

Fig. 31-3 Sequelae, namely absence of interdental papillae and gingival crater formation. (Source: Courtesy of Dr. Marcio Grisi.)

because gingival craters may favor plaque accumulation and disease recurrence. Gingivectomy and/or gingivoplasty procedures may be helpful to treat superficial craters; for deep craters, periodontal flap surgery or even regenerative surgery represent more suitable options (Holmstrup & Westergaard 2008).

Supportive periodontal care

During this phase, the main goals are compliance with oral hygiene practices and the control of the predisposing factors as previously explained.

Treatment of necrotizing periodontal diseases in continuously and severely immunocompromised patients

HIV-positive patients

HIV-positive patients may not be aware of their serologic status. Occurrence of NPDs in systemically healthy individuals is suggestive of HIV infection, and therefore the affected individuals should be screened for HIV (Hodge *et al*. 1994; Horning & Cohen 1995; Holmstrup & Westergaard 2008). Although no sound scientific evidence is available to support a specific therapeutic protocol for NPDs in HIV-positive patients (Winkler *et al*. 1989; Ryder 2000; Yin *et al*. 2007), a commonly used treatment includes debridement of bacterial deposits, alone or combined with the irrigation of the site with iodine povidone, based on its hypothetic anesthetic and bleeding control effects (Yin *et al*. 2007), or with chlorhexidine. Careful consideration should be made regarding the use of systemic antimicrobials, because of the risk of overinfection with *Candida* spp. Metronidazole has been recommended because of its relatively narrow spectrum and limited effects on Gram-positive bacteria, which may prevent *Candida* spp. overgrowth (Winkler *et al*. 1989; Ryder 2002; Yin *et al*. 2007). Other authors have suggested that HIV-positive patients may not need antibiotic prophylaxis for the treatment of NPDs (Lucartorto *et al*. 1992), and there are no clear data to support the two protocols. In non-responding cases, the use of antifungals may be beneficial, including clotrimazole lozenges, nystatin vaginal tablets, systemic fluconazole, or itraconazole, mainly in cases of severe immune suppression (Ryder 2002; Yin *et al*. 2007). The decision on which treatment protocol should be selected, together with ultrasonic debridement (i.e. alone or with irrigation with povidone iodine or chlorhexidine; with or without adjunctive systemic metronidazole; with or without antifungals) may depend on the systemic status of the patient and the severity of the lesion. Therefore, in HIV-positive patients, systemic status should be closely monitored, including viral load and hematologic and immune status, leading to a customized periodontal treatment plan (Robinson 2002; Ryder 2002; Yin *et al*. 2007).

Children with severe malnourishment, extreme living conditions, and/or severe (viral) infections

NPDs in children in certain regions of Africa (including noma) is associated with a severely compromised immune response caused by severe malnourishment, extreme living conditions, and severe (viral) infections. Very limited information is available on the management of this condition. Recommendations for the prevention of noma include: encouraging good nutritional practices, promotion of breast-feeding during the first 3–6 months of life, immunization against endemic communicable diseases, proper oral hygiene practices, segregation of livestock from human living areas, and education about the etiology and consequences of noma (Enwonwu 2006). Yet it is clear that the elimination of the primary causes would require improvement in living conditions through the eradication of poverty.

If the condition has already developed, and it is in an acute phase, management should include the following (Enwonwu 2006): correction of dehydration and electrolyte imbalance, treatment of associated diseases (e.g. malaria and measles), testing for HIV infection, the administration of antibiotics (e.g. penicillin and metronidazole), local wound care with antiseptics, and removal of tissue sloughs and sequestra. Surgery should only be performed once the acute phase has been controlled.

Treatment of endo-periodontal lesions

Treatment of EPLs has always been a challenge for clinicians, because they are normally associated with a poor tooth prognosis. However, it is important to bear in mind that not all EPLs should lead to tooth extraction; many cases are treatable and may have a favorable prognosis over time (Rotstein & Simon 2004; Sunitha *et al*. 2008) (see Fig. 31-4). Understanding the biological factors that influence the prognosis of a tooth with an EPL is crucial for effective treatment planning (see Chapter 19). In brief, EPLs may occur in acute or chronic forms. For example, acute lesions associated with a recent traumatic or iatrogenic event (e.g. root fracture or perforation) are normally accompanied by an abscess and pain, whereas in subjects with periodontitis or in periodontal maintenance,

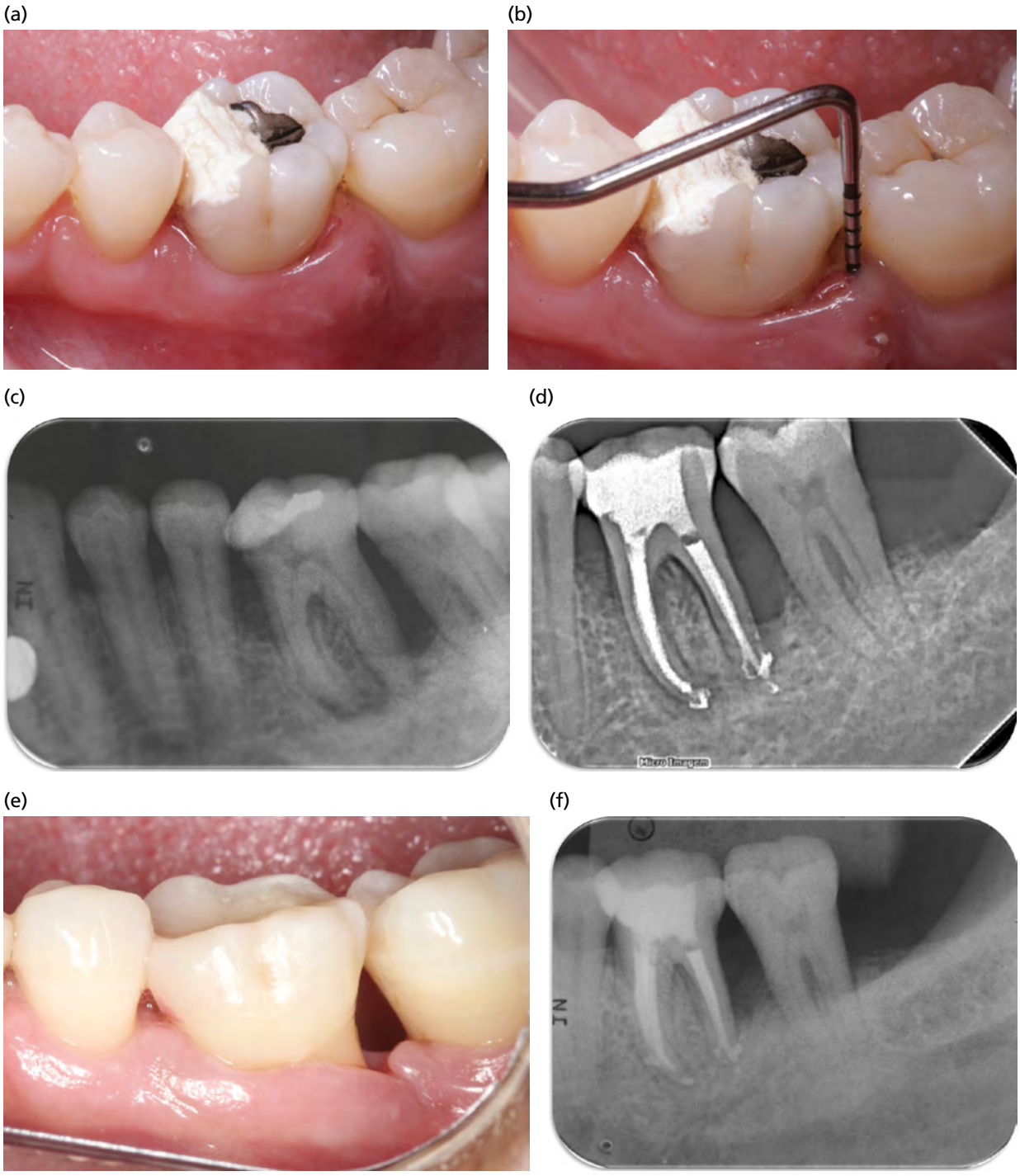

Fig. 31-4 Endo-periodontal lesion without root damage (grade 3) in a non-periodontitis patient, with acute presentation (tooth 36). (a, b) Clinical examination showed presence of periodontal pocket of 10 mm, sinus tract and absence of vitality, and (c) radiographic examination showed evidence of severe bone loss. Treatment included: *session 1* – first phase of endodontic treatment, with access and cleaning of the root canal, medication with calcium hydroxide; *session 2* (30 days after the first session) – scaling and root planning, systemic clarithromycin (500 mg, two times a day [b.i.d.], 3 days), calcium hydroxide was changed; *session 3* (30 days after the second session) – root canal filling (d). At 6 months post-treatment, there were no clinical signs of inflammation (e) and radiographic bone stability was observed (f). (Source: Courtesy of Dr. Mauro Santamaria.)

EPLs normally present slow and chronic progression without evident symptoms. A classification system for these lesions has been recently proposed and is presented in Chapter 19 (Herrera *et al*. 2018). This is relevant, since the precise classification of a condition is the first step towards defining effective treatment protocols.

Prognosis of teeth with endo-periodontal lesions

Determining the prognosis of a tooth affected by an EPL is one of the most difficult steps in managing these lesions, and it should be based on the following criteria: (1) presence/absence of root damage;

(2) presence of periodontitis; (3) anatomic problems (e.g. grooves); (4) severity and extent of the periodontal defect on the affected tooth (including furcation involvement) (Rotstein & Simon, 2004; Schmidt *et al*. 2014, Rotstein 2017; Herrera *et al*. 2018).

One of the main reasons for the proposal of the new classification scheme for EPLs in 2018 (Herrera *et al*. 2018; Chapter 19) was the inability of the previous classification systems to establish clinical criteria able to define the prognosis of a tooth affected by these lesions. According to the classification system proposed in 2018, the three main prognoses for a tooth with an EPL are: (1) hopeless, (2) poor, and (3) favorable. These prognoses vary according to the different categories proposed in the new classification, especially with EPLs associated or not with root damage.

EPLs with root damage are associated with root fracture, perforation of the pulp chamber/root canal, or root resorption. The teeth affected by such lesions usually have a hopeless prognosis, and usually extraction is the only option. The exceptions to these cases will be discussed later in this chapter and include partial fractures, small perforations, or minor root resorptions (see *Steps in the management of an endo-periodontal lesion*). The prognosis of EPLs without root damage mainly depend on the presence of periodontitis and the degree of periodontal destruction around the affected tooth. In periodontitis patients, the dysbiosis present in the oral cavity is so profound that changing this ecology back to symbiosis becomes a real challenge (Socransky & Haffajee 2002; Haffajee *et al*. 2006; Teles *et al*. 2006, 2013) and this may influence the treatment of the EPLs in patients with periodontitis. Similarly, the more severe is the periodontal destruction around the tooth affected by an EPL, the poorer is the prognosis.

Should endo-periodontal lesions with hopeless or poor prognosis be treated?

The decision of whether or not to treat a tooth with EPLs with a hopeless or poor prognosis has been a topic of debate, mainly due to the multiple biological implications and therapeutic outcomes associated with such cases. Interpreting the literature in this area is not easy, because most of the published clinical studies dealing with EPLs are case reports or case series. In addition to the fact that these studies do not provide robust data for evidence-based practice, they normally present only cases that have shown a favorable prognosis after one or more therapeutic modalities. This makes it difficult to establish the percentage of treatment success for EPLs associated with a poor prognosis, or even the actual survival rate of such cases. Some authors have made the therapeutic decision to extract the teeth affected by EPLs with poor prognosis (Pecora *et al*. 1996; Casap *et al*. 2007; Blanchard *et al*. 2010; Keceli *et al*. 2014), while others have successfully treated such cases with a single therapy or a combination of protocols (Table 31-1).

A few unconventional therapeutic options have been proposed for the treatment of teeth with EPLs and hopeless prognosis, including intentional replantation of teeth after performing disinfecting procedures (Oishi 2017; Zakershahrak *et al*. 2017; Yan *et al*. 2019). In theory, a tooth with an EPL of poor prognosis could be treated and remain in the mouth until the clinician is able to evaluate the post-treatment improvement in the long term. However, the function of that tooth in the patient's mouth needs to be considered on the decision of maintaining or extracting the tooth. General questions are important to determine the real viability of leaving this tooth in the mouth, such as if that tooth will be a prothesis abutment, or it needs an indirect rehabilitation (e.g. fixed prosthesis). It is important to remember that multirooted teeth with poor prognosis (e.g. affected by deep periodontal pockets, tooth mobility, or furcation defects), should not be left in the mouth of patients who need complex oral rehabilitation treatment, because these teeth are highly likely to be lost over time (Ekuni *et al*. 2009; Nibali *et al*. 2016).

Steps in the management of an endo-periodontal lesion

The treatment of EPLs have some peculiarities due to the great variability on the prognosis of the tooth affected by such lesions. The clinical characteristics of EPLs and the full mouth periodontal condition greatly influence treatment decision. Thus, before treatment two critical tasks should be accomplished: (1) to determine differential diagnosis between EPL with or without root damage, and (2) to decide whether to extract or to maintain the tooth (e.g. EPLs with tooth damage normally leads to tooth extraction). If the decision is to maintain the tooth, proceed to next steps of evaluation: (3) full-mouth periodontal assessment, and (4) decide whether to extract or to maintain the tooth (e.g. EPLs without tooth damage but with severe periodontal destruction that will be involved in an oral rehabilitation treatment normally should not be maintained). If the decision is to keep the tooth, proceed to the treatment phase, (5) endodontic and periodontal treatments (Fig. 31-5).

Differential diagnosis between endo-periodontal lesions with or without root damage

Because EPLs with root damage normally lead to tooth extraction, the first step of its management should be the precise differential diagnosis between a lesion with or without root damage. As described in Chapter 19, the main risk factors for the occurrence of an EPL with root damage are trauma and iatrogenic events (Herrera *et al*. 2018). Detailed dental history, and clinical and radiographic examination are normally able to determine the presence of cracks, fractures, perforations, and external root resorption (i.e. root damage). The signs/symptoms may be evident, facilitating the diagnosis, as in the case of a patient reporting a recent episode of trauma in the

Table 31-1 Treatment protocols for endo-periodontal lesions reported in publications including ≥10 lesions and their main characteristics.

Reference	Country	Study design	Number of volunteers	Mean age (or range) (years)	Number of teeth	EPL diagnostic	Full-mouth periodontal diagnosis	Treatment	Maximum follow-up	Prognosis
Ustaoglu *et al.* (2020)	Turkey	RCT	45	40	45 (intrabody defects)	Primary periodontal lesion with secondary endodontic involvement or true combined EPLs in single-rooted teeth	ND	Root canal treatment, OHI, supragingival scaling and SRP, OFD, T-PRF, and GTR	9 months	Favorable
Oh *et al.* (2019)	Korea	Retrospective study	41	ND	52	EPL	ND	Root canal treatment, OHI, supragingival scaling, and SRP, OFD + Bio-Oss© with or without bioresorbable collagen membranes	5 years	Favorable
Saida *et al.* (2018)	Japan	Case series	17	55.5	17	Primary endodontic lesions with secondary periodontal involvement, periodontal lesions, and "true" combined lesion	ND	Tooth extraction, cleaning of alveolus and dental root, resection of 2–3 mm of apical roots, sealing of the apical foramen, Emdogain© on the root surfaces, tooth insertion in the alveolus	2 years	Favorable
Tewari *et al.* (2018)	India	RCT	35	42.1	35	Periodontitis patient with at least one non vital tooth with concurrent EPL with apical radiolucency along with communication through periodontal pocket	Chronic periodontitis	SRP, root canal treatment, OFD after 21 days or 3 months of SRP/root canal	6 months	Favorable
Song *et al.* (2018)	South Korea	Retrospective study	83	43.12	83	EPL: Class D, Class E, Class F (Kim & Kratchman 2006)	ND	Endodontic microsurgery	12 months	Favorable
Raheja *et al.* (2014)	India	Clinical study	31	45.48	31	Combined EPL	ND	*Test*: Root canal (with CHX intracanal) + SRP + OFD *Control*: Root canal (without CHX intracanal) + SRP + OFD	6 months	Favorable (Test better than Control)
Song *et al.* (2012)	South Korea	Clinical study	172	11–71	172	EPL with endodontic or combined endo-periodontal origins	ND	OFD	10 years	Favorable

Kim *et al.* (2008)	South Korea	Clinical study	227	ND	263	Lesions of endodontic origin and combined endodontic-periodontal origin	ND	AMX 250 mg (t.i.d., 7 days) and ibuprofen 400 mg (1 hour before and after surgery), OFD, endodontic microsurgery	5 years	Favorable
Casap *et al.* (2007)	Israel	Case series	20	44.8	30	Subacute periodontal infection due to EPL, root fracture and/or periapical lesion	ND	Tooth extraction and implant placement	72 months	Hopeless
Pecora *et al.* (1996)	USA	Case series	9	41	32	Vertical root fractures (13), horizontal root fractures (8), root perforations (4), combined endodontic-periodontal involvement (7)	ND	Tooth extraction and implant placement	6 months	Hopeless

AMX, amoxicillin; CHX, chlorhexidine; EPL, endo-periodontal lesion; GTR, guided tissue regeneration; ND, not described; OFD, open flap debridement; OHI, oral hygiene instructions; RCT, randomized clinical trial; SRP, scaling and root planing; T-PRF, titanium-prepared platelet rich fibrin; t.i.d., three times a day.

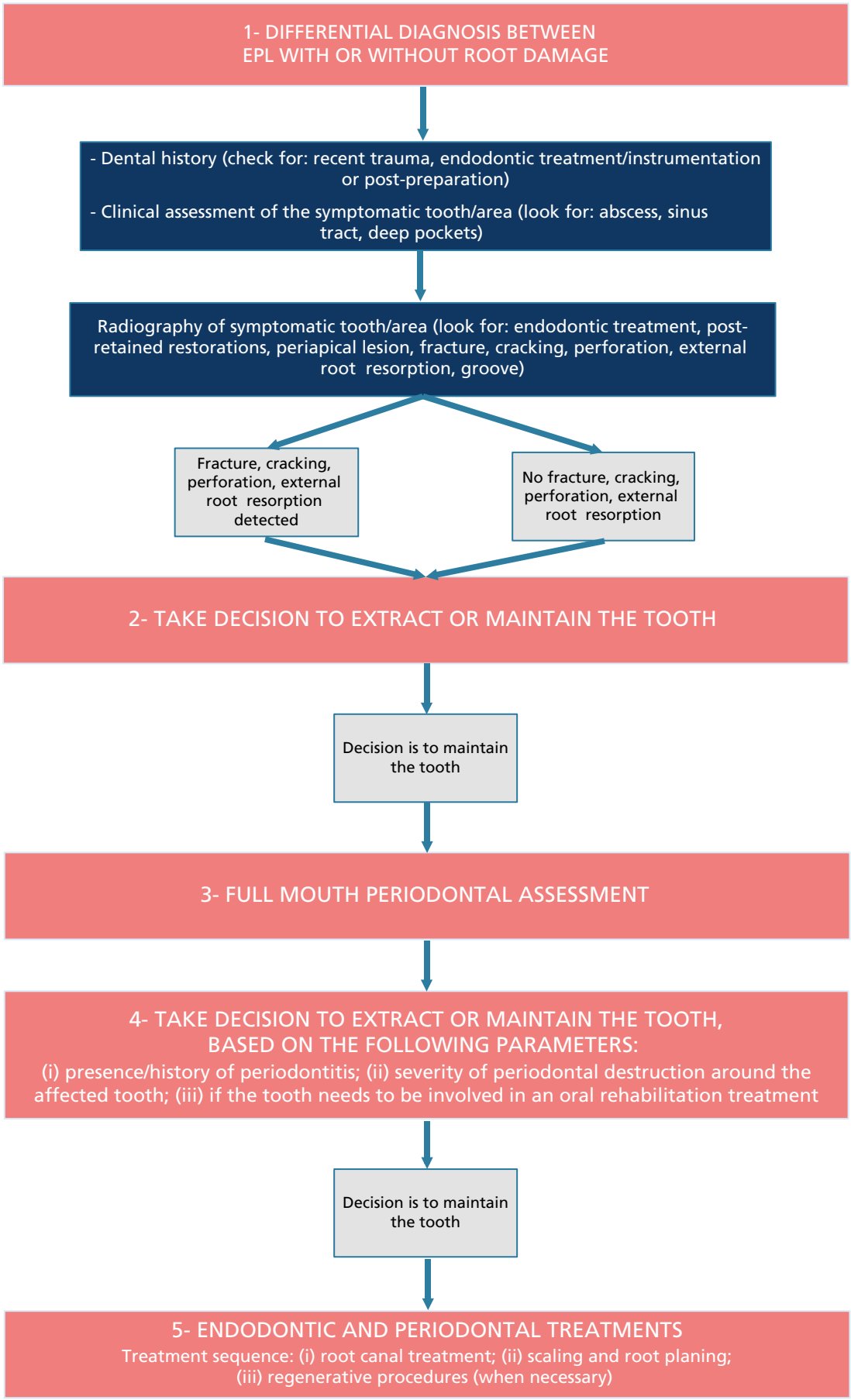

Fig. 31-5 Steps in the management of an endo-periodontal lesion (EPL).

trauma in the same region of a tooth presenting symptomatology or an abscess. Similarly, a patient with recent history of endodontic treatment and/or post preparation may indicate a diagnosis of perforation. Usually, radiography together with the presence of a deep pocket (or furcation involvement) would detect a fracture, crack, or perforation in such cases. However, caution should be taken in order to avoid misdiagnosis. For example, sometimes tomography is needed in order to confirm the diagnosis: a radicular groove might mimic a vertical root fracture on a radiograph (Attam *et al*. 2010) or a perforation may be overlooked in normal radiography (Fig. 31-6). Careful radiographic/tomographic evaluation and clinical examination of the root anatomy is of great importance at this stage to assess the integrity of the root and to help with differential diagnosis (Herrera *et al*. 2018). Nevertheless, if the clinical information does not allow the clinician to reach a definitive diagnosis, the clinician may decide to perform periodontal access surgery in order to examine the root surface. However, such surgeries can only be performed in the absence of clinical signs of an acute periodontal process (Sooratgar *et al*. 2016; Dhoum *et al*. 2018; Tewari *et al*. 2018). If there are difficulties in identifying any fracture lines or root damage during surgical procedures, the use of methylene blue and microscopic inspection have been suggested (Floratos & Kratchman 2012; Taschieri *et al*. 2016).

Decision to extract or to maintain the tooth (with root damage)

EPLs with root damage normally have very poor prognosis, but some cases associated with partial root damage may be treatable. Thus, if the EPL is associated with root damage, the extent of the damage should be carefully evaluated. Complete vertical root fractures would lead to tooth extraction, but some authors have obtained good clinical results when treating teeth with incomplete root fractures, by means of periodontal surgery and apicoectomy (Taschieri *et al*. 2016) or regenerative procedures (Floratos & Kratchman 2012). Intentional extraction, retrograde root canal treatment, and intentional replantation has also been suggested as a treatment option for incomplete fractures (Oishi 2017). Furthermore, teeth with external root resorption have also been successfully treated by means of open flap debridement and regenerative techniques (White & Bryant 2002). Also, *in vitro* and animal studies have suggested that chamber/root canal perforations may be treatable and treatment success depends on the size, location, time of diagnosis and treatment, severity of periodontal destruction, and biocompatibility of the repair material used (Jew *et al*. 1982; Himel *et al*. 1985; Beavers *et al*. 1986; Dazey & Senia 1990; Lee *et al*. 1993; Fuss & Trope 1996; Lomcali *et al*. 1996; Rotstein 2017). Overall, the best outcomes of treatment were observed for small perforations which were immediately sealed. Trioxide aggregate seems to be the most commonly used material to seal root perforations (Rotstein 2017).

Full-mouth periodontal assessment

If the decision based on the presence/absence of root damage is to maintain the tooth, a full-mouth periodontal assessment should be conducted in order to detect if the patient has periodontitis. Unfortunately, it is not common to find complete full-mouth periodontal information in the available scientific literature. Most interventional studies only report on the clinical characteristics of the "tooth" affected by an EPL (Table 31-1). In addition to the full-mouth periodontal evaluation, it is important to carefully determine the extent of the periodontal destruction around the tooth affected by the EPL. Several parameters should be assessed at the tooth level: probing depth, attachment level, presence of cavities, bleeding on probing, suppuration and mobility, as well as tooth vitality/sensibility and percussion tests (Herrera *et al*. 2018).

Decision to extract or to maintain the tooth (without root damage)

Based on the periodontal clinical parameters, the clinician should again take the decision to maintain or extract the tooth. At this stage, this decision should take into account the following: (1) presence/history of periodontitis, (2) severity of periodontal destruction around the affected tooth (grade of the lesion, Chapter 19), (3) if the tooth needs to be involved in oral rehabilitation treatment. If the tooth is to be maintained, anti-infective treatment of endodontic and periodontal tissues should begin.

Endodontic and periodontal anti-infective treatments

At this stage, all EPLs would require endodontic and periodontal treatment, but the concomitant resolution of these combined infectious processes is a challenge for clinicians. A wide spectrum of different anti-infective therapeutic options has been proposed. Table 31-1 presents a summary of the characteristics of the studies reporting on the treatment of at least 10 cases of EPLs (Kim *et al*. 2008; Song *et al*. 2012; Raheja *et al*. 2014; Saida *et al*. 2018; Song *et al*. 2018; Tewari *et al*. 2018; Oh *et al*. 2019; Ustaoglu *et al*. 2020). Overall, these studies have used the following treatment options (not in sequence order): non-surgical endodontic therapy, non-surgical periodontal therapy, or a combination of non-surgical endodontic therapy and non-surgical and/or surgical periodontal therapy. Periodontal surgeries normally consisted of an open flap debridement alone or in combination with regenerative (e.g. enamel matrix derivatives) or resective procedures, with or without local or systemic antimicrobials. In addition, over the years, the use of regenerative therapies has become more common in the treatment of EPLs (Fig. 31-7).

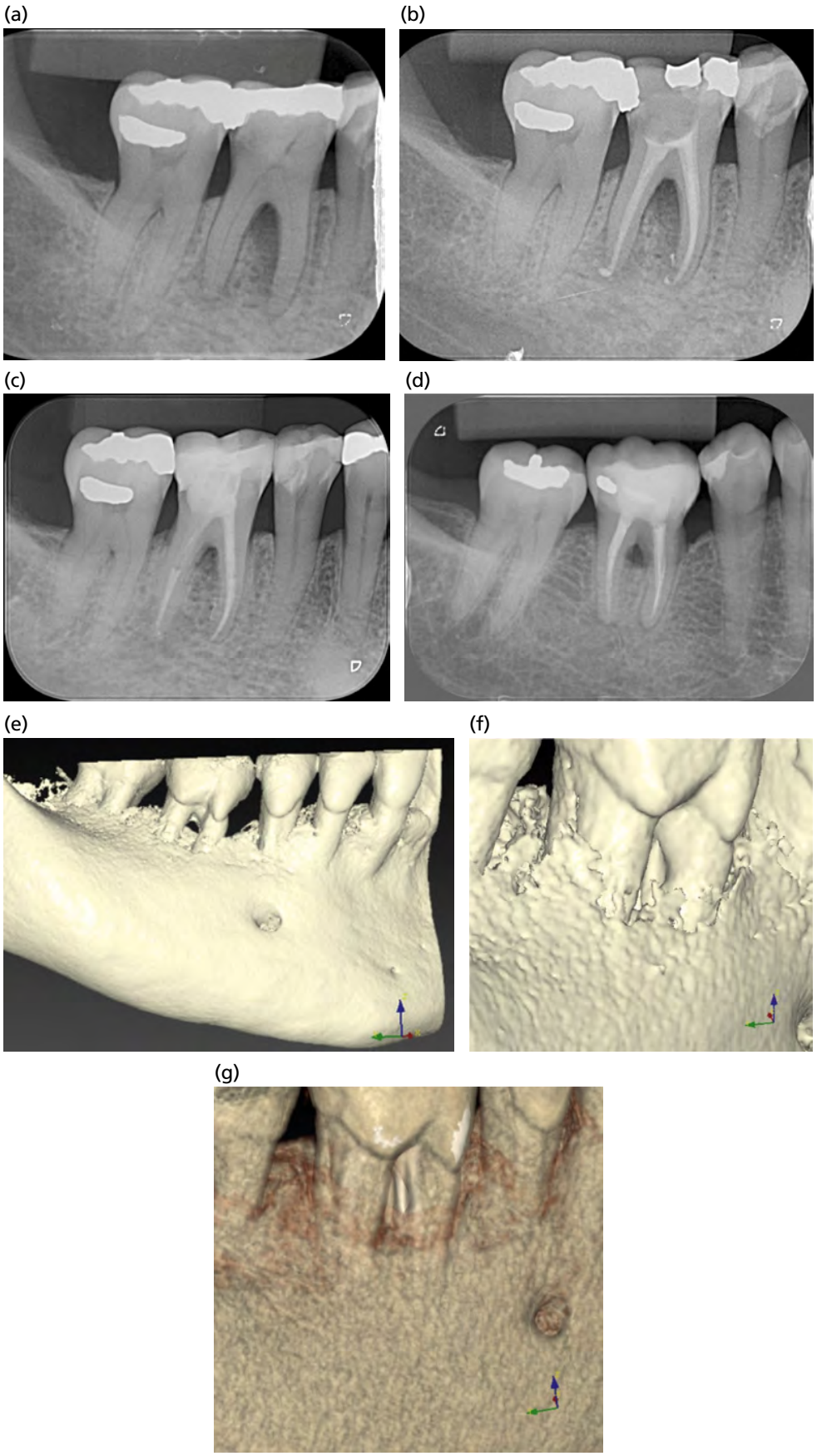

Fig. 31-6 Endo-periodontal lesion without root damage (grade 2) in a patient with periodontitis (tooth 46). (a) The tooth presented with class II furcation, bleeding on probing, and absence of vitality. (b) Treatment involved scaling and root planing and root canal treatment. (c) 6 months post-treatment, radiographic bone gain was observed. (d) During the supportive periodontal therapy session, 30 months post-treatment, bone resorption in the furcation region was detected, and (e–g) the 3D image of the tomography showed a perforation in the mesial root, with a new diagnosis of endo-periodontal lesion with root damage. Tooth extraction was recommended. (Source: Courtesy of Dr. Marcio Grisi.)

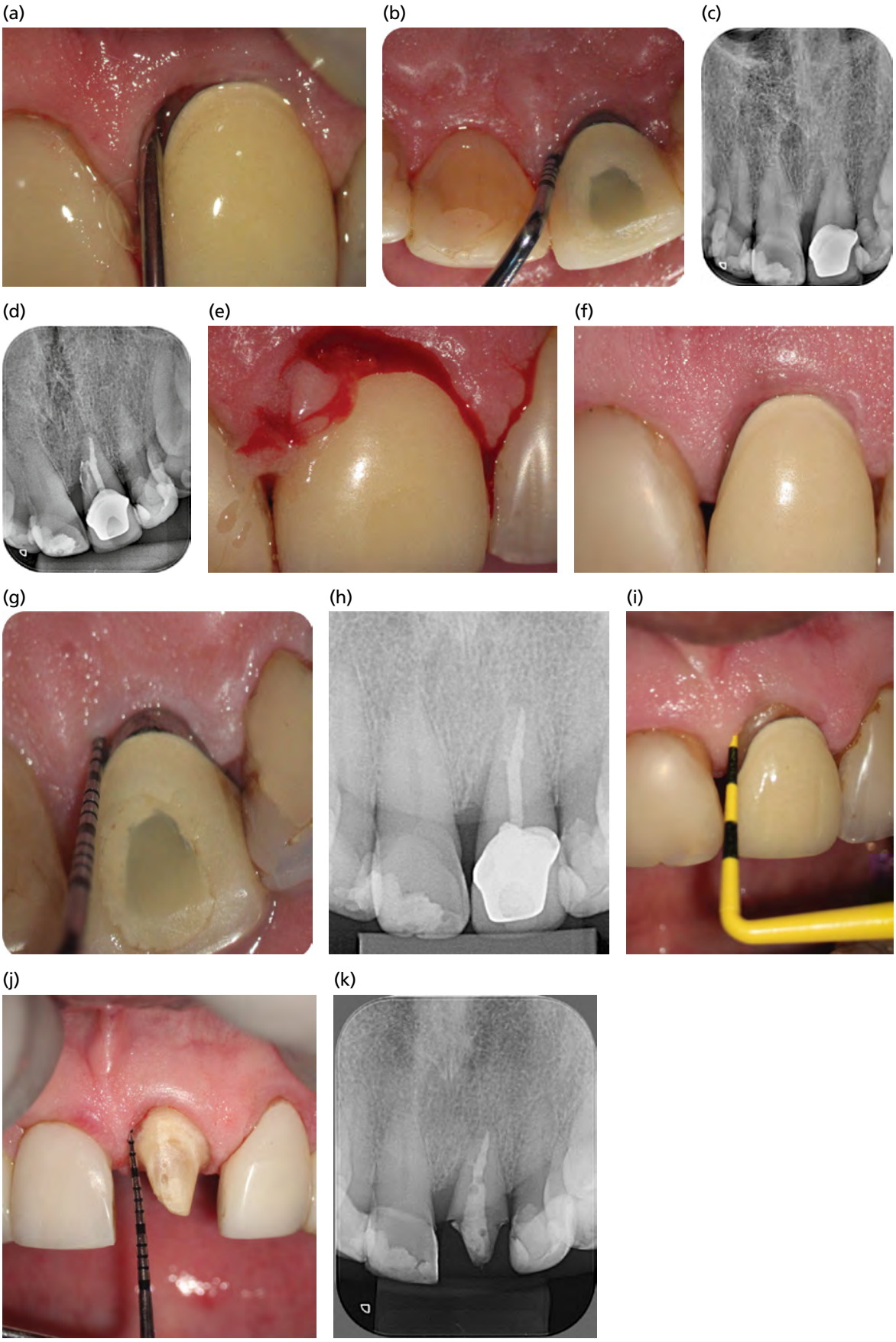

Fig. 31-7 Endo-periodontal lesion without root damage (grade 3) in non-periodontitis patient. Clinical examination showed deep periodontal pockets in the (a) buccal and (b) palatal surfaces, (c) radiographic bone loss and absence of vitality. The treatment included: root canal treatment (d) immediately followed by scaling and root planing with the application of enamel protein derivatives (Emdogain®), without surgical access (e). At 6 months post-treatment, clinical findings compatible with health were observed in the (f) buccal, and (g) palatal surfaces, and (h) bone gain was detected. At 24 months post-treatment, periodontal health was maintained (i) and the tooth was prepared for the next phases of the rehabilitation treatment (j, k). (Source: Courtesy of Dr. Marcio Grisi.)

The sequence order of the anti-infective treatment of EPLs has been a topic of debate. A systematic review published in 2014 (Schmidt *et al*. 2014), including 23 studies and 111 teeth with EPLs, and using tooth loss and probing pocket depth reduction as outcomes variables, concluded that there is some evidence to support the notion that root canal treatment should be the first therapeutic procedure for EPLs. However, this conclusion should be interpreted with caution as a marked heterogeneity was observed among the included studies, regarding the treatment protocols used. Thus, it is not yet fully established in the literature that endodontic treatment should always precede periodontal treatment in the management of EPLs.

The time lapse between endodontic and periodontal treatment in the management of EPLs have also been assessed and discussed. Most authors have stated that a time lapse of 1–3 months between endodontic and periodontal treatment should be respected, in order to facilitate adequate periapical and periodontal healing (Solomon *et al*. 1995; Chapple & Lumley 1999; Zehnder *et al*. 2002; Vakalis *et al*. 2005; Abbott & Salgado 2009; Oh *et al*. 2009; Raheja *et al*. 2014). However, an observation period of at least 6–12 months before re-evaluation of the first treatment stage of EPLs was advocated by Zehnder (2001), while Gupta *et al*. (2015) suggested that non-surgical periodontal treatment may be performed simultaneously with endodontic treatment. More robust studies in this area are necessary in order to determine the long-term clinical results of teeth affected by EPLs and treated by different treatment modalities and sequence orders.

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Part 12: Additional Therapy

Chapter 32

Periodontal Surgery

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Introduction

Periodontal surgery must be considered as an adjunctive to cause-related therapy and, therefore, the various surgical methods described in this chapter should be evaluated on the basis of their potential to facilitate removal of subgingival deposits and self-performed infection control, with the ultimate goal being to enhance the long-term maintenance of periodontal health.

The recently published EFP S3 level clinical guideline for the treatment of periodontitis stages I–III (Sanz *et al*. 2020) recommends that patients, once diagnosed, should be treated according to a pre-established stepwise approach to therapy that, depending on the disease stage, should be incremental, each including different interventions. *The first and second steps of periodontal therapy* are commonly referred to as cause-related therapy and include, in the first step, all needed behavioural change and motivation to undertake successful removal of supragingival dental biofilm by the patient and all measures headed toward risk factor control (smoking, glycaemic control, etc.). The second step includes all professional interventions aimed at reducing/eliminating the subgingival biofilm and calculus (subgingival instrumentation), with or without the use of adjunctive therapies (antimicrobials, anti-inflammatory, etc.).

These first and second steps of therapy should be used for all patients with periodontitis, irrespective of their disease stage, only in teeth with loss of periodontal support and/or periodontal pocket formation. The response to these two steps should be assessed once the periodontal tissues have healed (periodontal re-evaluation), usually between 6 and 12 weeks after the completion of the second step of therapy. Only when the endpoints of therapy (no periodontal pockets >4 mm with bleeding on probing (BoP) or no deep periodontal pockets [≥6 mm]) have not been achieved, then the third step of therapy should be considered.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

When the treatment is successful in achieving stable periodontitis, defined by gingival health on a reduced periodontium (BoP in <10% of the sites; shallow probing depths of 4 mm or less and no 4 mm sites with BoP), these patients should be placed in a supportive periodontal care (SPC) program. If these criteria are met but BoP is present at >10% of sites, then the patient is diagnosed as a patient with stable periodontitis. with gingival inflammation. Therefore, adequate measures for inflammation control should be implemented to prevent recurrent periodontitis, since periodontitis patients will always remain at increased risk of recurrent periodontitis in the presence of gingival inflammation.

The *third step of therapy* is aimed at treating those areas of the dentition not responding adequately to the second step (presence of pockets >4 mm with BoP or presence of deep periodontal pockets [≥6 mm]). The main purpose of this step of therapy is to gain further access to subgingival instrumentation, or in those lesions that add complexity in the management of periodontitis (intrabony and furcation lesions) to either regenerate or resect them. It may include the following interventions:

- Repeated subgingival instrumentation with or without adjunctive therapies
- Access flap periodontal surgery
- Resective flap periodontal surgery
- Regenerative periodontal surgery.

This chapter focuses on periodontal surgical techniques (access and resective flap periodontal surgeries) that specifically aim to gain further access to subgingival instrumentation and reduce pocket depths or other anatomical areas not suitable for subgingival instrumentation. Regenerative periodontal surgery and surgical treatment of furcation lesions are discussed in Chapters 38 and 33, respectively

The individual response to the third step of therapy should be re-evaluated to assess whether the previously defined endpoints of therapy have been achieved. In this case, patients should be placed in supportive periodontal care. However, in patients with severe stage III periodontitis these endpoints of therapy may not be achievable in all teeth and these sites will need close monitoring with frequent subgingival instrumentation.

Techniques in periodontal surgery (historical perspective)

Over the years, different surgical techniques have been introduced and used in periodontal therapy. Firstly, procedures were aimed to excise "*diseased gingiva*" (gingivectomy procedures), then tissue elimination included not only inflamed soft tissue but also "*infected and necrotic bone*" that required exposure of the alveolar bone (flap procedures). Other concepts, such as the importance of maintaining the mucogingival complex (i.e. a wide zone of gingiva) and the possibility for regenerating the periodontal tissues, were subsequently introduced and gave way to specific "tailor-made" techniques.

This section will describe the surgical procedures which represented important steps in the development of the surgical concepts of modern periodontal surgery.

Gingivectomy procedures

This surgical approach had already been described in the latter part of the nineteenth century, when Robicsek (1884) introduced the so-called *gingivectomy* procedure aimed at "pocket elimination" and usually combined with recontouring of the gingiva to restore its normal architecture. Robicsek (1884) and later Zentler (1918) described the procedure, indicating the incision line where the gum should first be excised. This incision was initially straight (Robicsek) (Fig. 32-1) and then scalloped (Zentler) (Fig. 32-2),

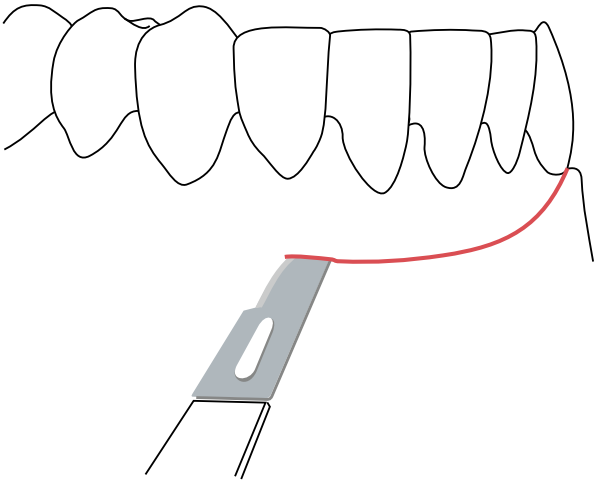

Fig. 32-1 Gingivectomy. Straight incision technique. (Source: Robicsek, 1884, reviewed in 1965 by the American Academy of Periodontology.Reproduced with permission from John Wiley & Sons.)

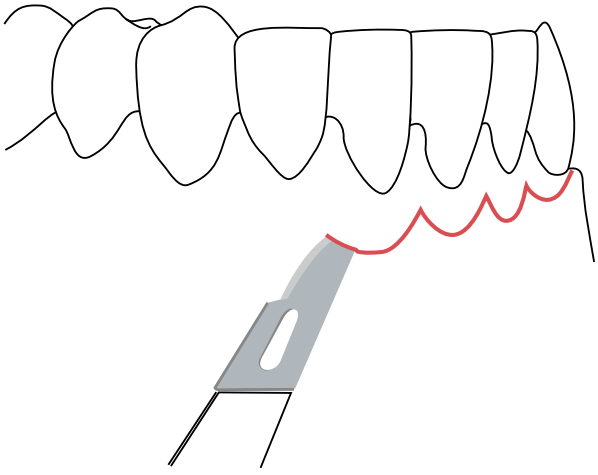

Fig. 32-2 Gingivectomy. Scalloped incision technique. (Source: Zentler 1918. Reproduced with permission from John Wiley & Sons.)

on both the labial and lingual aspects of each tooth. Subsequently, the diseased tissue was eliminated with a hook-shaped instrument and the exposed alveolar bone was scraped. The area was then covered with an antibacterial gauze or painted with disinfecting solutions. The deepened periodontal pocket was therefore eradicated, and the established dentition could be kept clean more easily.

In the second half of the twentieth century, the gingivectomy procedure was frequently employed in the treatment of periodontitis (Goldman 1951). It was defined by Grant *et al*. (1979) as being "the excision of the soft tissue wall of a pathologic periodontal pocket" and required precise steps to follow:

- Once the area was anesthetized, the bottom of each pocket was identified (Fig. 32-3a) and bleeding points were produced on the outer surface of the soft tissue (Fig. 32-3b). These bleeding points describing the depth of the pockets in the area were used as the guideline for the incision.
- The primary incision (Fig. 32-4), with either a scalpel or an angulated gingivectomy knife joined all the bleeding points with a beveled incision (external bevel) directed towards the base of the pocket, providing a thin and properly festooned margin of the remaining gingiva.
- Once the primary incision was completed on the buccal and lingual aspects of the teeth, the interproximal soft tissue was separated from the interdental periodontium by a secondary incision (Fig. 32-5). The incised tissues were carefully removed with a curette or a scaler (Fig. 32-6) and the exposed root surfaces were carefully debrided (Fig. 32-7). The gingival contours were then checked and, if necessary, corrected with the use of knives or rotating diamond burs.
- To protect the incised area during the period of healing, the wound surface was covered by a periodontal dressing (Fig. 32-8) that remained in position for 10–14 days.

Flap procedures

Original Widman flap

In 1918, Leonard Widman published one of the first detailed descriptions of the use of a flap procedure for pocket elimination. In his article "*The operative treatment of pyorrhea alveolaris*", Widman described a mucoperiosteal flap design that aimed to remove

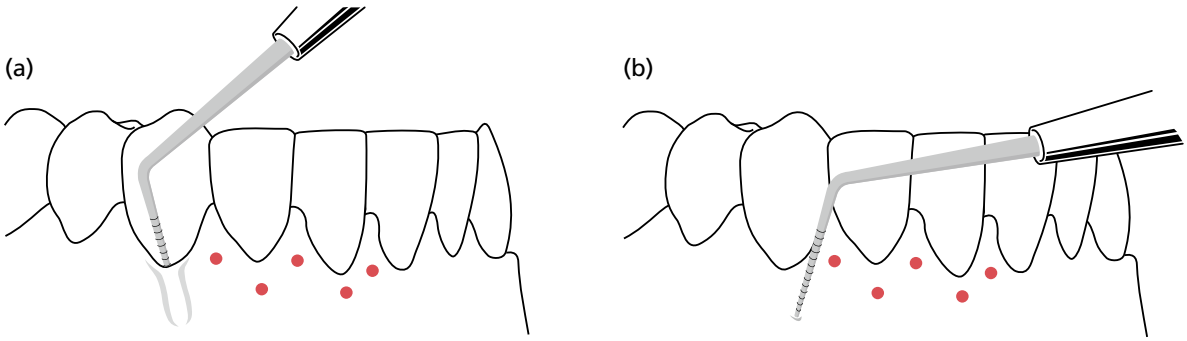

Fig. 32-3 Gingivectomy. Pocket marking. (a) An ordinary periodontal probe is used to identify the bottom of the deepened pocket. (b) When the depth of the pocket has been assessed, an equivalent distance is delineated on the outer aspect of the gingiva. The tip of the probe is then turned horizontally and used to produce a bleeding point at the level of the bottom of the probeable pocket.

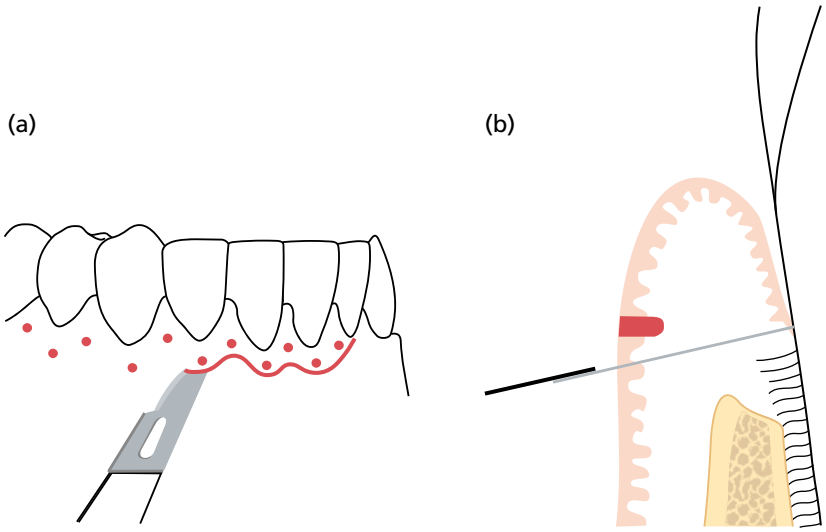

Fig. 32-4 Gingivectomy. (a) Primary incision. (b) The incision is terminated at a level apical to the "bottom" of the pocket and is angulated to give the cut surface a distinct bevel.

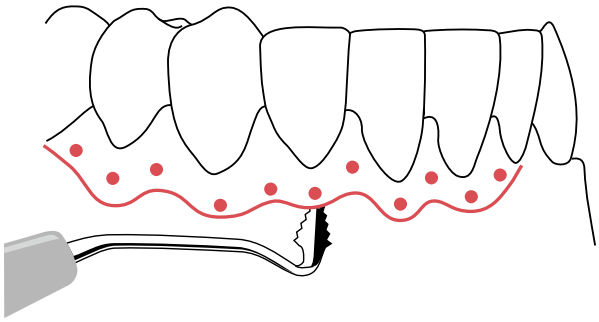

Fig. 32-5 Gingivectomy. The secondary incision through the interdental area is performed with a Waerhaug knife.

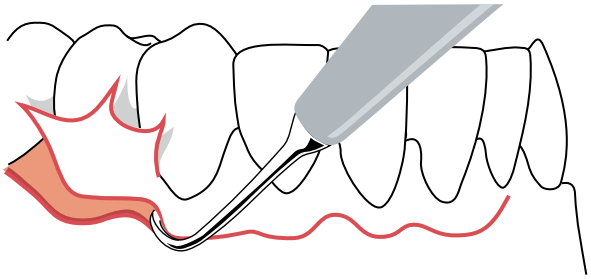

Fig. 32-6 Gingivectomy. The detached gingiva is removed with a scaler.

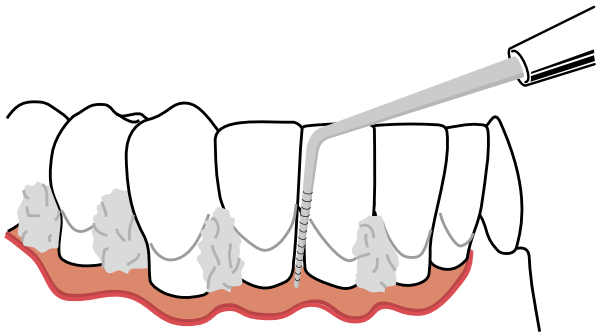

Fig. 32-7 Gingivectomy. Probing for residual pockets. Gauze packs have been placed in the interdental spaces to control bleeding.

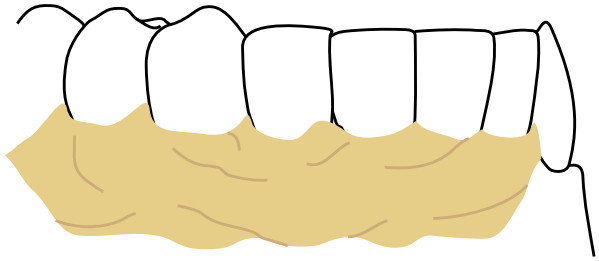

Fig. 32-8 Gingivectomy. The periodontal dressing has been applied and properly secured.

the pocket epithelium and the inflamed connective tissue, thereby facilitating optimal cleaning of the root surfaces. The technique consisted of two releasing incisions connected by a gingival incision that demarcated the area scheduled for surgery (Fig. 32-9). Buccal and lingual incisions using an internal bevel followed the outline of the gingival margin aiming

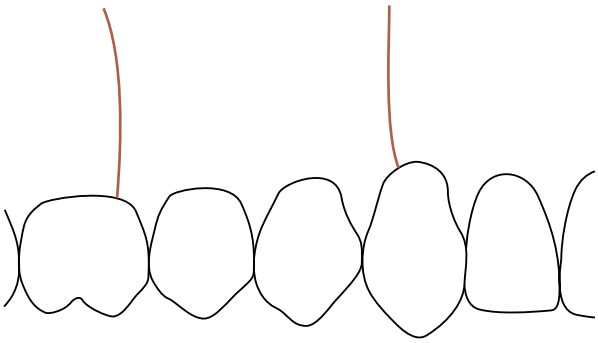

Fig. 32-9 Original Widman flap. Two releasing incisions demarcate the area scheduled for surgical therapy. A scalloped reverse bevel incision is made in the gingival margin to connect the two releasing incisions.

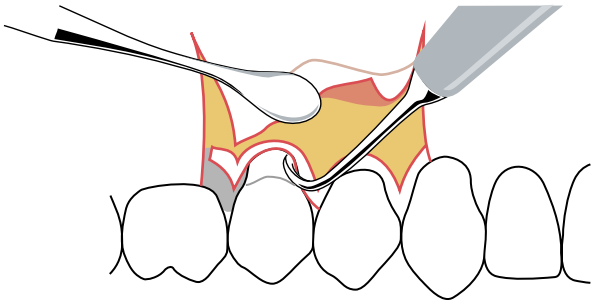

Fig. 32-10 Original Widman flap. The collar of inflamed gingival tissue is removed following the elevation of a mucoperiosteal flap.

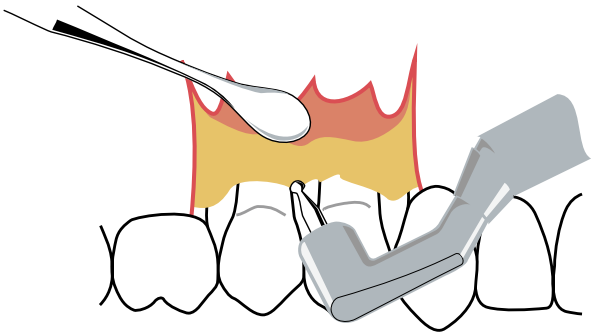

Fig. 32-11 Original Widman flap. By bone recontouring, a "physiologic" contour of the alveolar bone may be re-established.

to separate the pocket epithelium and the inflamed connective tissue from the non-inflamed gingiva. Then a mucoperiosteal flap was elevated exposing at least 2–3 mm of the marginal alveolar bone and after removing the collar of inflamed tissue around the neck of the teeth, the exposed root surfaces were carefully instrumented (Fig. 32-10). Bone recontouring was recommended to achieve an ideal anatomic form of the underlying alveolar bone (Fig. 32-11). Then buccal and lingual flaps were laid back over the alveolar bone and secured in this position with interproximal sutures (Fig. 32-12) often leaving the interproximal areas without soft tissue coverage of the crestal bone.

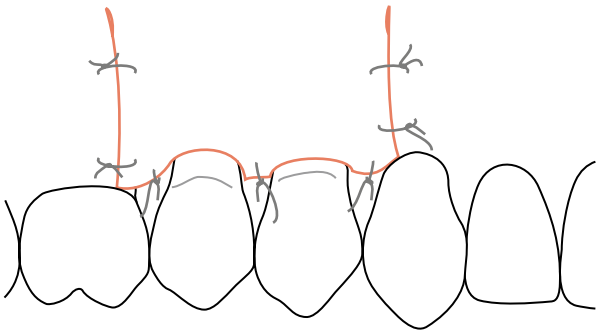

Fig. 32-12 Original Widman flap. The coronal ends of the buccal and lingual flaps are placed at the alveolar bone crest and secured in this position by interdentally placed sutures.

Neumann flap

Only a few years later, Neumann (1920) suggested the use of another flap design, which differed from the one described by Widman in that an *intracrevicular incision* is made through the base of the gingival pockets. Following flap elevation, the inside of the flap was curetted to remove the pocket epithelium and the granulation tissue, the root surfaces were subsequently debrided, and any irregularities of the alveolar bone crest were corrected. The flaps were then trimmed to allow both an optimal adaptation to the teeth and a proper coverage of the alveolar bone on both the buccal/lingual (palatal) and the interproximal sites. Neumann pointed out the importance of removing the soft tissue pockets, that is replacing the flap at the crest of the alveolar bone

Modified flap operation

In a publication from 1931, Kirkland described a surgical procedure called the *modified flap operation*, which involved intracrevicular incisions through the pockets on both the labial and the lingual aspects (Fig. 32-13), thus allowing the retraction of buccal and lingual full thickness flaps to permit proper root debridement, but without eliminating any soft or hard tissue, just the pocket epithelium and granulation tissue from the inner side of the flaps (Figs. 32-14, 32-15). The flaps were then replaced in their original position and secured with interproximal sutures (Fig. 32-16).

The *modified flap operation*, in contrast to the *original Widman flap* and the *Neumann flap*, did not include removal of non-inflamed tissues and apical displacement of the gingival margin, thus causing a minimal amount of trauma to the remaining periodontal tissues and a minimum of discomfort to the patient.

Apically repositioned flap

In the mid-1950s the focus of periodontal surgery shifted towards the aim of preserving *an adequate zone of attached gingiva* after surgery once the periodontal pockets had been eliminated. One of the first authors to describe a technique aimed at the preservation of

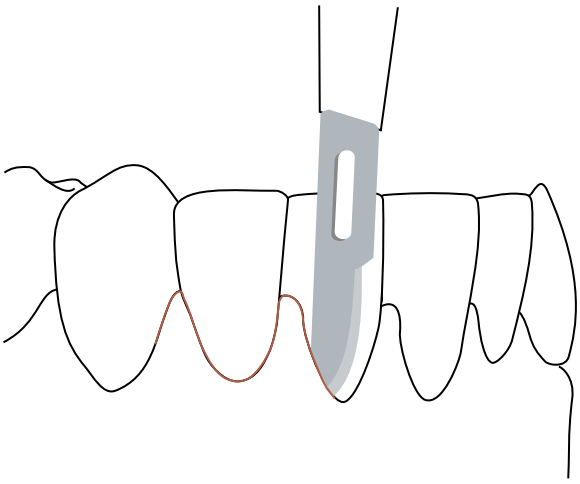

Fig. 32-13 Modified flap operation (the Kirkland flap). Intracrevicular incision.

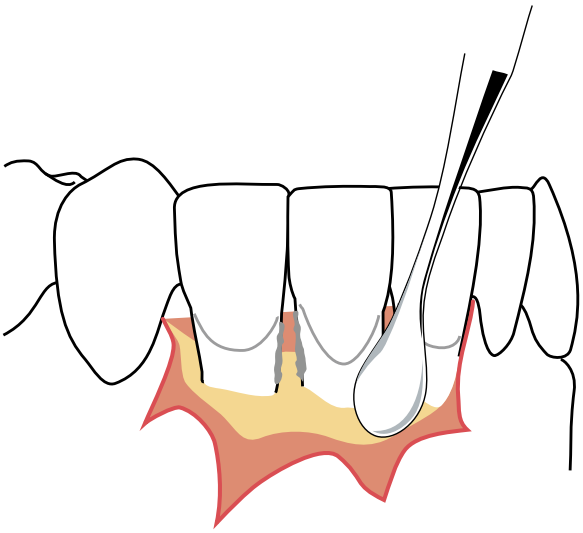

Fig. 32-14 Modified flap operation (the Kirkland flap). The gingiva is retracted to expose the "diseased" root surface.

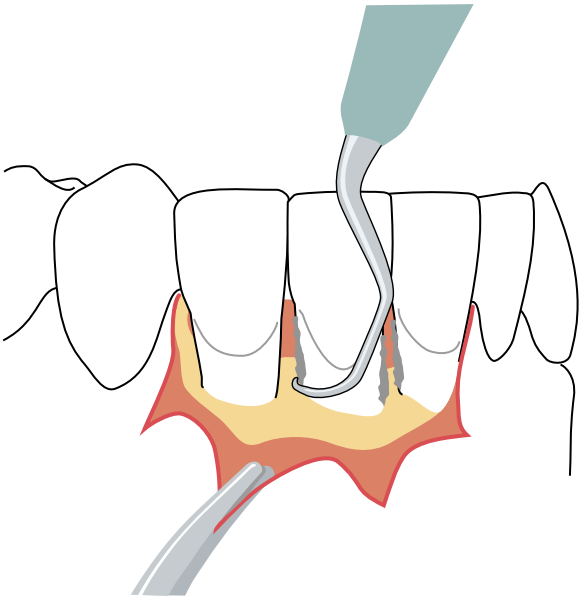

Fig. 32-15 Modified flap operation (the Kirkland flap). The exposed root surfaces are subjected to mechanical debridement.

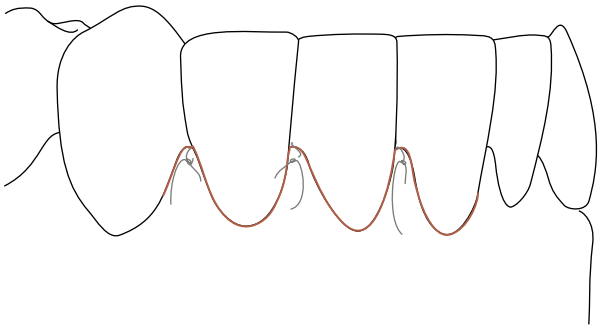

Fig. 32-16 Modified flap operation (the Kirkland flap). The flaps are repositioned at their original position and sutured.

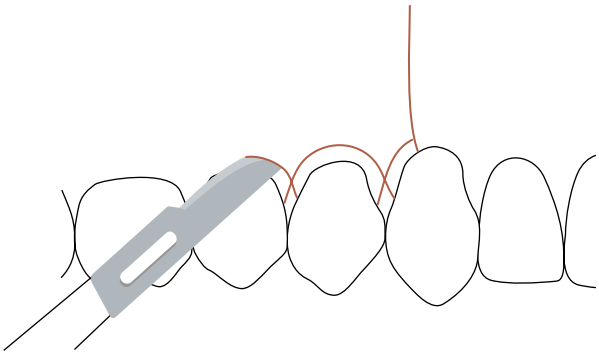

Fig. 32-17 Apically repositioned flap. Following a vertical releasing incision, the reverse bevel incision is made through the gingiva and the periosteum to separate the inflamed tissue adjacent to the tooth from the flap.

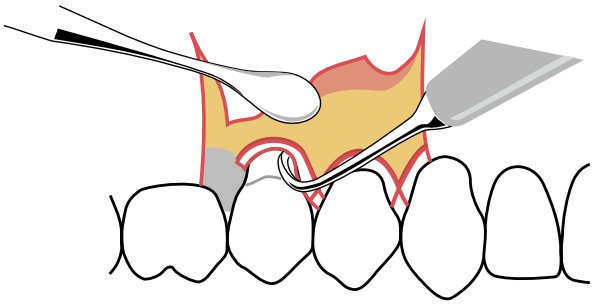

Fig. 32-18 Apically repositioned flap. A mucoperiosteal flap is raised and the tissue collar remaining around the teeth, including the pocket epithelium and the inflamed connective tissue, is removed with a curette.

gingiva was Nabers (1954) with the surgical technique for "repositioning of attached gingiva", which was later modified by Ariaudo and Tyrrell (1957). In 1962, Friedman described more precisely this surgical technique and proposed the term *apically repositioned flap*, because at the end of the surgical procedure, the entire complex of the soft tissues (gingiva and alveolar mucosa), rather than the gingiva alone, was displaced in the apical direction. Hence, instead of removing the excessive gingiva after the osseous surgery (if performed), the whole mucogingival complex was maintained and repositioned apically. This surgical technique was used on buccal surfaces in both upper and lower jaws and on lingual surfaces in the lower jaw, while a bevel flap technique (see later) had to be used on the palatal aspect of maxillary teeth where the lack of alveolar mucosa made it impossible to reposition the flap in an apical direction.

This apically repositioned flap technique (Friedman 1962) involved the following phases:

- A reverse bevel incision dependent on the pocket depth as well as the thickness and the width of the gingiva (Fig. 32-17). This beveling incision followed a scalloped outline ensuring maximal interproximal coverage of the alveolar bone when repositioning the flap. Vertical releasing incisions extending into the alveolar mucosa) were made at each of the end points of the reverse incision, making apical repositioning of the flap possible. When the gingiva was thin and only a narrow zone of keratinized tissue was present, the incisions were made close to the tooth.
- A full thickness mucoperiosteal flap including buccal/lingual gingiva and alveolar mucosa was raised beyond the mucogingival line in order to be able later to reposition the soft tissue apically. The marginal collar of tissue, including pocket epithelium and granulation tissue, was removed with curettes (Fig. 32-18), and the exposed root surfaces were carefully scaled and planed.
- The alveolar bone crest was then recontoured with the objective of recapturing the normal form of the alveolar crest, but at a more apical level (Fig. 32-19).
- Following careful adjustment, the buccal/lingual flaps were repositioned to the level of the newly recontoured alveolar bone crest and secured in this position (Figs. 32-20, 32-21).

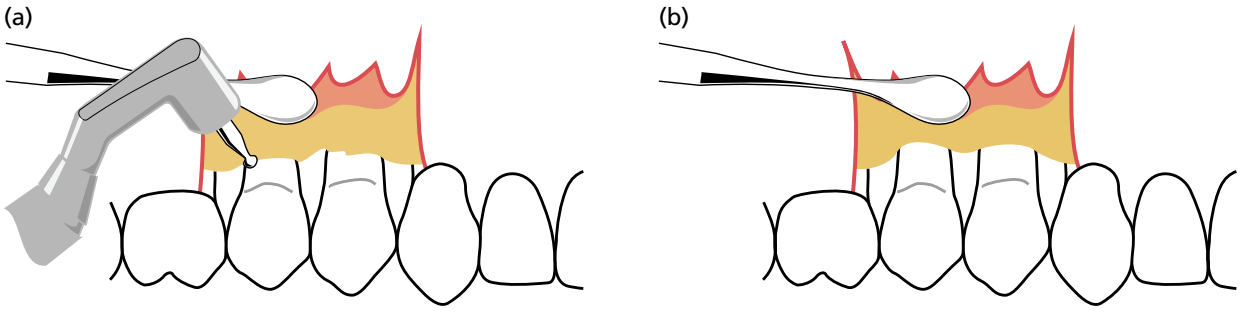

Fig. 32-19 Apically repositioned flap. Osseous surgery is performed with the use of a rotating bur (a) to recapture the physiologic contour of the alveolar bone (b).

- To handle periodontal pockets on the palatal aspect of the maxillary teeth, Friedman described a modification of the "apically repositioned flap", which he termed the *beveled flap* (Fig. 32-22), since this palatal flap was secondarily scalloped and thinned with a beveled incision once the tooth surfaces were debrided and osseous recontouring was performed (Fig. 32-23) so the gingival margins were adjusted to the alveolar bone crest (Fig. 32-24).
- Flaps were then secured in the apical position with interdental sutures (Fig. 32-25).

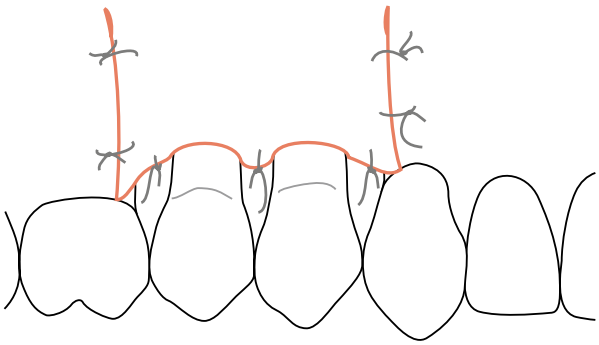

Fig. 32-20 Apically repositioned flap. The flaps are repositioned in an apical direction to the level of the recontoured alveolar bone crest and retained in this position by sutures.

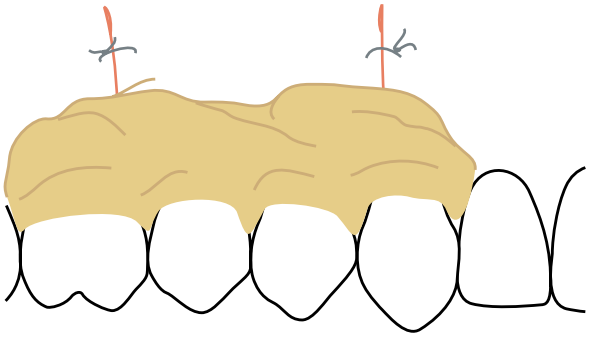

Fig. 32-21 Apically repositioned flap. A periodontal dressing is placed over the surgical area to ensure that the flaps remain in the correct position during healing.

Modified Widman flap

Ramfjord and Nissle (1974) described the *modified Widman flap* technique, which was also termed the *open flap curettage* technique. It should be noted that, while the *original Widman flap* technique included both apical displacement of the flap(s) and osseous recontouring (elimination of bony defects) to obtain

Fig. 32-23 Beveled flap. Scaling, root planing, and osseous recontouring are performed in the surgical area.

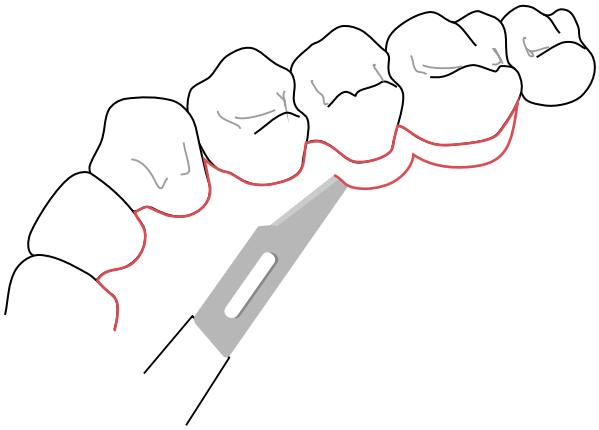

Fig. 32-24 Beveled flap. The palatal flap is replaced, and a secondary, scalloped, reverse bevel incision is made to adjust the length of the flap to the height of the remaining alveolar bone.

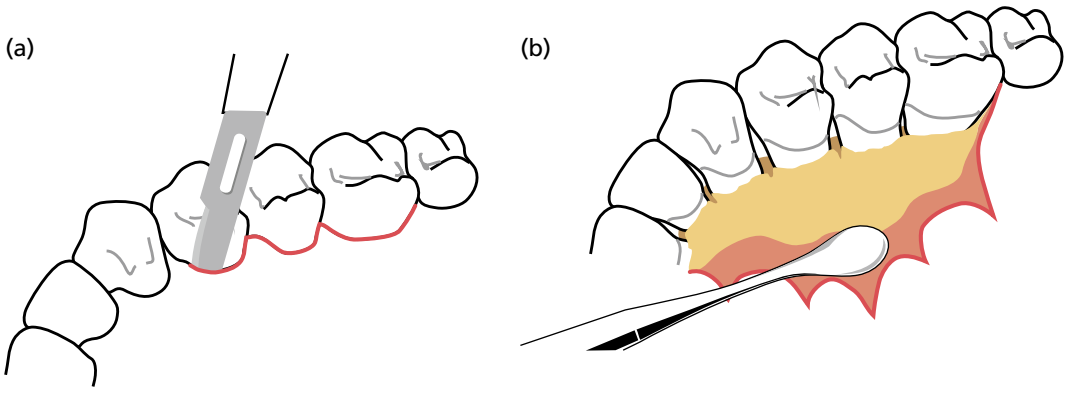

Fig. 32-22 Beveled flap. A primary incision is made intracrevicularly through the bottom of the periodontal pocket (a) and a conventional mucoperiosteal flap is elevated (b).

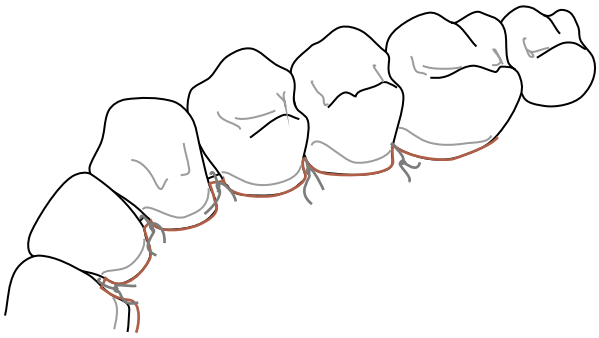

Fig. 32-25 Beveled flap. The shortened and thinned flap is replaced over the alveolar bone and in close contact with the root surfaces.

proper pocket elimination, the *modified Widman flap* technique is not intended to meet these objectives. The main advantages of the *modified Widman flap* technique in comparison to the procedures previously described were, according to Ramfjord and Nissle (1974): (1) the possibility of obtaining a close adaptation of the soft tissues to the root surfaces; (2) minimum of trauma to which the alveolar bone and the soft connective tissues are exposed; and (3) less exposure of the root surfaces, which from an esthetic point of view is an advantage in the treatment of anterior segments of the dentition.

This surgical design included an initial horizontal scalloped incision (Fig. 32-26) placed approximately 1 mm from the buccal gingival margin in order to separate properly the pocket epithelium from the flap. If the pockets on the buccal aspects of the teeth were <2 mm deep or if aesthetic considerations were important, an intracrevicular incision was recommended. A similar incision technique was used on the palatal aspect and these incisions extended as far as possible in between the teeth to allow enough interdental gingiva for proper coverage of the interproximal bone when the flap was repositioned and sutured. Vertical releasing incisions were not usually required. Then an intracrevicular incision was made around the teeth (*second incision*) to the alveolar crest (Fig. 32-27) thus facilitating the gentle separation of the collar of pocket epithelium and granulation tissue from the root surfaces. A *third incision* (Fig. 32-28) made in a horizontal direction close to the surface of the alveolar bone crest that separated the soft tissue collar of the root surfaces from the bone facilitated the raise of buccal and palatal full-thickness flaps exposing only a few millimeters of the alveolar bone crest (Ramfjord *et al*. 1977).

The pocket epithelium and the granulation tissues were then removed by means of curettes. The exposed roots were carefully scaled and planed, except for a narrow area close to the alveolar bone crest in which remnants of attachment fibers may be preserved. Angular bony defects are carefully curetted. The flaps were then trimmed and adjusted to the alveolar bone to obtain complete coverage of the interproximal bone (Fig. 32-29). If this adaptation cannot be achieved by soft tissue recontouring, some bone could be removed from the outer aspects of the alveolar process in order to facilitate proper flap adaptation. The flaps were sutured together with individual interdental sutures.

Distal wedge procedures

In many cases the treatment of periodontal pockets on the distal surface of distal molars is complicated by the presence of bulbous tissues over the tuberosity or by a prominent retromolar pad. This area frequently presents limited amounts of keratinized gingiva or the presence of distal angular bony defects which makes the removal of this tissue by gingivectomy contraindicated (Fig. 32-30). These tissues should then be reduced in size rather than

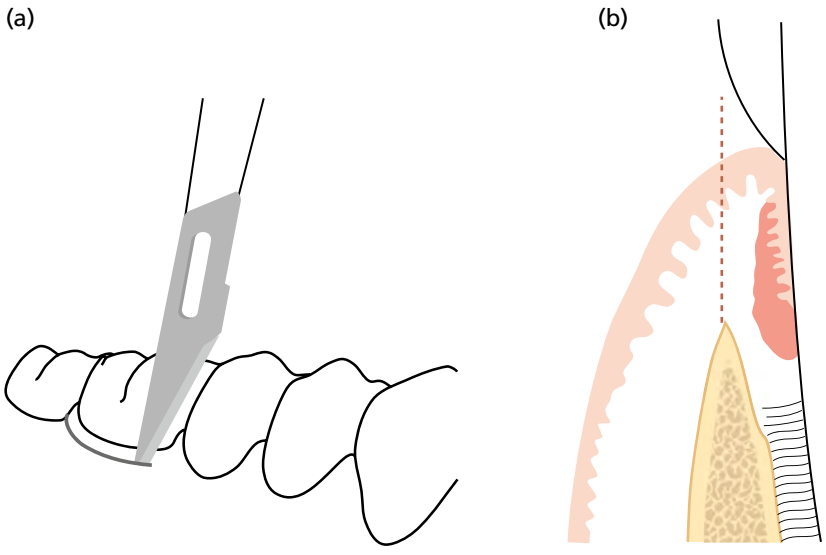

Fig. 32-26 Modified Widman flap. The initial incision is placed 0.5–1 mm from the gingival margin (a) and parallel to the long axis of the tooth (b).

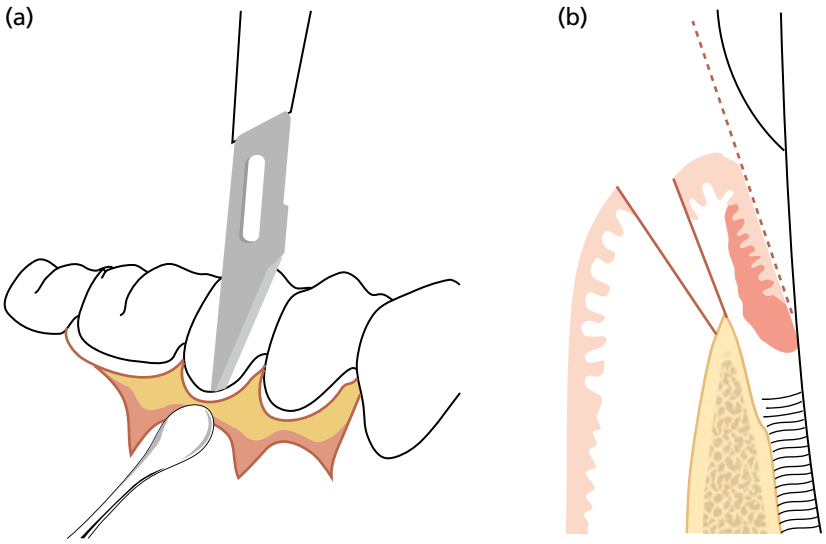

Fig. 32-27 Modified Widman flap. Following careful elevation of the flaps, a second intracrevicular incision (a) is made to the alveolar bone crest (b) to separate the tissue collar from the root surface.

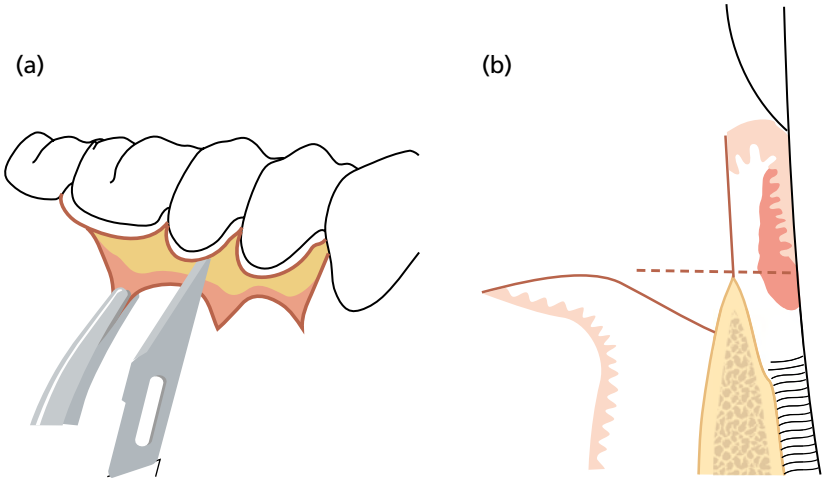

Fig. 32-28 Modified Widman flap. A third incision is made perpendicular to the root surface (a) and as close as possible to the bone crest (b), thereby separating the tissue collar from the alveolar bone.

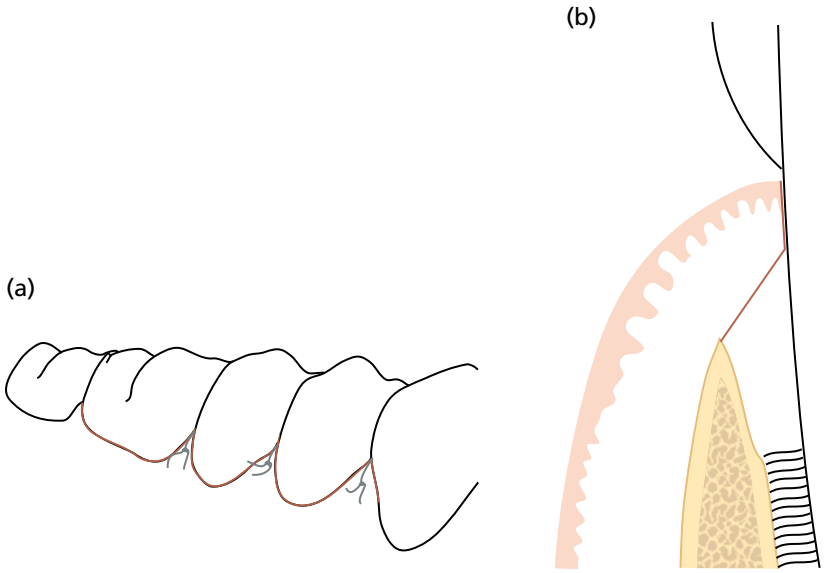

Fig. 32-29 Modified Widman flap. (a) Following proper debridement and curettage of angular bone defects, the flaps are carefully adjusted to cover the alveolar bone and sutured. (b) Complete coverage of the interdental bone as well as close adaptation of the flaps to the tooth surfaces should be accomplished.

removed *in toto*, which is accomplished by the distal wedge procedure (Robinson 1966). This technique involves incision of the buccal and lingual/palatal flaps, with vertical incisions through the tuberosity or retromolar pad, forming a triangular wedge (Fig. 32-31a). The facial and lingual walls of the tuberosity or retromolar pad are then deflected and the incised wedge of tissue is dissected and separated from the bone (Fig. 32-31b). The walls of the facial and lingual flaps are then reduced in thickness by undermining incisions (Fig. 32-31c). Loose tags of tissue are removed, and the root surfaces are debrided. If necessary, the bone is recontoured. This surgical design facilitates access to the osseous defect and makes it possible to preserve sufficient amounts of gingiva and mucosa to achieve soft tissue coverage.

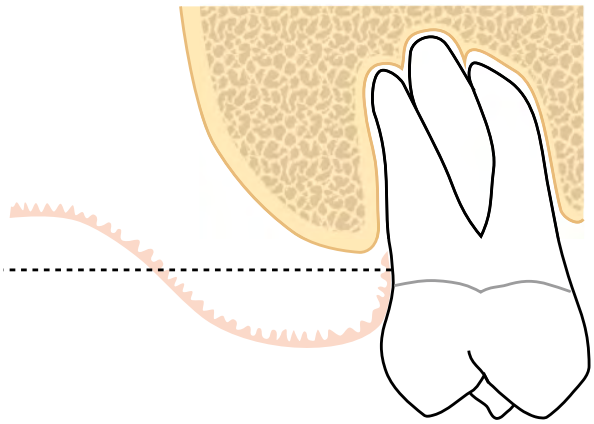

Fig. 32-30 Distal wedge procedure. Simple gingivectomy incision (dashed line) can be used to eliminate a soft tissue pocket and adjacent fibrous tissue pad behind a maxillary molar.

The buccal and lingual flaps are then replaced over the exposed alveolar bone, and the edges trimmed to avoid overlapping wound margins. The flaps are secured in this position with interrupted sutures (Fig. 32-31d). The sutures are removed after approximately 1 week. Depending on the anatomy of the tuberosity or retromolar area, different surgical designs have been described with the purpose of eliminating the excessive tissue and at the same time preserving keratinized tissue (Fig. 32-32). One such design is the modified distal wedge procedure that includes two parallel reverse bevel incisions, one buccal and one palatal, made from the distal surface of the molar to the posterior part of the tuberosity, where they are connected with a buccolingual incision (Figs. 32-33. 32-34, 32-35).

Osseous surgery

The principles of osseous surgery in periodontal therapy were outlined by Schluger (1949) and Goldman (1950). They pointed out that alveolar bone loss caused by inflammatory periodontal disease often

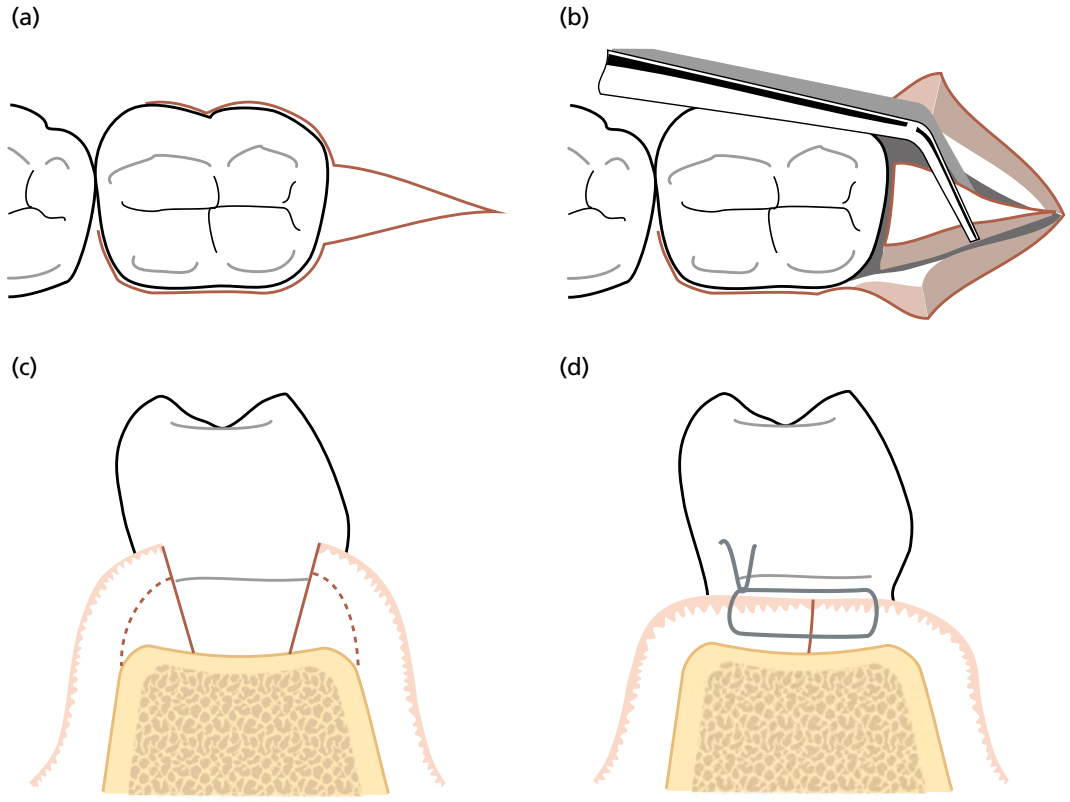

Fig. 32-31 Distal wedge procedure. (a) Buccal and lingual vertical incisions are made through the retromolar pad to form a triangle behind a mandibular molar. (b) A triangular-shaped wedge of tissue is dissected from the underlying bone and removed. (c) Walls of the buccal and lingual flaps are reduced in thickness by undermining incisions (dashed lines). (d) The flaps, which have been trimmed and shortened to avoid overlapping wound margins, are sutured.

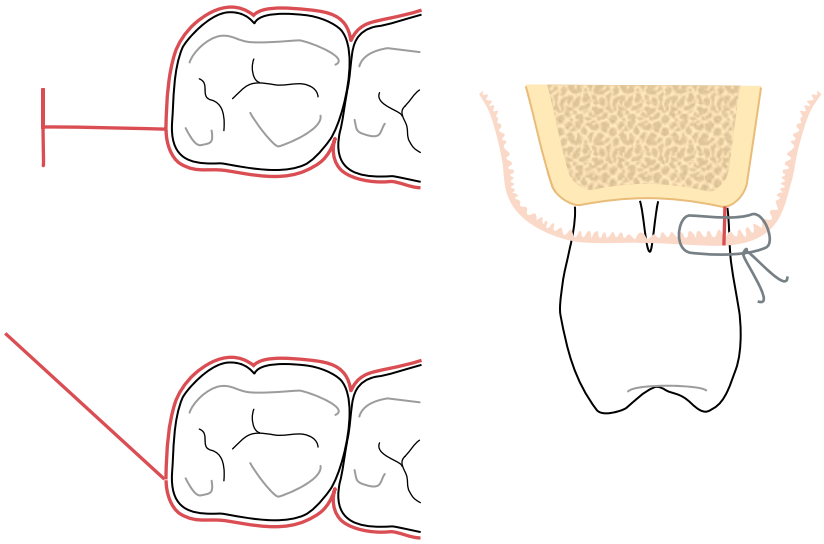

Fig. 32-32 Modified incision techniques in distal wedge procedures. To ensure optimal flap adaptation at the furcation site, the incision technique may be modified. The amount of attached keratinized tissue present as well as the accessibility to the retromolar area has to be considered when placing the incision.

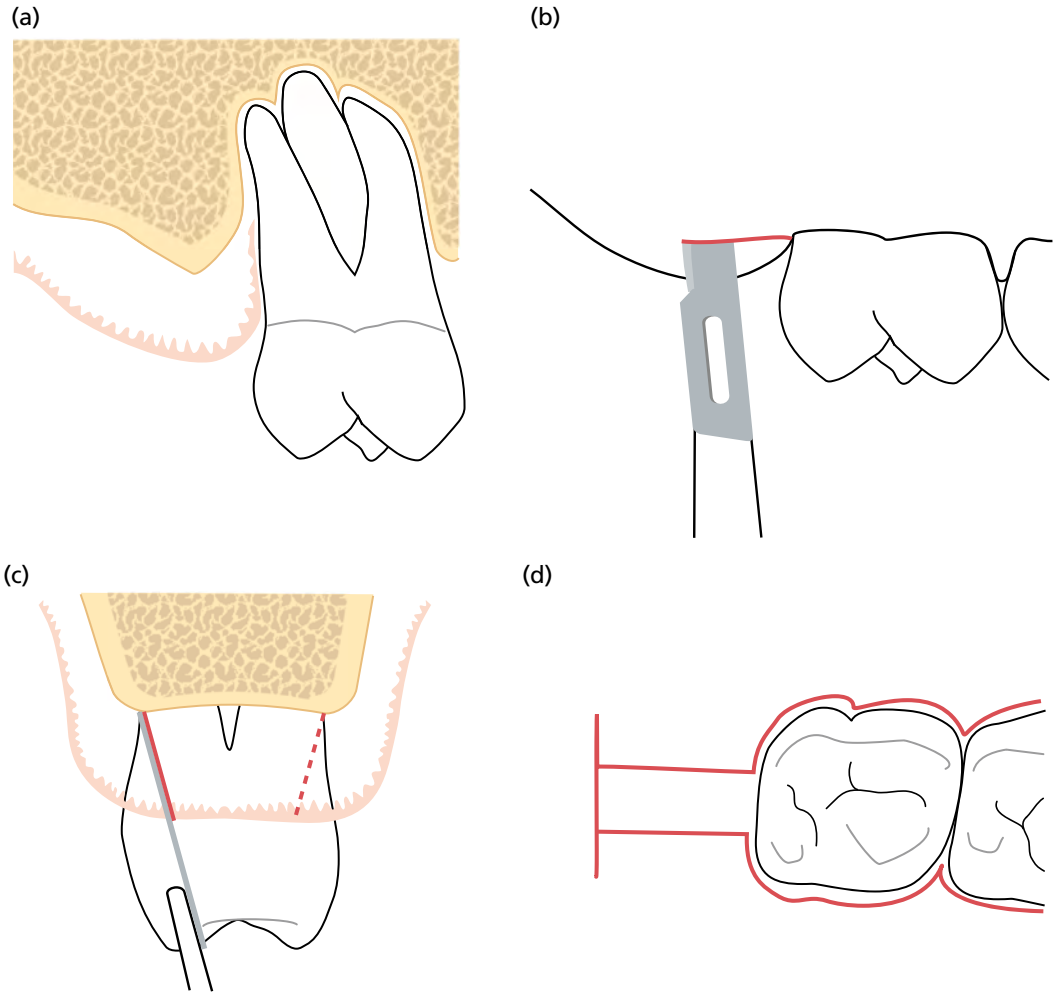

Fig. 32-33 Modified distal wedge procedure. (a) A deep periodontal pocket combined with an angular bone defect at the distal aspect of a maxillary molar. (b–d) Two parallel reverse bevel incisions, one buccal and one palatal, are made from the distal surface of the molar to the posterior part of the tuberosity, where they are connected with a buccolingual incision (d). The buccal and palatal incisions are extended in a mesial direction along the buccal and palatal surfaces of the molar to facilitate flap elevation.

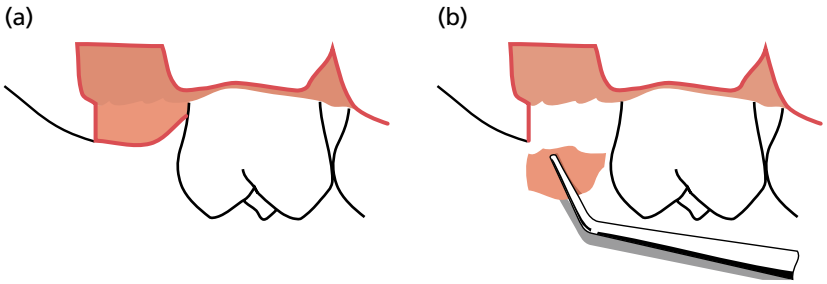

Fig. 32-34 Modified distal wedge procedure. (a) Buccal and palatal flaps are elevated and (b) the rectangular wedge is released from the tooth and underlying bone by sharp dissection and then removed.

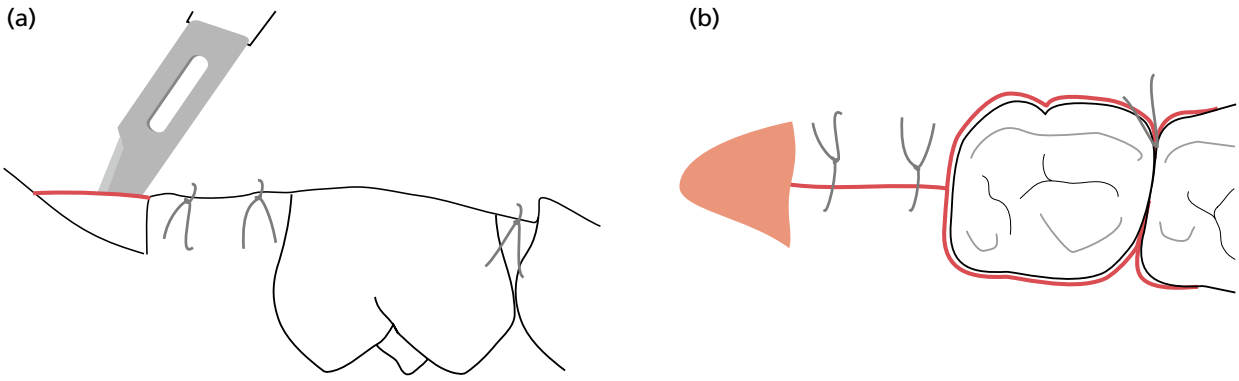

Fig. 32-35 Modified distal wedge procedure. (a, b) Following bone recontouring and root debridement, the flaps are trimmed and shortened to avoid overlapping wound margins and sutured. A close soft tissue adaptation should be accomplished to the distal surface of the molar. The remaining fibrous tissue pad distal to the buccolingual incision line is "levelled" by the use of a gingivectomy incision.

resulted in an uneven outline of the bone crest and because they thought that these gingival contours were closely dependent on the contour of the underlying bone as well as the proximity and anatomy of adjacent tooth surfaces, the elimination of soft tissue pockets often had to be combined with osseous reshaping and the elimination of osseous craters and angular bony defects to establish and maintain shallow pockets and optimal gingival contour after surgery.

Osteoplasty

The term *osteoplasty* was introduced by Friedman in 1955. The purpose of osteoplasty was to reshape the alveolar bone *without* removing any "supporting" bone. Examples of osteoplasty are the thinning of thick osseous ledges and the establishment of a scalloped contour of the buccal (lingual and palatal) bone crest (Fig. 32-36). In flap surgery without bone recontouring, interdental morphology may sometimes preclude optimal mucosal coverage of the bone postsurgically, even if pronounced scalloping of soft tissue flaps is performed. In such a situation, removal of non-supporting bone by vertical grooving to reduce the buccolingual dimension of the bone in the interdental areas may facilitate flap adaptation, thereby reducing the risk of bone exposure during healing as well of ischemic necrosis of unsupported mucosal flaps due to flap margin deficiencies.

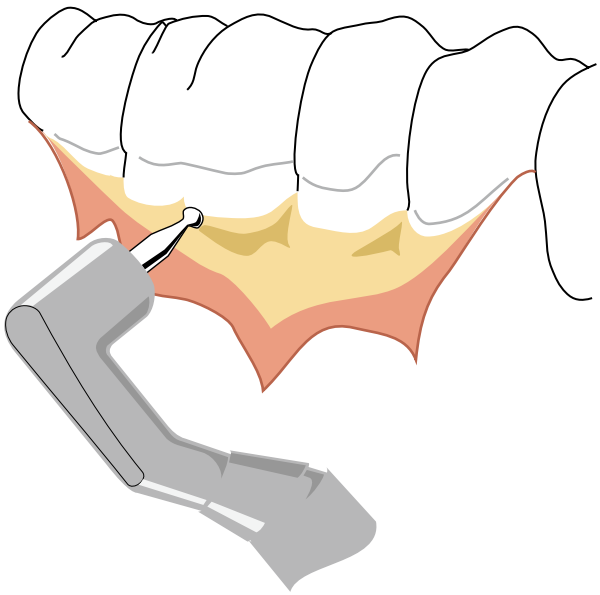

Fig. 32-36 Osteoplasty. Thick osseous ledges in a mandibular molar region area are eliminated with the use of a round bur to facilitate optimal flap adaptation.

Removal of non-supporting bone may sometimes also be required to gain access for intrabony root surface debridement. The levelling of interproximal craters and the elimination (or reduction) of bony walls of circumferential osseous defects are often referred to as "osteoplasty" since usually no resection of supporting bone is required (Fig. 39-37).

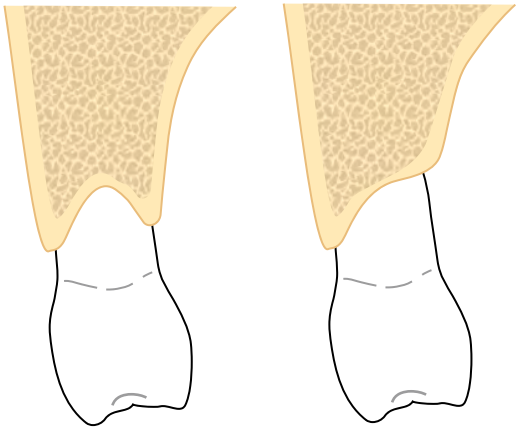

Fig. 32-37 Osteoplasty. Levelling of an interproximal bone crater through the removal of the palatal bone wall. For aesthetic reasons, the buccal bone wall is maintained to support the height of the soft tissue.

Ostectomy

Ostectomy involves the elimination of *supporting bone* that is directly involved in the attachment of the tooth. The objective of ostectomy was to establish a "*physiologic*" anatomy of the alveolar bone (positive architecture), but at a more apical level. However, the need for this positive architecture of the alveolar bone has never been demonstrated and extensive bone removal of supporting bone in molar areas may cause the opening of a furcation defect or cause extensive gingival recession. Therefore, as a general rule, supporting bone should not be removed. Currently, ostectomy is only indicated in the presence of craters where its access for instrumentation or for improved flap adaptation requires reduction of the buccal and/or lingual crater walls to the base of the osseous defect (Fig. 32-38a). When bone resection has been carried out in the interdental area, the buccal and lingual/palatal bone margins may subsequently be recontoured to compensate for discrepancies in bone height resulting from the interdental bone resection. However, this reduction should never compromise the opening of a furcation or the tooth periodontal support (Oschenbein 1986) (Fig. 32-38b).

Techniques in periodontal surgery (current perspective)

Objectives of surgical treatment

Traditionally, *pocket elimination/closure* has been a main objective of surgical periodontal therapy. The removal of the pocket by surgical means served two purposes: (1) the elimination of the pocket, which maintained an environment conducive to progression of periodontitis and (2) the root surface was made accessible for professional debridement and for self-performed tooth cleaning after healing.

From these two objectives, the necessity for pocket elimination has been challenged, since a zero-pocket dentition after periodontal therapy seems to be unrealistic. However, long-term cohort studies evaluating the incidence of progression of periodontitis after successful periodontal therapy have demonstrated that presence of residual pockets (probing pocket depth [PPD] ≥6 mm) and persistent BoP (open pockets) in sites with deep probing depths (PPD >4 mm + BoP) are significantly associated with disease progression (Claffey & Egelberg 1995; Matuliene *et al*. 2008). Therefore, the current end point of periodontal therapy is to achieve a dentition with no sites with deep pockets. This new information has thus formed the basis of the role played by periodontal surgery in the preservation of teeth, because presence of residual disease after the second step of periodontal therapy requires further treatment as part of the third step of periodontal therapy. However, *increased pocket depth* should not be the only indication for periodontal surgery, since the *probeable depth*, that is the distance from the gingival margin to the point where tissue

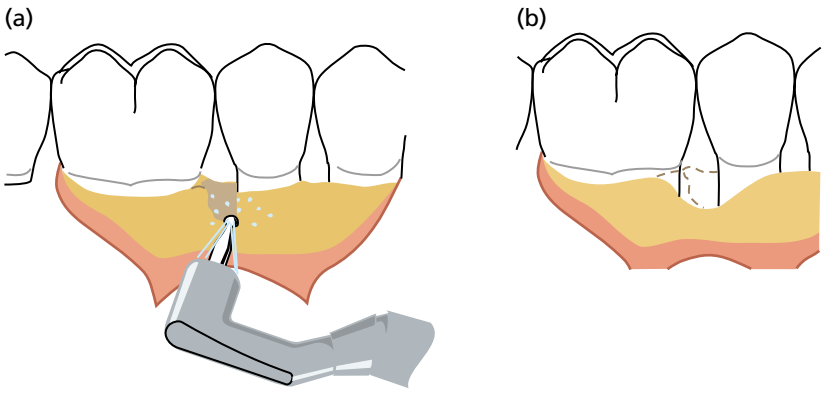

Fig. 32-38 Ostectomy. (a) Combined one- and two-wall osseous defect on the distal aspect of a mandibular bicuspid has been exposed following reflection of mucoperiosteal flaps. Since aesthetics is not a critical factor to consider in the posterior tooth region of the mandible, the bone walls are reduced to a level close to the base of the defect using rotating round burs under continuous saline irrigation. (b) Osseous recontouring completed. Note that some supporting bone has to be removed from the buccal and lingual aspect of both the second bicuspid and the first molar in order to provide a hard tissue topography which allows a close adaptation of the covering soft tissue flap.

resistance stops further periodontal probe penetration, may not correspond to the "true" depth of the pocket, mainly in the presence of gingival inflammation (see Chapter 22). Furthermore, there is no established correlation between *probeable* pocket depth and the presence or absence of active disease. This means that signs other than increased probing depth should be present to justify surgical therapy. These include clinical signs of inflammation, especially exudation and BoP (to the bottom of the pockets), as well as aberrations of gingival morphology.

In conclusion, the main objective of periodontal surgery is to contribute to the long-term preservation of the periodontium by facilitating plaque removal and infection control, and periodontal surgery can serve this purpose by:

- Creating accessibility for proper professional scaling and root planing
- Establishing a dentition without deep pockets and open pockets
- Establishing a gingival morphology which facilitates self-performed infection control.

In addition, periodontal surgery may aim to regenerate the periodontal attachment lost due to destructive disease (regenerative procedures in periodontal therapy are discussed in Chapter 38) or to change the anatomy of furcation lesions to improve accessibility for infection control (treatment of furcation lesions are discussed in Chapter 33)

Indications for surgical treatment

Impaired access for scaling and root planing

The difficulties in accomplishing proper root debridement with a non-surgical approach increase with (1) increasing depth of the periodontal pockets, (2) increasing width of the tooth surfaces, and (3) the presence of root fissures, root concavities, furcations, and defective margins of dental restorations in the subgingival area.

Provided a correct technique and suitable instruments are used, it is usually possible properly debride pockets that are up to 5 mm deep (Waerhaug 1978; Caffesse *et al*. 1986). However, this 5 mm limit cannot be used as a universal rule of thumb. Reduced accessibility and the presence of one or several of the above-mentioned impeding conditions may prevent proper debridement of shallow pockets, whereas at sites with good accessibility and favorable root morphology, proper debridement can be accomplished even in deeper pockets (Badersten *et al*. 1981; Lindhe *et al*. 1982b).

It is often difficult to ascertain by clinical means whether subgingival instrumentation has been properly performed. Following scaling, the root surface should be smooth – roughness will often indicate the presence of remaining subgingival calculus. It is also important to monitor carefully the gingival reaction to subgingival debridement. If inflammation persists and if bleeding is elicited by gentle probing in the subgingival area, the presence of subgingival deposits should be suspected (Fig. 32-39).

Fig. 32-39 Evaluation following non-surgical instrumentation reveals persistent signs of inflammation, bleeding following pocket probing, and a probing depth of ≥6 mm. Flap elevation to expose the root surface for proper cleaning should be considered.

If such symptoms are not resolved by repeated subgingival instrumentation, surgical treatment should be performed to expose the root surfaces for proper cleaning.

Impaired access for self-performed plaque control

The level of infection control that can be maintained by the patient is determined not only by his/her interest and dexterity, but also, to some extent, by the morphology of the dentogingival area. The patient's responsibilities in an infection-control program must include the cleansing of the supragingival tooth surfaces and the marginal part of the gingival sulcus.

Pronounced gingival hyperplasia and presence of gingival craters (Fig. 32-40) are examples of morphologic aberrations that may impede proper home care. Likewise, the presence of restorations with defective marginal fit or adverse contour and surface characteristics at the gingival margin may seriously compromise plaque removal.

In the treatment of periodontitis, the dentist should prepare the dentition in such a way that home care can be effectively managed. At the completion of treatment, the following objectives should have been met:

- No sub- or supragingival dental deposits
- No open pockets (no BoP to the bottom of the pockets >4 mm)
- No deep pockets (pockets ≥ 6 mm)
- No plaque-retaining aberrations of gingival morphology
- No plaque-retaining parts of restorations in relation to the gingival margin.

These requirements lead to the following indications for periodontal surgery:

- Accessibility for proper root debridement
- Pocket depth reduction
- Establishment of a morphology of the dentogingival area conducive to infection control
- Correction of gross gingival aberrations
- Shift of the gingival margin to a position apical to plaque-retaining restorations

Contraindications for periodontal surgery

Patient cooperation

Because optimal postoperative infection control is decisive for the success of periodontal treatment (Rosling *et al*. 1976; Nyman *et al*. 1977; Axelsson & Lindhe 1981), a patient who fails to cooperate during the cause-related phase of therapy should not be exposed to surgical treatment. Even though short-term postoperative infection control entails frequent professional treatments, the long-term responsibility for maintaining good oral hygiene must rest with the patient. Theoretically, even the poorest oral hygiene performance by a patient may be compensated for by frequent recall visits for supportive therapy (e.g. once a week), but it is unrealistic to consider larger groups of patients being maintained in this manner. A typical recall schedule for periodontal patients involves professional consultations for supportive periodontal therapy once every 3–6 months. Patients who cannot maintain satisfactory oral hygiene standards over such a period should normally not be considered to be candidates for periodontal surgery.

Smoking

Although smoking negatively affects wound healing (Siana *et al*. 1989), it may not be considered a contraindication for surgical periodontal treatment. The clinician should be aware, however, that less reduction of PPD, smaller gains in clinical attachment, and less bone regeneration might occur in patients who smoke than in patients who do not smoke (Labriola *et al*. 2005; Javed *et al*. 2012; Patel *et al*. 2012).

General health conditions

It is important to re-evaluate the patient's medical history before any surgical intervention to identify whether there is any medical condition that may preclude periodontal surgery or whether certain

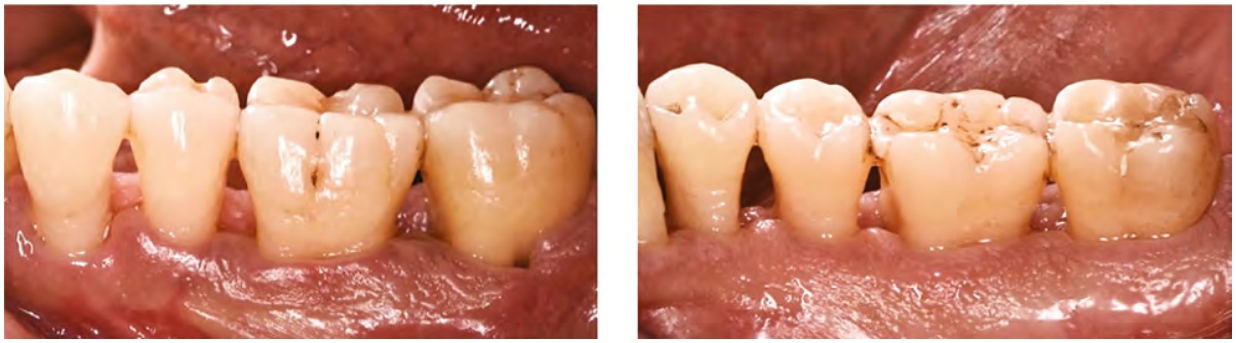

Fig. 32-40 Example of a proximal soft tissue crater, which favors plaque retention and thereby impedes the patient's plaque control.

precautions should be taken, for example prescription of prophylactic antibiotics or the use of local anesthetics without epinephrine. Consultation with the patient's physician should also be considered.

Selection of the surgical technique

Because each of the surgical procedures described is designed to deal with a specific situation or to meet a certain objective, it must be understood that in most patients no single standardized technique alone can be applied when periodontal surgery is undertaken. Therefore, in each surgical field, different techniques are often used and combined in such a way that the overall objectives of the periodontal surgical therapy are met. As a general rule, periodontal surgical techniques that preserve or induce the formation of periodontal tissue should be preferred over those that resect or eliminate tissue.

Gingivectomy

The obvious indication for gingivectomy is the reshaping of abnormal gingival contours such as gingival craters and gingival hyperplasia (see Fig. 32-40). In these cases, the technique is often termed *gingivoplasty*. Gingivectomy as such, is usually not indicated since the external beveled incision will lead to the removal of the entire zone of gingiva. As an alternative, an *internal beveled gingivectomy* may be performed in situations with just soft tissue pockets (pockets not extending beyond the mucogingival junction), without the presence of bony craters or any infrabony lesion (Fig. 32-41). These limitations, combined with the development of surgical methods which have a broader field of application, have led to less frequent use of gingivectomy.

Flap procedures

Flap operations can be used in all cases where surgical treatment of periodontitis is indicated. Periodontal flap procedures are particularly indicated at sites where pockets extend beyond the mucogingival junction and/or where treatment of bony defects and furcation involvements is required.

The advantages of flap operations include:

- Existing gingival tissue is preserved
- Marginal alveolar bone is exposed allowing the identification of bony defects for their adequate treatment
- Furcation areas are exposed, and the degree of involvement and the "tooth–bone" relationship can be identified
- Flap can be repositioned at its original level or shifted apically, thereby making it possible to adjust the gingival margin to the local conditions
- Flap procedure preserves the oral epithelium and hence healing takes place mostly by primary intention. As a consequence, the postoperative period is usually less unpleasant to the patient when compared with gingivectomy.

Classifications of different flap modalities used in the treatment of periodontitis often make distinctions between tissue-eliminating (resective) and tissue-preserving flaps (access/conservative). Furthermore, flaps can be distinguished between those involving both buccal and lingual marginal tissues versus only buccal (standard versus single flaps) and those preserving or not the interdental tissues (standard versus papilla preservation flaps).

From a didactic point of view, it seems appropriate to distinguish periodontal surgical therapy with regard to how to deal with (1) the soft tissue component and (2) the hard tissue component of the periodontal pocket at a specific tooth site (Fig. 32-42).

Depending on the surgical technique used, the soft tissue flap would either be apically positioned at the level of the bone crest (apically positioned flap) or maintained in a coronal position (access and papilla preservation flaps) at the completion of the surgical intervention. The maintenance of the presurgical soft tissue height is of importance from an esthetic point

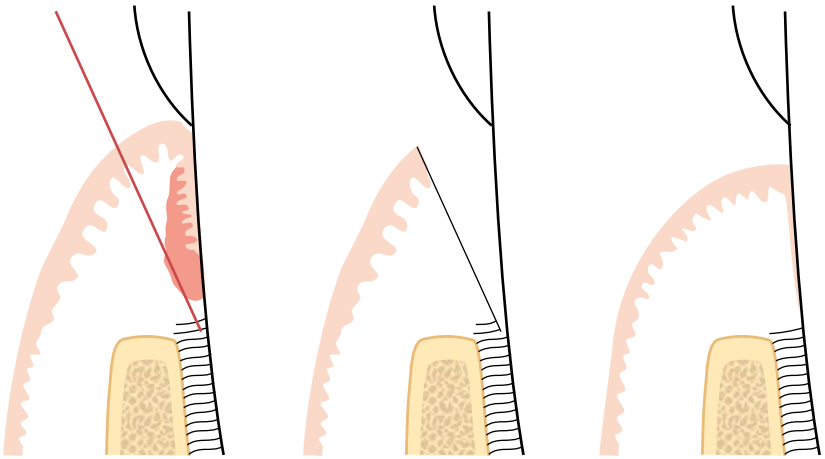

Fig. 32-41 Internal beveled gingivectomy. Schematic illustration of the incision technique in case of the presence of only a minimal zone of gingiva.

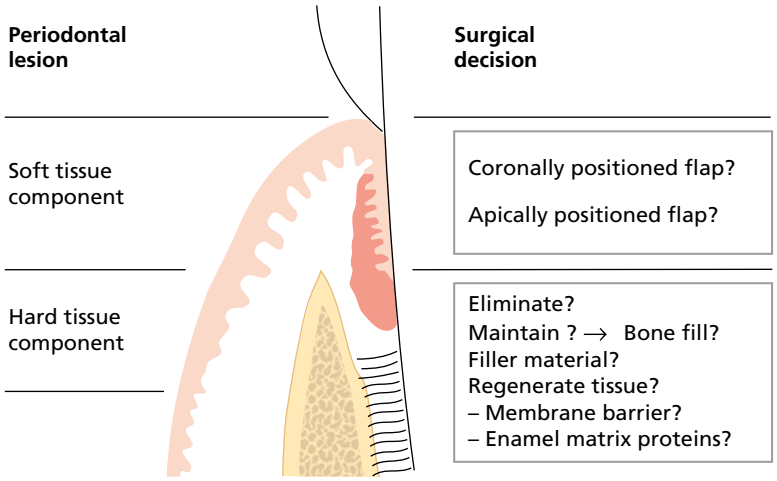

Fig. 32-42 Surgical decisions. Treatment decisions with respect to the soft and the hard tissue component of a periodontal pocket.

of view, particularly in the anterior tooth region. However, long-term results from clinical trials have shown that major differences in the final position of the soft tissue margin are not evident when comparing between access and resective surgical flap procedures. In many patients it may be of significance to position the flap coronally in the anterior tooth region in order to give the patient a prolonged time of adaptation to the inevitable soft tissue recession. In the posterior tooth region, however, an apical position should be the standard.

Independent of flap position, the goal should be to achieve complete soft tissue coverage of the alveolar bone, not only at buccal/lingual sites but also at proximal sites. It is therefore of utmost importance to carefully plan the incisions in such a way that this goal is achieved at the termination of the surgical intervention once the flaps have been re-positioned and sutured

The reported difference in final positioning of the gingival margin between surgical techniques is also dependent on the degree of osseous recontouring performed (Townsend-Olsen *et al*. 1985; Lindhe *et al*. 1987; Kaldahl *et al*. 1996; Becker *et al*. 2001). During conventional periodontal surgery, one would usually opt for the conversion of an intrabony defect into a suprabony defect, which then is eliminated by apical repositioning of the soft tissue flap(s). Osseous recontouring of angular bony defects and craters is an excisional technique, which should be used with caution and discrimination. However, the therapist is often faced with the dilemma of deciding whether or not to eliminate an angular bony defect. There are a number of factors that should be considered in the treatment decision, such as:

- Esthetics
- Tooth/tooth site involved
- Defect morphology (intrabony component and defect angle)
- Amount of remaining periodontium.

Since alveolar bone supports the soft tissue, bone recontouring will result in recession of the soft tissue margin. For esthetic reasons, one may therefore be restrictive in eliminating interproximal bony defects in the anterior tooth region.

Defect morphology is a variable of significance for repair/regeneration during healing (Rosling *et al*. 1976; Cortellini *et al*. 1993, 1995a). Whereas two- and, especially, three-wall defects may show great potential for repair/regeneration, one-wall defects and interproximal craters will rarely result in such resolution. Further, the removal of intrabony connective tissue/granulation tissue during a surgical procedure will always lead to crestal resorption of bone, especially in sites with thin bony walls. This results in reduction of the vertical dimensions of the bone tissue at the site.

The treatment options available for the hard tissue defect may include:

- Eliminating the osseous defect by resecting bone (osteoplasty and/or ostectomy). In cases of an approximal crater of limited depth, it may often be sufficient to reduce/eliminate the bone wall on the lingual side of the crater, thereby maintaining the bone support for the soft tissue on the facial aspect (see Fig. 32-37). In addition to esthetics, the presence of furcation lesions may limit the extent to which bone recontouring can be performed (Oschenbein 1986).
- Maintaining the area without osseous resection and either using regenerative procedures (these procedures in periodontal therapy are discussed in Chapter 38) or minimally invasive flap procedures aimed to preserve the marginal tissues and provide maximum blood clot stability and protection of self-periodontal regeneration (see detailed description later in this chapter).

Instruments used in periodontal surgery

Surgical procedures used in periodontal therapy often involve specific instruments for the different phases within the surgical intervention:

- Incision and excision (scalpels and knives)
- Deflection and re-adaptation of mucosal flaps (periosteal elevators)
- Removal of adherent fibrous and granulomatous tissue, root debridement (scalers and curettes)
- Removal of dental and osseous tissue (bone rongeurs, chisels, and burs)
- Suturing (sutures and needle holders, suture scissors).

Instruments should be kept in good working condition and maintenance should ensure that scalers, curettes, chisels, and knives are sharp and the hinges of scissors, rongeurs, and needle holders are properly lubricated.

The set of instruments used for the various periodontal surgical procedures should have a comparatively simple design. As a general rule, the number and varieties of instruments should be kept to a minimum and should be stored in sterile "ready-to-use" packs or trays. A commonly used standard tray combines the basic set of instruments used in periodontal surgery, together with periodontal instruments. The instruments listed below are often found on a standard tray (Fig. 32-43):

- Mouth mirrors
- Graduated periodontal probe/explorer
- Nabers (furcation) probe
- Handles for disposable surgical blades
- Mucoperiosteal elevator and tissue retractor
- Scalers and curettes
- Ultrasonic tips
- Tissue pliers
- Tissue scissors
- Needle holder.

Additional equipment may include:

- Syringe for local anesthesia
- Syringe for irrigation
- Aspirator tip
- Physiologic saline
- Plastic instrument

Specific surgical instruments

Knives used for drawing the incisions are available with fixed or replaceable blades. The advantage of disposable blades is that they are always sharp and are manufactured in different shapes (Fig. 32-43). Special handles mount blades in angulated positions, which may facilitate their use for reverse bevel incisions and for harvesting palatal autografts.

The proper healing of the periodontal wound is critical for the success of the operation. It is therefore important that the manipulations of soft tissue flaps are performed with minimum tissue damage. Care should be exercised in the use of periosteal elevators when flaps are deflected and retracted for optimal visibility. Surgical pliers and tissue retractors that pierce the tissues should not be used in the marginal area of the flaps. Needle holders with small beaks and atraumatic sutures should be used.

Scalers and curettes are used in periodontal surgery for both excising the granulation tissue and for scaling and root planing the roots once the area has been accessed after raising the flaps. Rotating fine-grained diamond stones may also be used within infrabony pockets, root concavities, and entrances to furcations (Fig. 32-44). An ultrasonic device with sterile saline solution as coolant may also be used for root debridement during surgery. Continuous irrigation

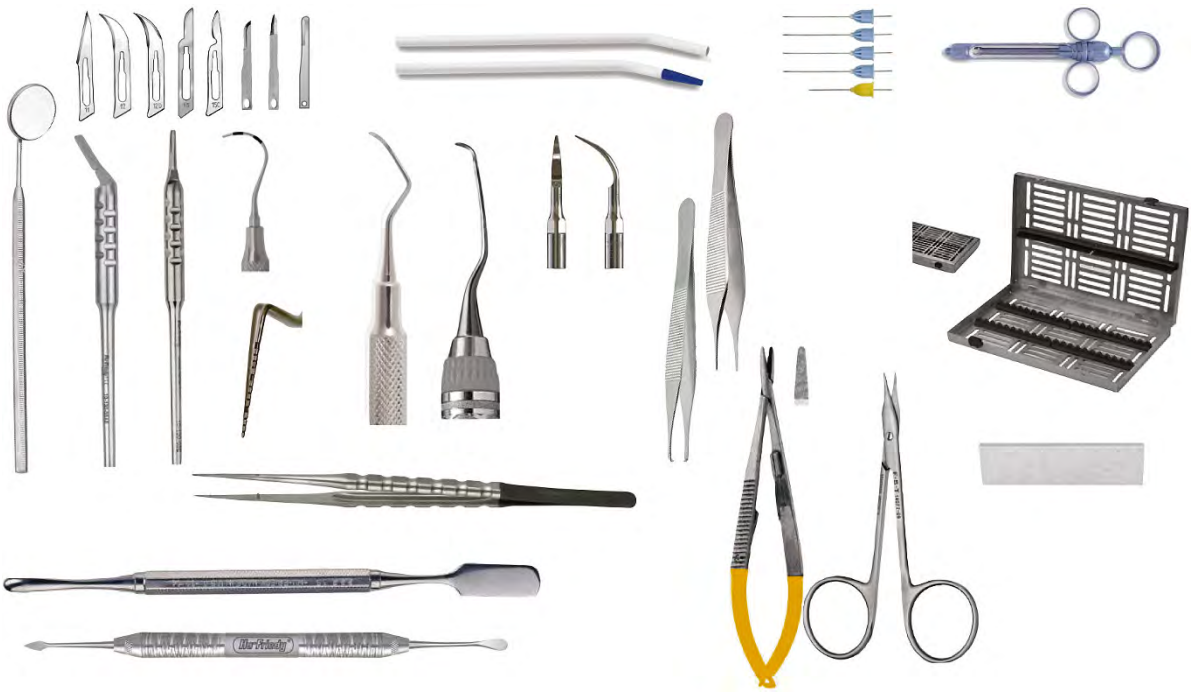

Fig. 32-43 Set of instruments used for periodontal surgery and included in a standard tray

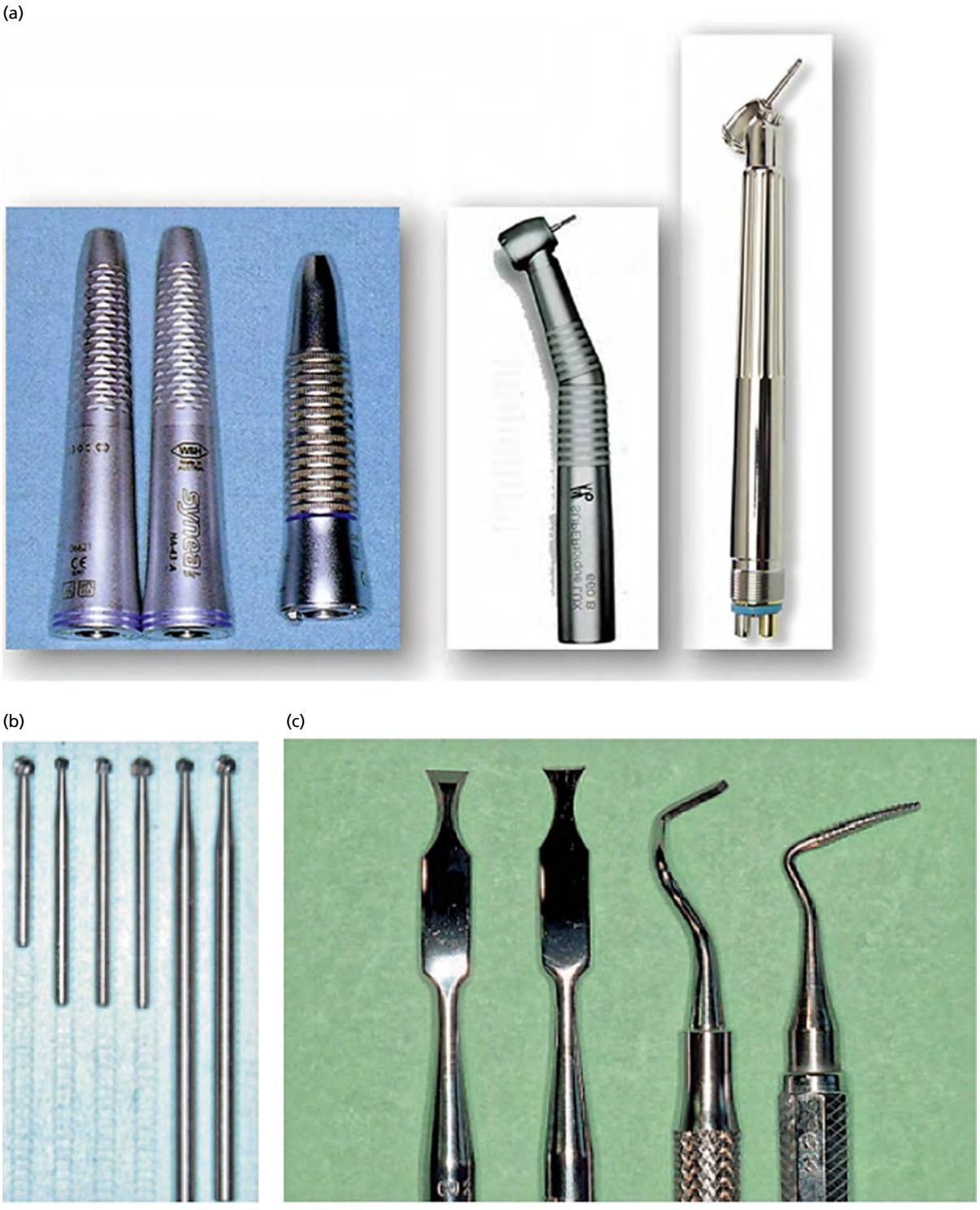

Fig. 32-44 (a) Examples of rotatory instruments mounted on straight or high-speed handpieces, using either (b) short or long trunk round burrs. (c) Examples of instruments used for bone recontouring (bone chisels and files).

of saline during the instrumentation of the roots is recommended to rinse away the blood and improve the visibility in the surgical field.

Sharp bone chisels or bone rongeurs (Fig. 32-44) are used during resective flap procedures to eliminate non-supportive bone (osteoplasty) or less frequently supportive bone (ostectomy). These instruments are recommended when removing the bone adjacent to the root surfaces because the use of burs may eliminate sound dental tissue, leading to hypersensitivity and loss of cementum. When used, surgical burs should be used with ample rinsing with sterile physiologic saline to ensure cooling and removal of tissue remnants.

Hemorrhage is rarely a problem in periodontal surgery. The characteristic oozing type of bleeding can normally be controlled with a pressure pack (sterile gauze moistened with saline). Bleeding from small vessels can be stopped by clamping and tying using a hemostat and resorbable sutures. If the vessel

is surrounded by bone, bleeding may be stopped by crushing the nutrient canal in which the vessel runs with a blunt instrument.

Visibility in the field of operation is secured by using effective suction. The lumen of the aspirator tip should have a smaller diameter than the rest of the tube, in order to prevent clogging.

The patient's head may be covered by autoclaved cotton draping or sterile disposable plastic/paper draping. The surgeon and all assistants should wear protective sterile gowns, surgical gloves, and protective eyewear.

Step by step flap surgical procedure

Local anesthesia in periodontal surgery

Pain management is an ethical obligation and will improve patient satisfaction (e.g. increased confidence and improved cooperation) as well as recovery and return to function after periodontal surgical procedures. To prevent pain during the performance of a periodontal surgical procedure, the entire area of the dentition scheduled for surgery, the teeth as well as the periodontal tissues, requires proper local anesthesia.

Anesthetics from the chemical group amino amides, e.g. lidocaine, mepivacaine, and articaine, are the "gold standard" for dental local anesthetics in periodontal surgery. In light of the specific need for bone penetration these anesthetics should be administered at high concentrations and with the appropriate additional vasoconstriction since these anesthetic solutions will cause an increase in the local blood flow, thus decreasing the duration of anesthesia. With the addition of vasoconstrictors (e.g. epinephrine >1:100 000 or >5 mg/mL) to dental local anesthetic solutions; the duration is considerably prolonged, the depth of anesthesia may be enhanced, and bleeding during surgery is reduced. In fact, the use of a dental local anesthetic without a vasoconstrictor during a periodontal surgical procedure is counterproductive because of the increased bleeding in the area of surgery and the reduced depth of the anesthesia. However, although the cardiovascular effects of the usually small amounts of epinephrine used during a periodontal surgical procedure are of little practical concern in most individuals, accidental intravascular injections, unusual patient sensitivity, and unanticipated drug interactions (or excessive doses), can result in potentially serious health hazards, and therefore, a careful medical history must be taken before any periodontal surgery. In patients with a history of serious cardiovascular events, only low dosages should be administered or even local anesthetics without a vasoconstrictor can be used.

Injections of dental local anesthetics prior to a periodontal surgical procedure may be routine for the dentist but is often a most unpleasant experience for the patient. Reassurance and psychological support are essential and will increase the patient's confidence in their dentist. The creation of a relaxed atmosphere to decrease the patient's fear in the unusual surgical environment is a useful way of increasing the patient's own defense mechanisms against pain perception (e.g. release of endogenous endorphins).

Anesthesia for periodontal surgery is obtained by nerve block and/or by local infiltration. In cases of flap surgery, complete anesthesia must be attained before commencing the operation because it may be difficult to supplement anesthesia after the bone surface has been exposed. In addition, the pain elicited by needle insertion can be significantly reduced if the mucosa at the puncture site is anesthetized in advance by the use of a suitable topical ointment or spray.

Local infiltration may have a greatly decreased rate of success in areas where inflammation remains in the periodontal tissues. The suggested reason for this is that tissue pH tends to be low in inflamed areas and anesthetic solutions are less potent at low pH because there is a greater proportion of charged cation molecules than uncharged base molecules. Because of this, diffusion of the local anesthetic into the axoplasm is slower, with subsequent delayed onset and decreased efficacy.

As a rule, analgesia of the teeth and the soft and hard tissues of the mandible should be obtained by a mandibular block and/or a mental block. In the anterior region of the mandible, canines and incisors can often be anesthetized by infiltration, but there are often anastomoses over the midline. These anastomoses must be anesthetized by bilateral infiltration or by bilateral mental blocks. The buccal soft tissues of the mandible are anesthetized by local infiltration or by blocking the buccal nerve. Local infiltration, performed as a series of injections in the buccal fold of the treatment area, has of course the added advantage of providing a local ischemic effect if a suitable anesthetic is used.

The lingual periodontal tissues must also be anesthetized. This is accomplished by blocking the lingual nerve and/or by infiltration into the floor of the mouth close to the site of operation. If necessary, to obtain proper ischemia, and only then, supplementary injections may be made in the interdental papillae (intraseptal injections).

Local anesthesia of the teeth and buccal periodontal tissues of the maxilla can easily be obtained by injections into the mucogingival fold of the treatment area. If larger areas of the maxillary dentition are scheduled for surgery, repeated injections (into the mucogingival fold) have to be performed, for example at the central incisor, canine, second premolar, and second molar. In the posterior maxillary region, a tuberosity injection can be used to block the superior alveolar branches of the maxillary nerve. However, because of the vicinity to the pterygoid venous plexus, this type of block anesthesia is not recommended due to the risk of intravenous injection and/or hematoma formation.

The palatal nerves are most easily anesthetized by injections made at right angles to the mucosa and placed about 10 mm apical to the gingival margin adjacent to teeth included in the operation. In cases of advanced bone loss, the pain produced by injecting into the non-resilient palatal mucosa can be

minimized if the injections are performed from the buccal aspect, that is through the interdental gingiva. Sometimes blocks of the nasopalatine nerves and/or the greater palatine nerves can be applied. Supplementary blocking of the greater palatine nerve should be considered, especially for periodontal surgery involving molars.

Incisions and flap elevation

Before incisions are made, a careful periodontal examination should be carried out to identify the teeth on which periodontal surgery should be performed, since flap elevation in teeth with shallow pockets will cause attachment loss and gingival recession. Once all the area is anesthetized, deep bone sounding using a periodontal probe should help the surgeon to identify the areas with deepest pockets and bone defects and thus to properly design the incisions based on the specific objectives of the periodontal surgery.

Scalloped internal beveled horizontal incisions parallel to the gingival margin are the basic incisions in periodontal flap surgery. The amount of scalloping (distance between the incision and the gingival margin) will depend on the surgical technique selection and the objective of the surgery. When the main aim is surgical access for root instrumentation, mainly in anterior maxillary areas, the amount of scalloping should be minimal, and flaps should be repositioned to the same level as before the surgery in order to minimize postoperative gingival recession (access flaps or open flap debridement). Alternatively, when the aim is not only access for deep root instrumentation, but also pocket reduction, the soft tissue component of the periodontal pocket can be excised with the scalloped incision (apically positioned flaps) (Fig. 32-45). This is particularly

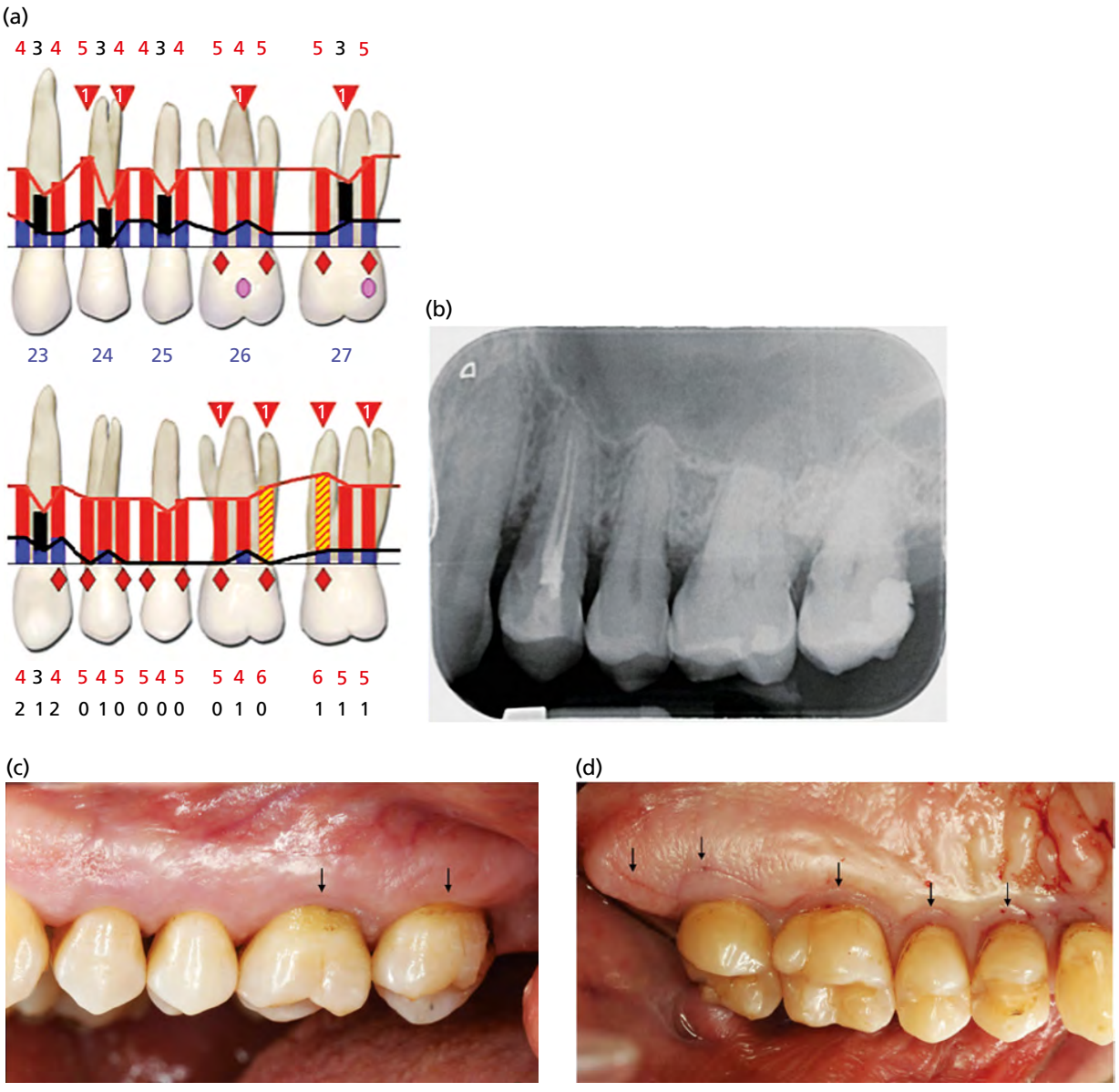

Fig 32-45 Periodontal flap surgery in a posterior maxillary sextant. (a) Preoperative probing depths. Deep probing depth ≥5 mm in interproximal palatal sites. (b) Periapical radiograph depicting horizontal bone loss pattern. (c) Buccal flap design: intracrevicular incision in premolars and minimal scalloping in the molars (see black arrows). (d) Palatal flap design: 2–3 mm scalloping incision and wide parallel incision at the distal wedge (see black arrows)

needed in palatal flaps where the apical positioning of the flaps is impossible and pocket reduction can only be attained by the scalloping during the first incision and by the thinning of the palatal flap. In the buccal flap, depending on the amount of keratinized tissue present, the scalloping can be combined with the apical positioning of the flaps once they have been elevated beyond the mucogingival junction.

As a general rule, periodontal surgeries are planned by sextants, isolating the anterior segment (from cuspid to cuspid) from the posterior areas of the dentition. Surgical designs for anterior periodontal surgeries are conditioned by the expected esthetic outcomes and the presence/absence of bone lesions (infrabony defects or craters). Anterior periodontal surgeries are usually minimally invasive and aim to preserve the interdental soft tissues. These surgical designs will be described independently in this chapter. Posterior periodontal surgeries, however, are usually aimed at pocket reduction and improving the patient's accessibility for plaque control and are frequently designed as apically positioned flaps. The need for vertical releasing incisions in these posterior surgeries will depend on the disease pattern and the degree of periodontal destruction in the mesial and distal teeth of the planned surgery. Distally, buccal and lingual flap incisions are usually followed by distal wedge designs depending on the presence of deep pockets in the distal aspect of the last molar and the amount of keratinized tissue present (Fig. 32-46). Mesially, there is usually no need to use vertical incisions, although the presence of a deep pocket between the cuspid and the first premolar sometimes require a releasing incision to prevent raising the flap mesial to the cuspid and being able at the same time to apically position the flap. Independent of flap position, the goal should be to achieve complete soft tissue coverage of the alveolar bone, not only at buccal/lingual sites but also at proximal sites. It is therefore of utmost importance to carefully plan the incisions in such a way that this goal is achieved at the termination of the surgical intervention. Internal beveled incisions are aimed towards the bone surface and once performed, mucoperiosteal flaps (full thickness) should be elevated with a fine periosteal elevator. Depending on the objective of the surgery,

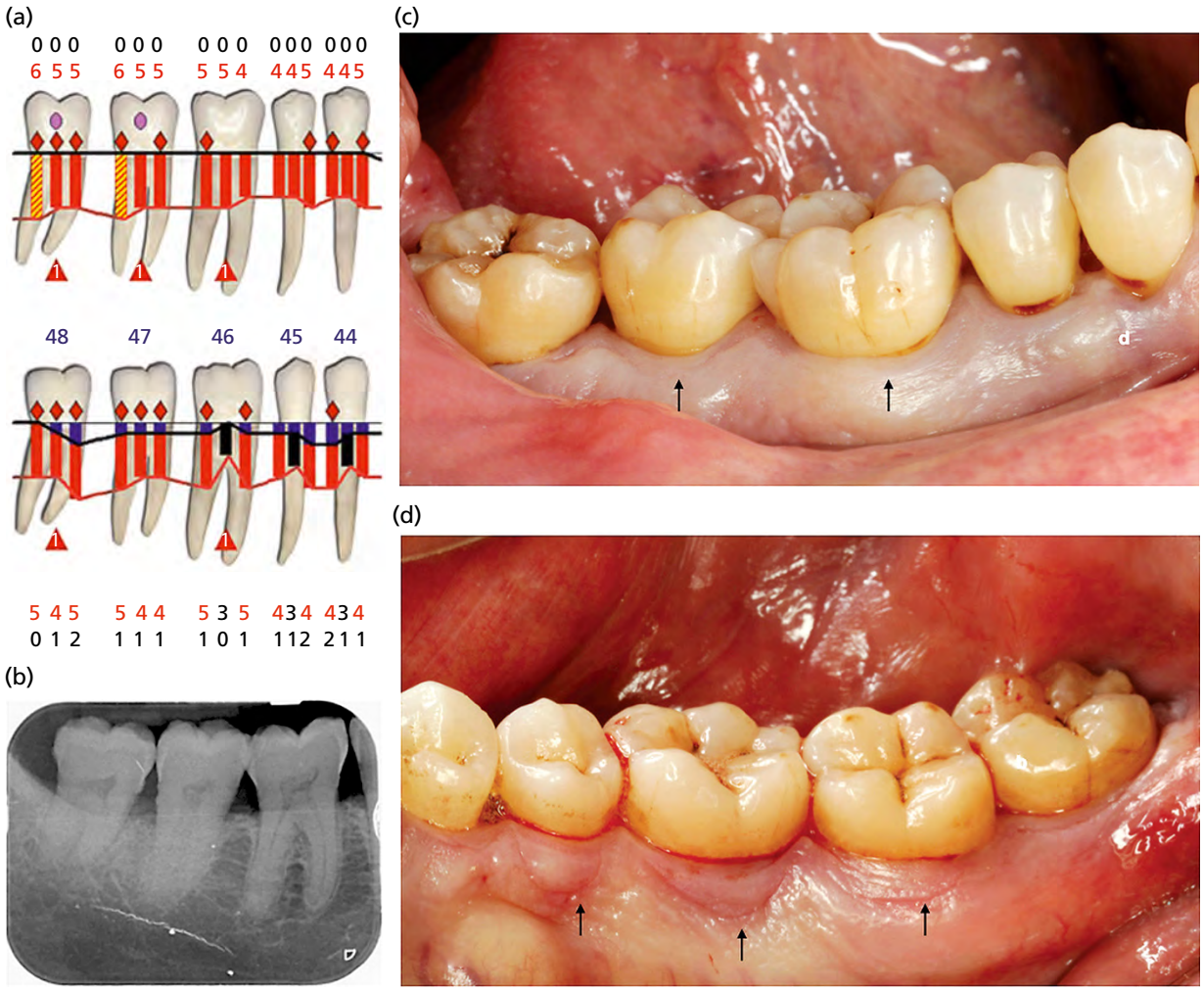

Fig 32-46 Periodontal flap surgery in a posterior mandibular sextant. (a) Preoperative probing depths. Deep probing depth ≥5 mm in interproximal palatal sites. (b) Periapical radiograph depicting horizontal bone loss pattern. (c) Buccal flap design: intracrevicular incision in premolars and minimal scalloping in the molars (see black arrows). (d) Lingual flap design: 2–3 mm scalloping incision and wide parallel incision at the distal wedge (see black arrows)

the amount of alveolar bone exposed would be minimal in access flap surgeries or extensive in apically positioned flaps that need to elevate the flaps beyond the mucogingival junction (in the buccal flap) (Fig. 32-46).

Bone recontouring

Once the flaps have been raised, the remaining granulation tissue should be removed in order to evaluate the full morphology of the periradicular bone and to decide whether bone recontouring is needed or not, or whether a regenerative procedure is indicated when deep infrabony, crater, or furcation defects are present (see Chapter 38). In posterior sextants, when bone lesions and furcation lesions are not amenable for regeneration (shallow and intermediate craters), they should be eliminated by bone recontouring (osteoplasty and/or ostectomy) (Figs. 32-47, 32-48).

Root instrumentation

Root instrumentation can be performed with hand or ultrasonic instruments according to the operator's preferences. Ultrasonic (sonic) instrumentation offers the additional benefits of improved visibility due to the irrigating effect of the cooling solution (sterile saline). For root instrumentation within intrabony defects, root concavities, and entrances to furcations, the use of rotating fine-grained diamond stones may be used.

An important consideration in periodontal surgery is to make the exposed root surface biologically compatible with a healthy periodontium. In addition to mechanical debridement, agents such as EDTA and enamel matrix proteins (EMD) have been used for root surface conditioning and biomodification. Root surface conditioning is aimed at removing the smear layer and the external hydroxyapatite layers to expose the collagenous matrix of the root cementum. Biomodification with the use of EMD is aimed at preventing the epithelial downgrowth and enhancing cellular responses conducive to new attachment by expressing the cementoblast phenotype of the cells repopulating the treated root surface.

Although in the past root conditioned was carried out by etching the root surface with agents operating at a low pH (e.g. citric acid or tetracycline HCl). This acidic environment may exert immediate necrotizing effects on the surrounding periodontal ligament and other periodontal tissues, and currently these agents have been replaced by EDTA that attains similar effect on the root surface operating at a neutral pH (Blomlöf & Lindskog 1995a, b) (Figs. 32-47, 32-48).

Suturing

At the end of surgery, the flaps should be placed at the intended position and properly adapted to each other and to the tooth surfaces. Preferably, full coverage of the buccal/lingual (palatal) and interdental

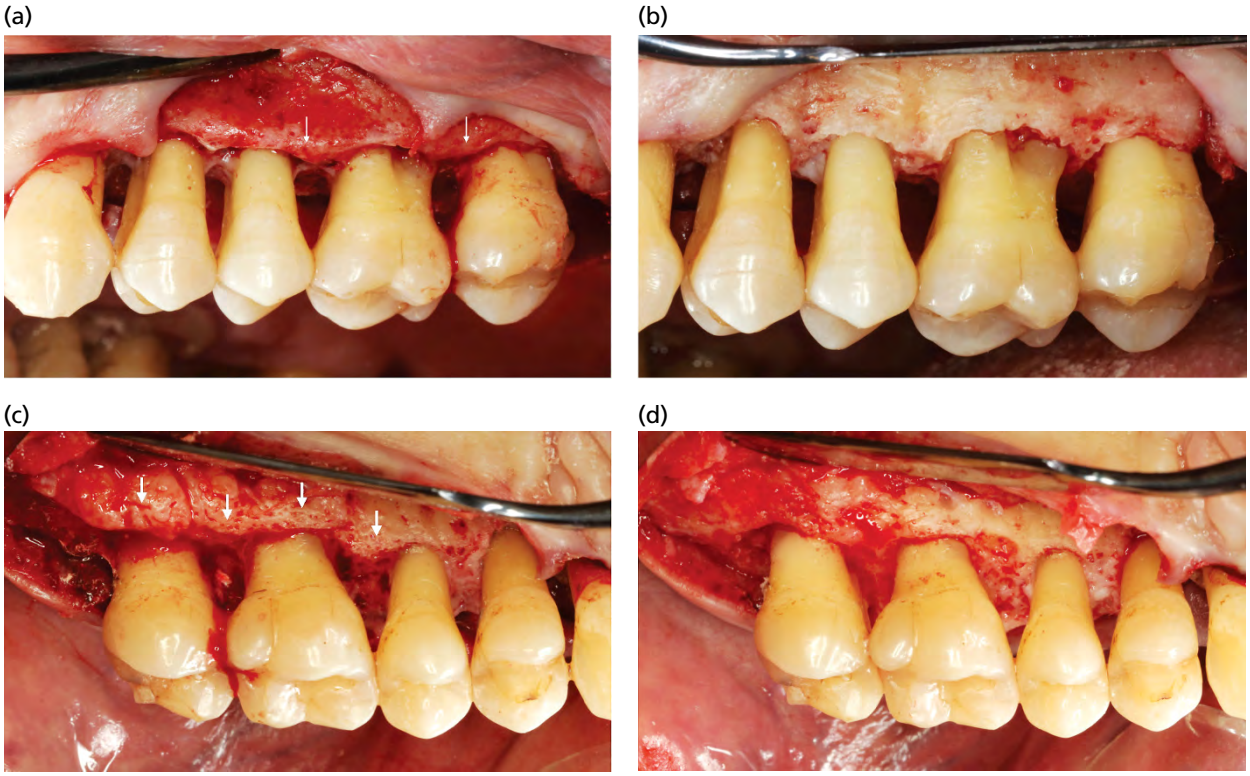

Fig 32-47 (a) Full thickness buccal flap depicting narrow ledges of bone with incipient buccal furcations (white arrows). (b) Full thickness palatal flap depicting wide bone balconies and shallow interproximal craters. (c) Minimal osteoplasty to eliminate interproximal ledges of bone (white arrows). (d) Wide osteoplasty to eliminate bone balconies and create interproximal smooth ramps to eliminate craters.

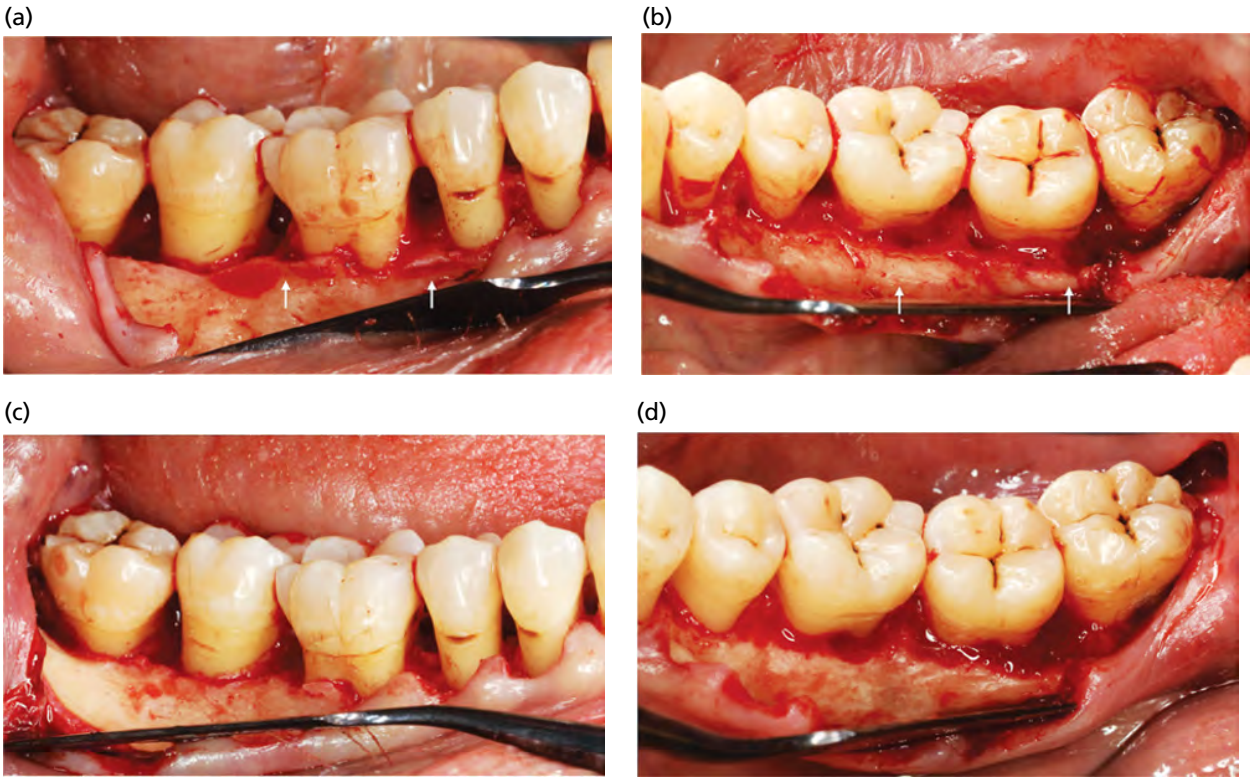

Fig 32-48 (a) Full thickness buccal flap depicting narrow ledges of bone with incipient buccal furcations (white arrows). (b) Full thickness lingual flap depicting wide bone balconies and shallow interproximal craters (white arrows). (c) Minimal osteoplasty to eliminate interproximal ledges of bone. (d) Wide osteoplasty to eliminate bone balconies and to create interproximal smooth ramps to eliminate craters.

alveolar bone should be obtained by full (primary) closure of the soft tissue flaps. If this can be achieved, healing is by first intention and postoperative bone resorption is minimal. Therefore, prior to suturing, the flap margins should be trimmed to properly fit the buccal and lingual (palatal) bone margin as well as the interproximal areas; excessive soft tissue must be removed. If the amount of flap tissue present is insufficient to cover the interproximal bone, the flaps at the buccal or lingual aspects of the teeth must be recontoured and, in some cases, even displaced coronally. Following proper trimming, the flaps are secured in the correct position by sutures. Sutures should not interfere with incision lines and must not pass through the tissues near the flap margins or too close to a papilla, because this may result in tearing of the tissues (Figs. 32-49, 32-50)

The use of non-irritating, monofilamentous materials is recommended. These materials are non-resorbable and extremely inert, do not adhere to tissues, and are therefore easy to remove. "Wicking", the phenomenon of bacteria moving along or within multistrand (braided) suture materials, should also be avoided. The dimensions usually preferred are 5/0, but even finer suture material (6/0 or 7/0) may be used. Sutures are removed after 7–14 days.

Since the flap tissue following the final preparation is thin, small diameter, curved non-traumatic reverse-cutting needles should be used. Since buccal and lingual/palatal flaps should be adapted around teeth, needles should be shaped as 3/8 of a circle to undertake the flaps without been clotted under the contact points

The three most frequently used sutures in periodontal flap surgery are:

- Interrupted interdental sutures
- Suspensory sutures
- Continuous sutures.

The *interrupted interdental suture* (Fig. 32-51) provides a close interdental adaptation between the buccal and lingual flaps with equal tension on both units. This type of suture is therefore not recommended when the buccal and lingual flaps are repositioned at different levels. When this technique of suturing is employed, the needle is passed through the buccal flap from the external surface, across the interdental area, and through the lingual flap from the internal surface, or vice versa. When closing the suture, care must be taken to avoid tearing the flap tissues.

In order to avoid placing the suture material between the mucosa and the alveolar bone in the interdental area, an alternative technique with the interrupted interdental suture can be used if the flaps have not been elevated beyond the mucogingival line. With the use of a curved needle, the suture is anchored in the attached tissue on the buccal aspect of the proximal site, brought to the lingual side through

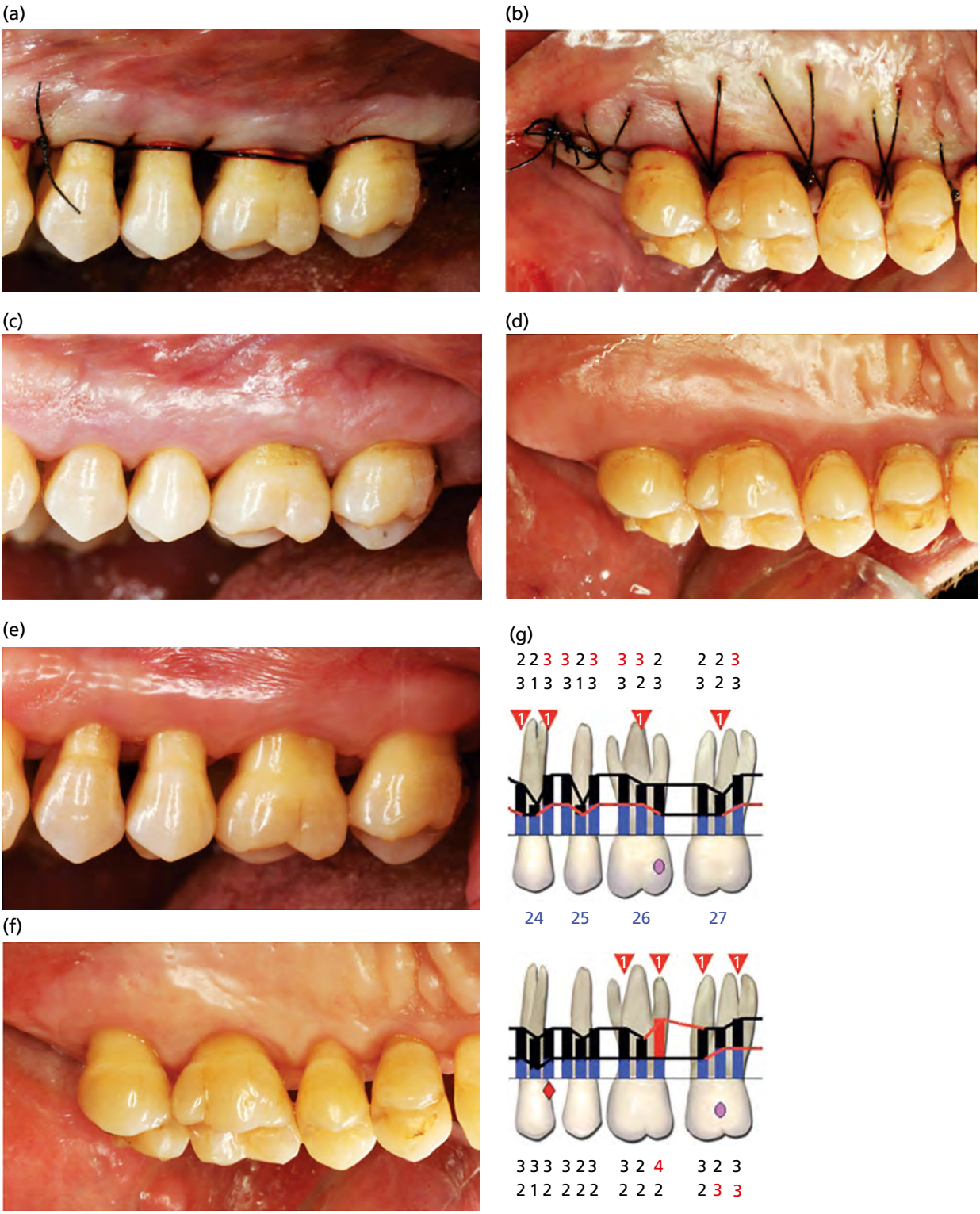

Fig. 32-49 (a) Flap suturing on the buccal side. Continuous anchored suturing to maintain the flap adapted to the bone crest. (b) Flap suturing on the palatal side. Continuous anchored suturing with wide horizontal mattress sutures to maintain the flap adapted to the bone crest. (c) Buccal side of the left posterior sextant after subgingival instrumentation. (d) Palatal side of the left posterior sextant after subgingival instrumentation. (e) Buccal side of the left posterior sextant one year after periodontal surgery. Note differences in the position of the gingival margin. (f) Palatal side of the left posterior sextant one year after periodontal surgery. Note the wide access for cleaning the interdental areas. (g) Probing depths one year after periodontal surgery. Note that there are no probing depths >4 mm and no bleeding on probing.

the proximal sites, and anchored in the attached tissue on the lingual side. The suture is then brought back to the starting point and tied (Fig. 32-52). Hence, the suture will lie on the surface of the interdental tissue, keeping the soft tissue flaps in close contact with the underlying bone.

In regenerative procedures, which usually require a coronal advancement of the flap, a *modified mattress*

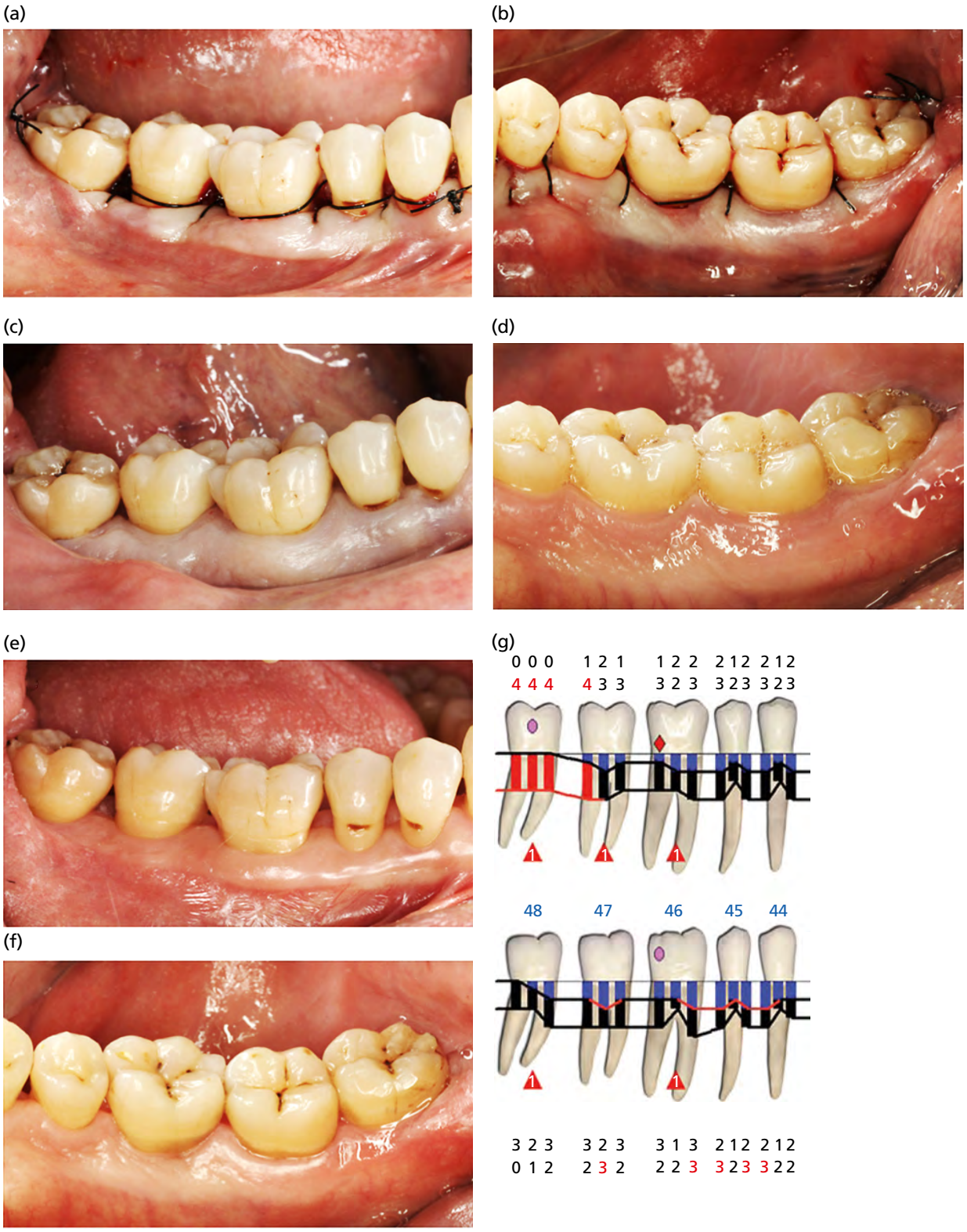

Fig. 32-50 (a) Flap suturing on the buccal side. Continuous anchored suturing to maintain the flap adapted to the bone crest. (b) Flap suturing on the lingual side. Continuous anchored suturing to maintain the flap adapted to the bone crest. Interrupted loop suture to close the distal wedge. (c) Buccal side of the right lower posterior sextant after subgingival instrumentation. (d) Lingual side of the right lower posterior sextant after subgingival instrumentation. (e) Buccal side of the right lower posterior sextant one year after periodontal surgery. Note differences in the position of the gingival margin and the closed entrance to the furcation. (f) Lingual side of the right posterior sextant one year after periodontal surgery. Note the access for cleaning at the interdental areas. (g) Probing depths one year after periodontal surgery. Note that there are no probing depths >4 mm and no bleeding on probing. Only class I furcation defects are present in the lingual aspect of the molar

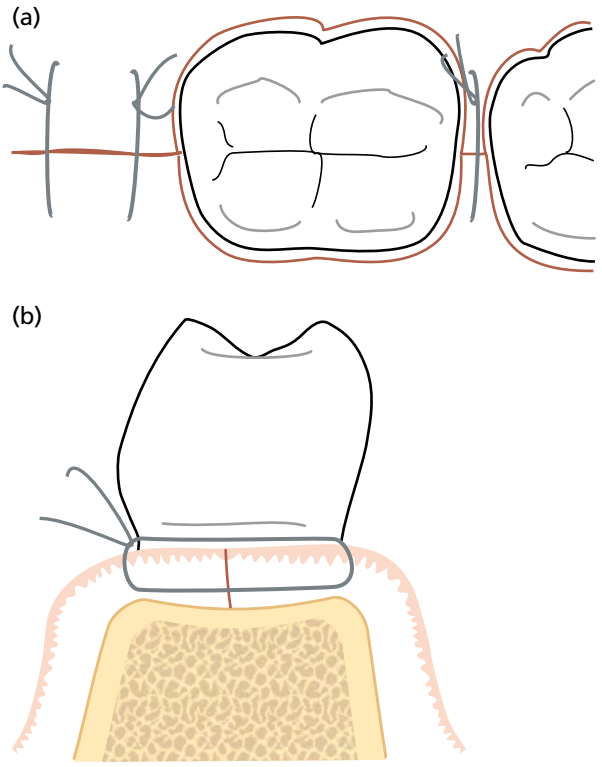

Fig. 32-51 Suturing. (a, b) Interrupted interdental suture.

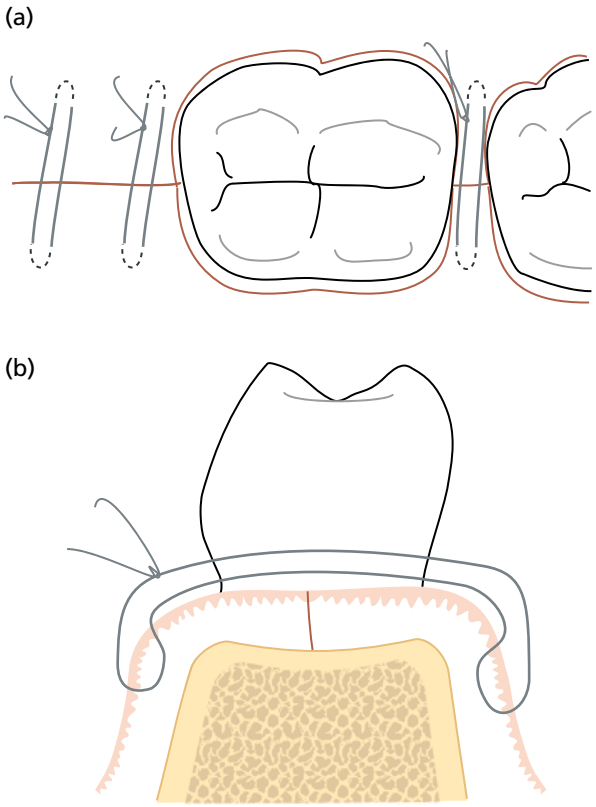

Fig. 32-52 Suturing. (a, b) Modified interrupted interdental suture. Note that with this suturing technique the suture lies on the surface of the interdental tissue keeping the soft tissue flaps in close contact with the underlying bone.

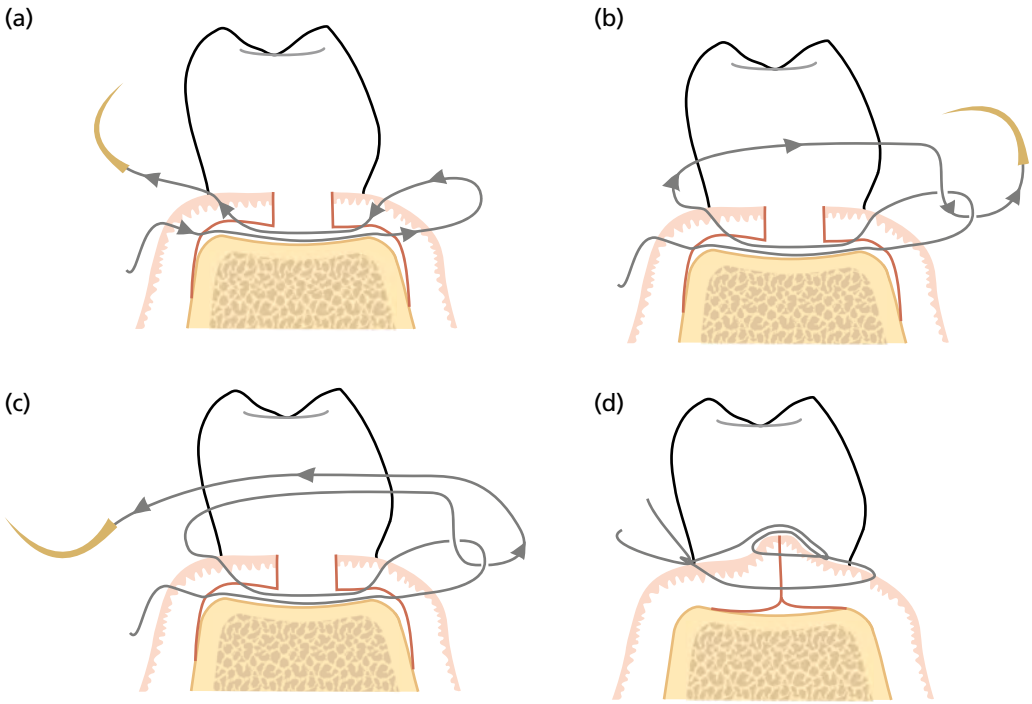

Fig. 32-53 Suturing. (a–d) Modified mattress suture.

suture may be used as an interdental suture to secure close flap adaptation (Fig. 32-53). As for the interrupted suture, the needle is passed through the buccal flap from the external surface, across the interdental area, and through the lingual flap from the internal surface. The suture is then run back to the buccal side by passing the needle through the lingual and buccal flaps. Thereafter, the suture is brought through the approximal site coronally to the tissue, passed through the loop of the suture on the lingual

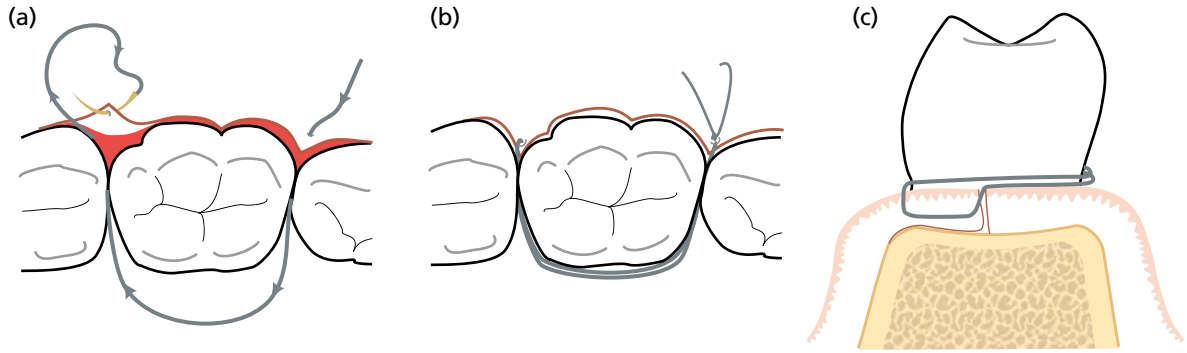

Fig. 32-54 Suturing. (a–c) Suspensory suture.

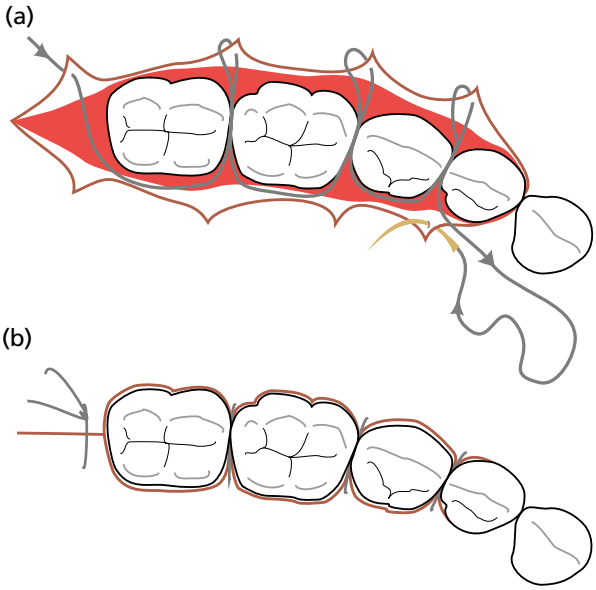

Fig. 32-55 Suturing. (a, b) Continuous suture.

aspect, and then brought back to the starting point on the buccal side and tied.

The *suspensory suture* (Fig. 32-54) is used primarily when the surgical procedure is of limited extent and involves only the tissue of the buccal or lingual aspect of the teeth. It is also the suture of choice when the buccal and lingual flaps are repositioned at different levels. The needle is passed through the buccal flap from its external surface at the mesial side of the tooth, the suture is placed around the lingual surface of the tooth, and the needle is passed through the buccal flap on the distal side of the tooth. The suture is brought back to the starting point via the lingual surface of the tooth and tied. If a lingual flap has been elevated as well, this is secured in the intended position using the same technique.

The *continuous suture* (Fig. 32-55) is commonly used when flaps involving several teeth are to be repositioned apically. When flaps have been elevated on both sides of the teeth, one flap at a time is secured in its correct position. The suturing procedure is started at the mesial/distal aspect of the buccal flap by passing the needle through the flap and across the interdental area. The suture is laid around the lingual surface of the tooth and returned to the buccal side through the next interdental space. The procedure is repeated tooth by tooth until the distal/mesial end of the flap is reached. Thereafter, the needle is passed through the lingual flap, with the suture laid around the buccal aspect of each tooth and through each interproximal space. When the suturing of the lingual flap is completed and the needle has been brought back to the first interdental area, the positions of the flaps are adjusted and secured in their proper positions by closing the suture. Thus, only one knot is needed.

Periodontal dressings are currently seldom used since results from clinical studies have shown that they may be unnecessary and may be usefully replaced by rinsing with chlorhexidine only (Sanz *et al*. 1989; Vaughan & Garnick 1989). Only in situations of bleeding risk during the initial phase of healing (e.g. in patients using anticoagulant medication) are periodontal dressings recommended; they should be soft to allow proper adaptation and must not interfere with healing. Cyanoacrylates have also been used as periodontal dressings with varying success.

Postsurgical care

In order to minimize postoperative pain and discomfort, surgical handling of tissues should be as atraumatic as possible. Care should be taken during surgery to avoid unnecessary tearing of the flaps, to keep the bone moistened, and to secure complete soft tissue coverage of the alveolar bone at suturing. With a carefully performed surgical procedure, most patients will normally experience only minimal postoperative problems. Pain is usually limited to the first days following surgery and is of a level that in most patients can be adequately controlled with drugs normally used for pain control. However, it is important to recognize that pain threshold is subjective and may vary between individuals. It is also important to give the patient information about the postsurgical sequence and communicate that uncomplicated healing is standard. Further, during the early phase of healing, the patient should be instructed to avoid chewing in the area subjected to surgical treatment.

Postoperative plaque control is the most important variable in determining the long-term result of periodontal surgery. Provided proper postoperative infection control levels are established, most surgical treatment techniques will result in conditions that favor the maintenance of a healthy periodontium. Although there are other factors of a more general nature affecting surgical outcome (e.g. the systemic status of the patient at the time of surgery and during healing), disease recurrence is an inevitable complication, regardless of surgical technique used, in patients not given proper postsurgical and maintenance care.

Since self-performed oral hygiene is often associated with pain and discomfort during the immediate postsurgical phase, regularly performed professional tooth cleaning is a more effective means of mechanical infection control following periodontal surgery. In the immediate postsurgical period, self-performed rinsing with a suitable antiplaque agent, for example twice daily rinsing with 0.1–0.2% chlorhexidine solution, is recommended. Although an obvious disadvantage with the use of chlorhexidine is the staining of the teeth and tongue, this is usually not a deterrent for compliance. Nevertheless, it is important to return to and maintain good mechanical oral hygiene measures as soon as possible, particularly since rinsing with chlorhexidine, in contrast to properly performed mechanical oral hygiene, is unlikely to have any influence on subgingival recolonization of plaque.

Maintaining good postsurgical wound stability is another important factor affecting the outcome of some types of periodontal flap surgery. If wound stability is judged an important part of a specific procedure, the procedure itself as well as postsurgical care must include measures to stabilize the healing wound (e.g. adequate suturing technique, protection from mechanical trauma to the marginal tissues during the initial healing phase). If a mucoperiosteal flap is replaced rather than repositioned apically, early apical migration of gingival epithelial cells will occur as a consequence of a break between root surface and healing connective tissue. Hence, maintenance of a tight adaptation of the flap to the root surface is essential and one may therefore consider keeping the sutures in place for longer than the 7–10 days usually prescribed following standard flap surgery.

Following suture removal, the surgically treated area is thoroughly irrigated with a dental spray and the teeth are carefully cleaned with a rubber cup and polishing paste. If the healing is satisfactory for starting mechanical tooth cleaning, the patient is instructed in gentle brushing of the operated area using a soft toothbrush. In this early phase following surgical treatment, the use of interdental brushes is abandoned due to the risk of traumatizing the interdental tissues. Visits are scheduled for supportive care at 2-week intervals to monitor the patient's plaque control closely. During this postoperative maintenance phase, adjustments to the methods for optimal self-performed mechanical cleaning are made depending on the healing status of the tissues. The time interval between visits for supportive care may gradually be increased, depending on the patient's plaque control standard (Figs. 32-49, 32-50).

Specific surgical interventions for papilla management

In the last three decades significant advances have been made in the evolution of flaps. During the early development of guided tissue regeneration, clinically it was felt that access flaps such as the modified Widman flap or the Kirkland modified flap operation would enhance the risk of membrane exposure. Thus, a quest for better flap adaptation and prevention of wound dehiscence began. In particular, the following flaps, aiming at preserving interdental papillary tissues, have been documented (Graziani *et al*. 2018).

Papilla preservation flap

In order to preserve the interdental soft tissues for maximum soft tissue coverage following surgical intervention involving treatment of proximal osseous defects, Takei *et al*. (1985) proposed a surgical approach called the *papilla preservation* technique. This surgical design fully maintained the interdental soft tissues and therefore was mainly indicated for the surgical treatment of anterior tooth regions or in posterior regions when regenerative techniques are used in the treatment of intrabony defects. This surgical design is initiated by intrasulcular incisions at the facial and proximal aspects of the teeth without cutting through the interdental papillae (Fig. 32-56a). Subsequently, an intrasulcular incision is made along the lingual/palatal aspect of the teeth followed with a semilunar incision across each interdental area from the line angles of the teeth. After freeing the interdental papilla carefully from the underlying hard tissues, the detached interdental tissue is pushed through the embrasure with a blunt instrument from the palatal to the buccal side and full thickness flaps are elevated (Fig. 32-56b). After thorough debridement of the root surfaces and bone defects (Fig. 32-57) the flaps are repositioned and sutured using cross mattress sutures (Figs. 32-58, 32-59).

Modified papilla preservation technique

Similarly, the modified papilla preservation technique was designed in order to obtain primary wound closure of the interproximal tissue over barrier membranes placed coronally to the alveolar crest (Cortellini *et al*. 1995b). Conceptually the flap is similar to the papilla preservation technique with an intrasulcular circumferential incision around the involved dentition, but the second incision is straight, instead of semilunar, with a slight internal bevel at the base of the buccal, instead of the palatal, area of the papilla. A mucoperiosteal flap is then elevated to

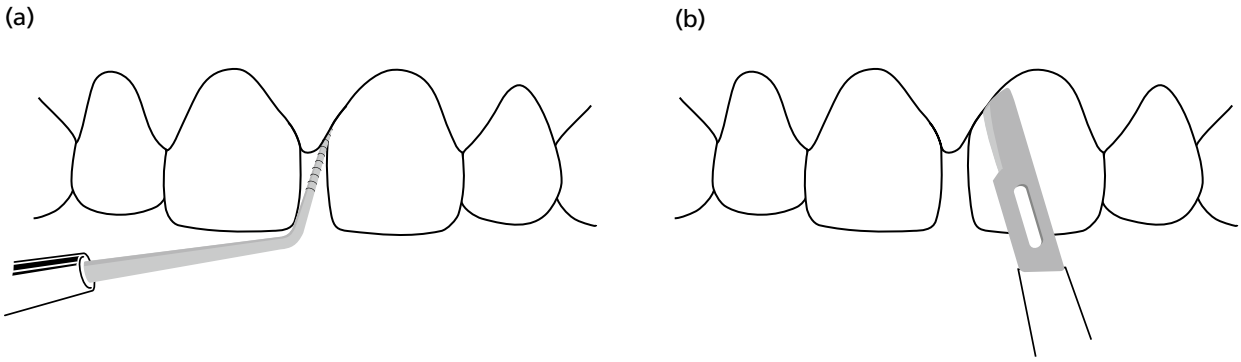

Fig. 32-56 Papilla preservation flap. (a) A deep pocket is present at an approximal tooth site. (b) Intracrevicular incisions are made at the facial and proximal aspects of the teeth.

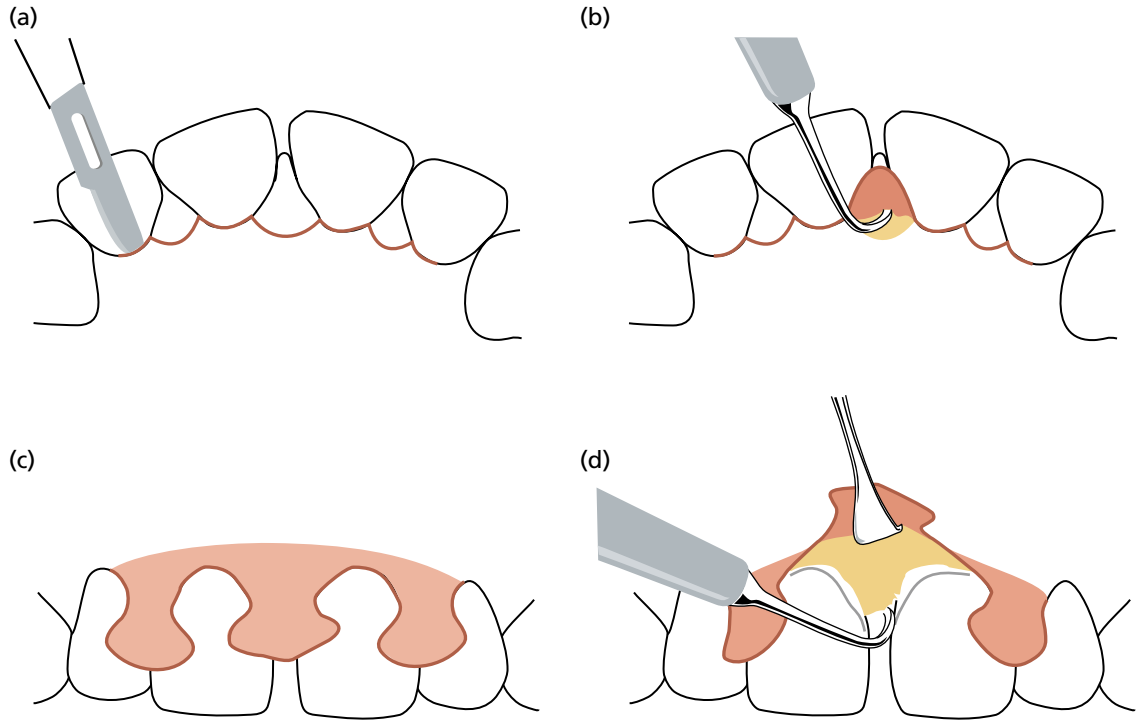

Fig. 32-57 Papilla preservation flap. (a) An intracrevicular incision is made along the lingual/palatal aspect of the teeth with a semilunar incision made across each interdental area. (b) A curette or a papilla elevator is used to carefully free the interdental papilla from the underlying hard tissue. (c, d) Detached interdental tissue is pushed through the embrasure with a blunt instrument to be included in the facial flap.

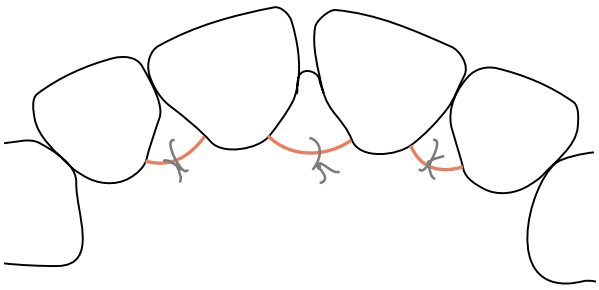

Fig. 32-58 Papilla preservation flap. The flap is replaced, and sutures are placed on the palatal aspect of the interdental areas.

the level of the buccal alveolar crest. The interdental papilla is then separated from the adjacent teeth and underlying alveolar bone and is dissected from buccal towards lingual until it remains pedunculated to the palatal full thickness flap, thus providing direct view of the defect (Fig. 32-60). Moreover, the flap was designed to be coronally repositioned through a split-thickness incision as it has been originally described to interproximally place a non-resorbable titanium-reinforced membrane in order to maintain an adequate supra-alveolar space for regeneration. Flap repositioning is performed through a two-layer suturing consisting of a horizontal internal mattress suture positioned buccally just above the mucogingival line and a vertical internal mattress suture placed between the buccal aspect of the interproximal papilla. Laurell's group then proposed for the latter a modified internal mattress suture for tissue repositioning, which involves a double stabilization both on the buccal and lingual aspect of the flap (Zybutz *et al*. 2000).

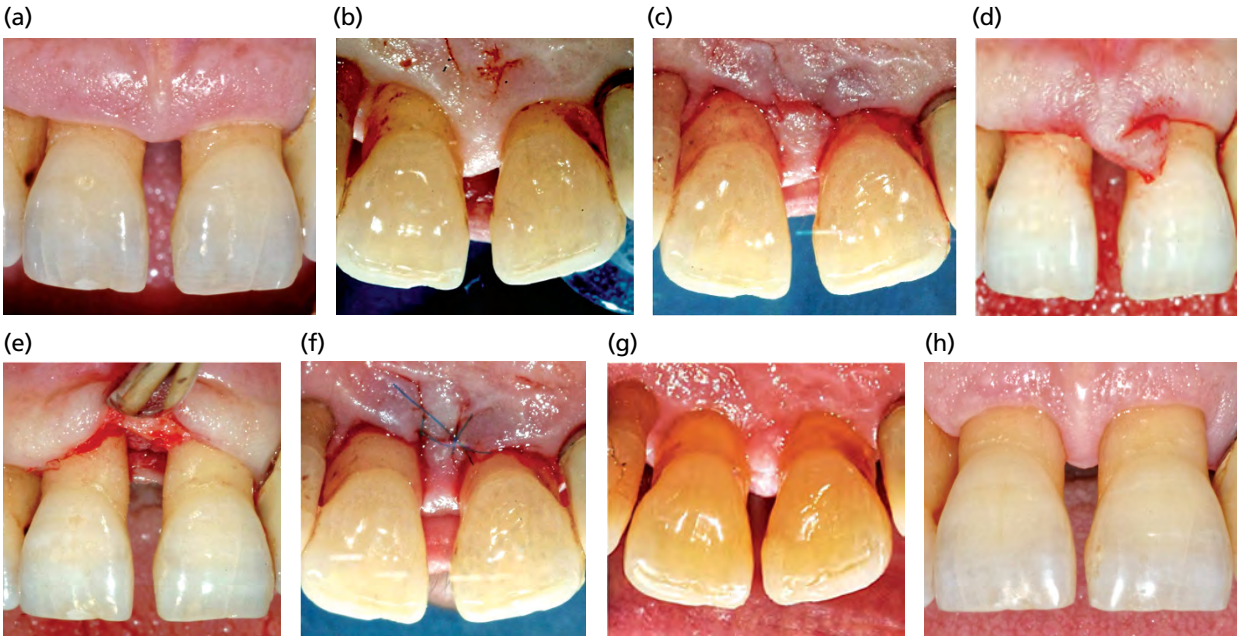

Fig. 32-59 Papilla preservation flap. (a) Preoperative buccal view. (b) Preoperative palatal view. (c) Semilunar palatal incision at the base of the papilla. (d) Flap elevation; note the entire papilla attached to the buccal flap. (e) Exposure of bone defect. (f) Suture. (g) Postoperative buccal view. (h) Postoperative palatal view.

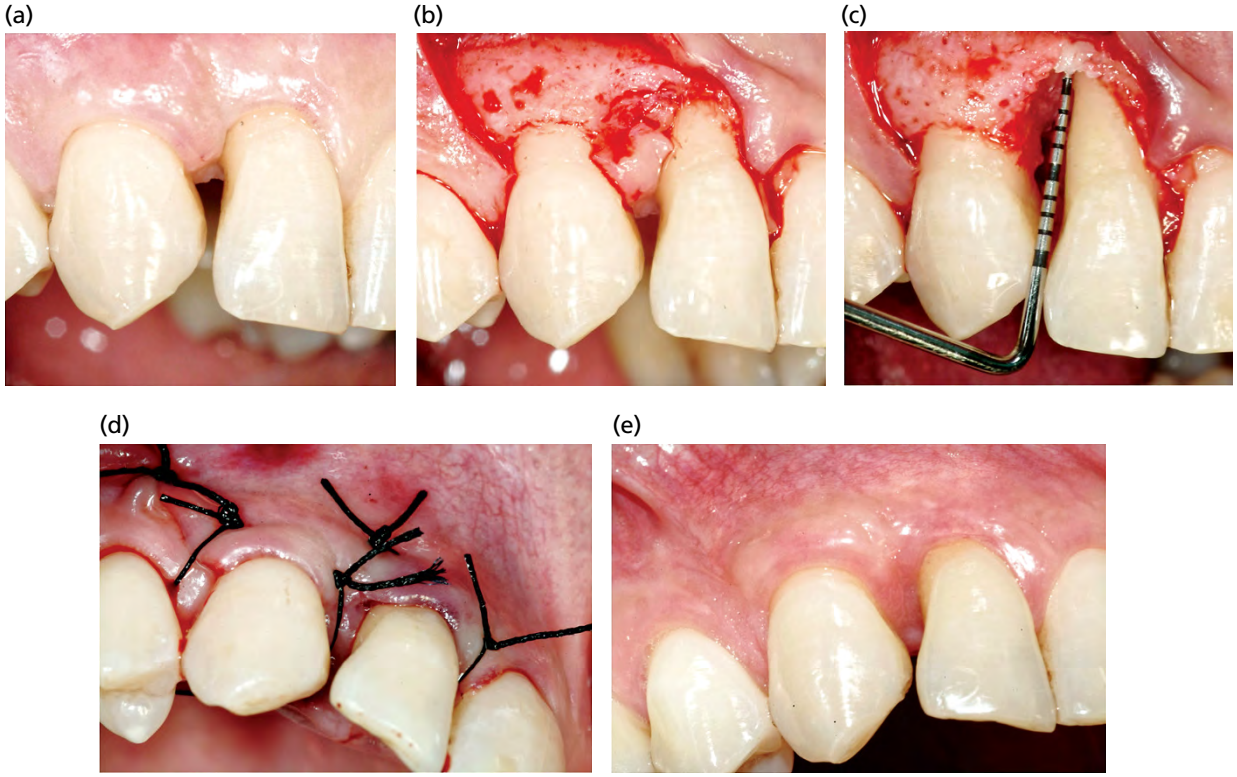

Fig. 32-60 Modified papilla preservation flap. (a) Preoperative buccal view. (b) Buccal incision at the base of the papilla. (c) Flap elevation and defect measurement. (d) Suture. (e) Postoperative buccal view.

Simplified papilla preservation flap

Both the papilla preservation technique and its modification were based on the indication of at least 2 mm of mesiodistal distance among the involved teeth. Thus, it was felt that in cases of reduced interdental spaces, intervention in the posterior regions and when non-supported membranes were used, a different flap should have been implemented. Accordingly, in 1999 the simplified papilla preservation flap was described (Cortellini *et al*. 1999). The flap is characterized by an oblique incision through the papilla going from the gingival margin at the

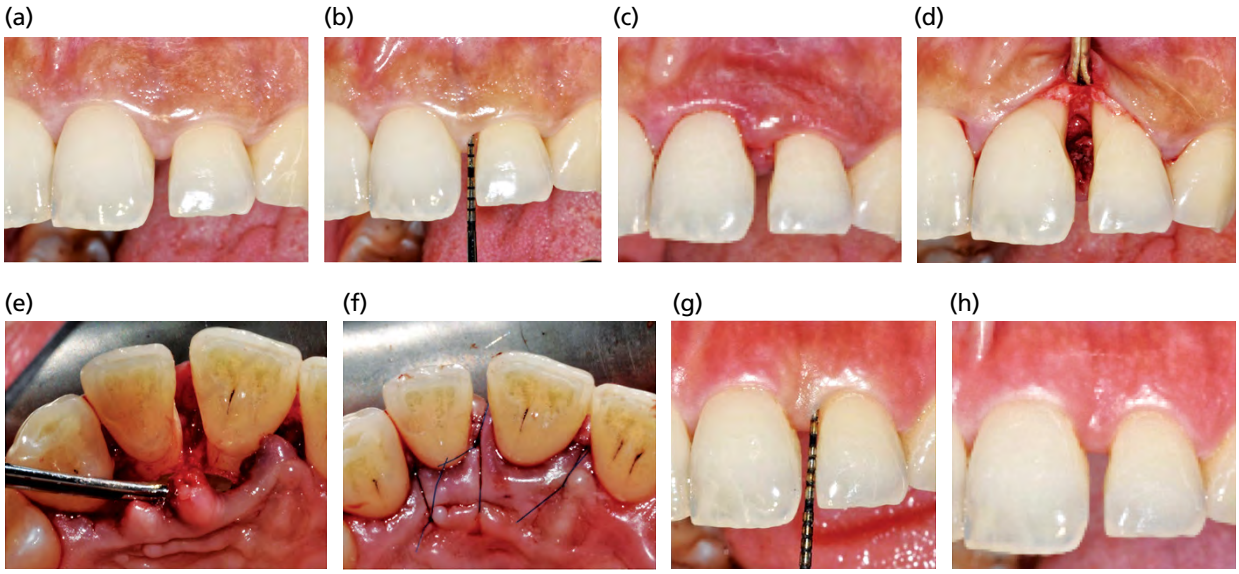

Fig. 32-61 Simplified papilla preservation flap. (a) Preoperative buccal view. (b) Preoperative probing. (c) Incision. (d) Defect exposure. (e) Palatal view. (f) Suture. (g) Postoperative probing. (h) Postoperative view

buccal line angle of the involved tooth towards the mid interproximal portion of the papilla of the adjacent tooth. The incision is performed maintaining the blade parallel to the tooth major axis, and a full-thickness flap is then elevated on the buccal aspect with the exposure of 2–3 mm of the alveolar bone. Then a buccolingual horizontal incision is performed at the base of the papilla extended to the palatal area until the palatal flap is elevated full thickness. The flap is sutured with a horizontal internal mattress suture (Fig. 32-61).

Minimally invasive surgical techniques

Papilla preservation techniques evolved, due to the continuous evolution of regenerative techniques and the advent of amelogenins, towards a more conservative surgical extension in order to favor a reduced postoperative morbidity and higher level of postsurgical attachment gain due to an increased wound stabilization. This involved a higher level of magnification, achieved through loops or microscopes, and a dedicated set of microinstruments. A minimally invasive surgical technique (MIST) was designed to gain access to a three-wall intrabony defect through a papillary incision as in the simplified papilla preservation flap or the modified papilla preservation technique approach (Cortellini & Tonetti 2007). Only the papilla associated with the defect is exclusively elevated through a careful elevation of the buccal and palatal components to a very limited extent up to 1–2 mm of alveolar bone crest. In general, adjunctive vertical release incisions are not performed, nor split incisions of the buccal flap in order to coronally elevate. The papilla is sutured with a single modified internal mattress suture, in order to obtain primary wound closure in the absence of tension (Fig. 32-62).

The concept of minimal invasiveness developed further with the single flap approach (SFA) (Trombelli *et al*. 2009) and the modified-MIST (M-MIST) (Cortellini & Tonetti 2009), both flaps characterized by the elevation of one side exclusively. The indications are mainly: (1) accessibility of the entire anatomical defect through one side only and (2) a defect that is located mainly lingually or buccally. In the SFA the part elevated can be either buccal or lingual according to the anatomical extension of the defect, whereas the M-MIST is mainly buccal, leaving the defects with lingual location to be treated with the MIST. In the M-MIST the extension is kept at a minimum to allow the reflection of a triangular buccal flap to expose the buccal bone crest, then a microblade dissects the supracrestal component of the buccal portion of the papilla from the granulation tissue within the intrabony defect. After degranulation a thorough root instrumentation is performed under the tip of the papilla that is left in place. In the SFA two-layer suturing is employed (internal mattress suture and a single interrupted one) whereas in the M-MIST a single internal modified mattress suture is applied (Fig. 32-63).

The biological rationale of such minimally invasive approaches is to enhance blood clot stability by improving protection of the surgical area. This translates to a higher clinical performance of such flaps compared with conventional flaps in terms of clinical attachment gain (Graziani *et al*. 2012). Accordingly, both flaps have been shown to determine clinical results that are not influenced by the presence of regenerative materials (Cortellini & Tonetti 2011; Trombelli et al. 2012) (Fig. 32-64).

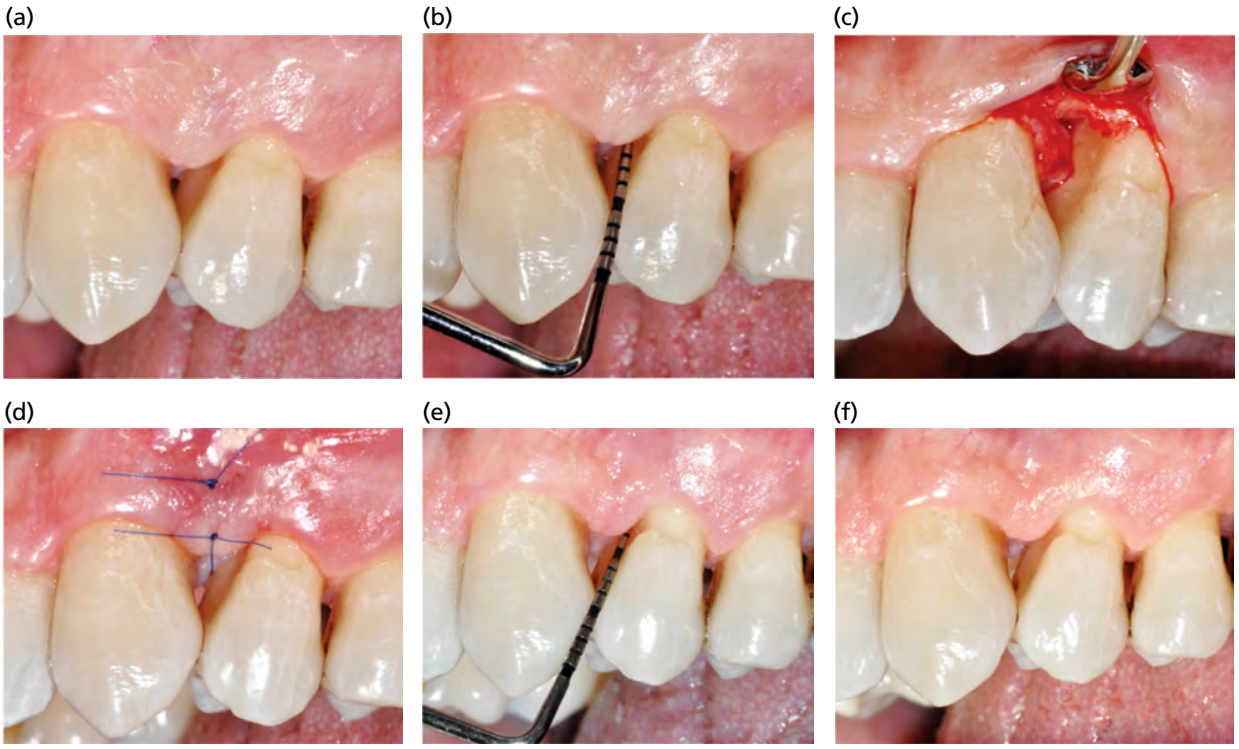

Fig. 32-62 Minimally invasive surgical technique. (a) Preoperative buccal view. (b) Preoperative probing. (c) Flap elevation. (d) Suture. (e) Postoperative view with probing. (f) Postoperative view

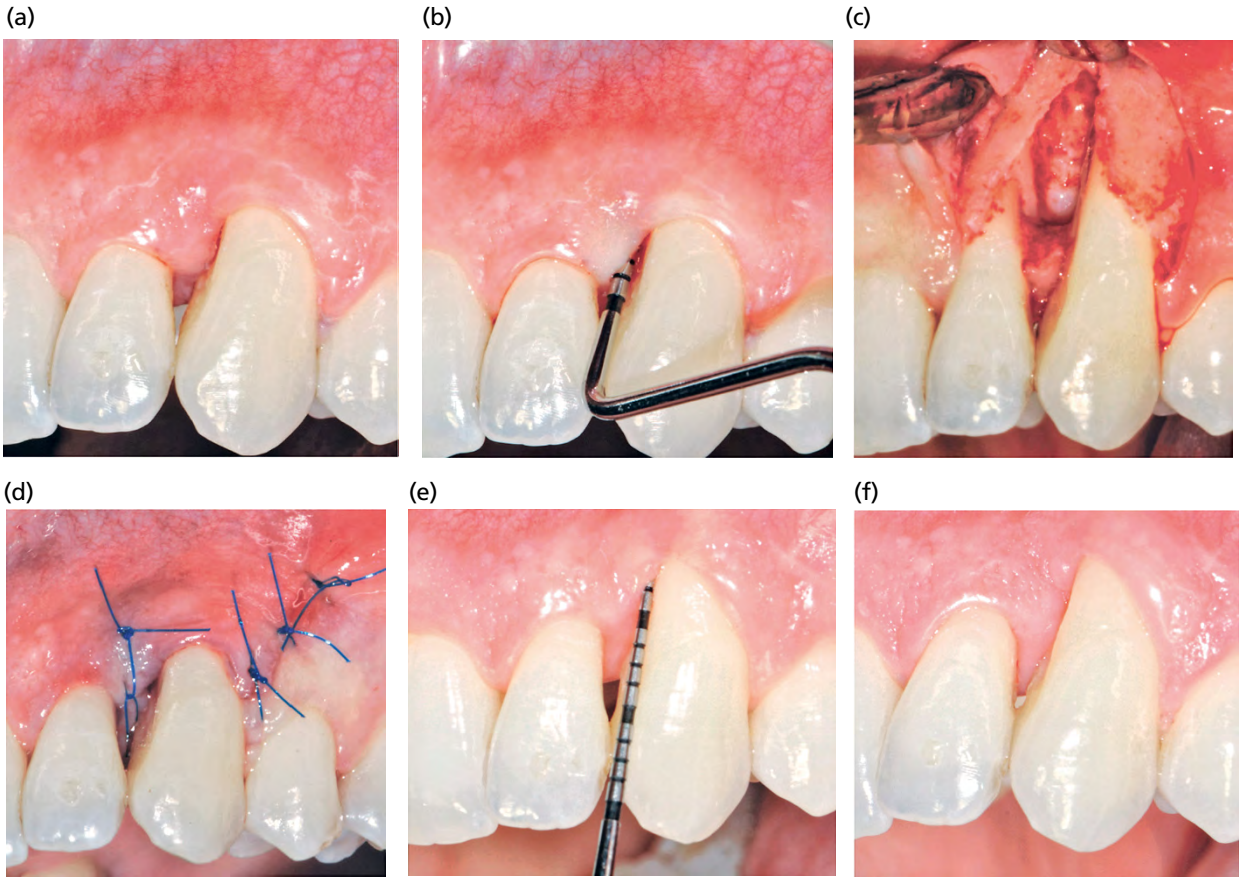

Fig. 32-63 Modified minimally invasive surgical technique. (a) Preoperative buccal view. (b) Preoperative probing. (c) Flap elevation. (d) Suture. (e) Postoperative view. (f) Postoperative probing.

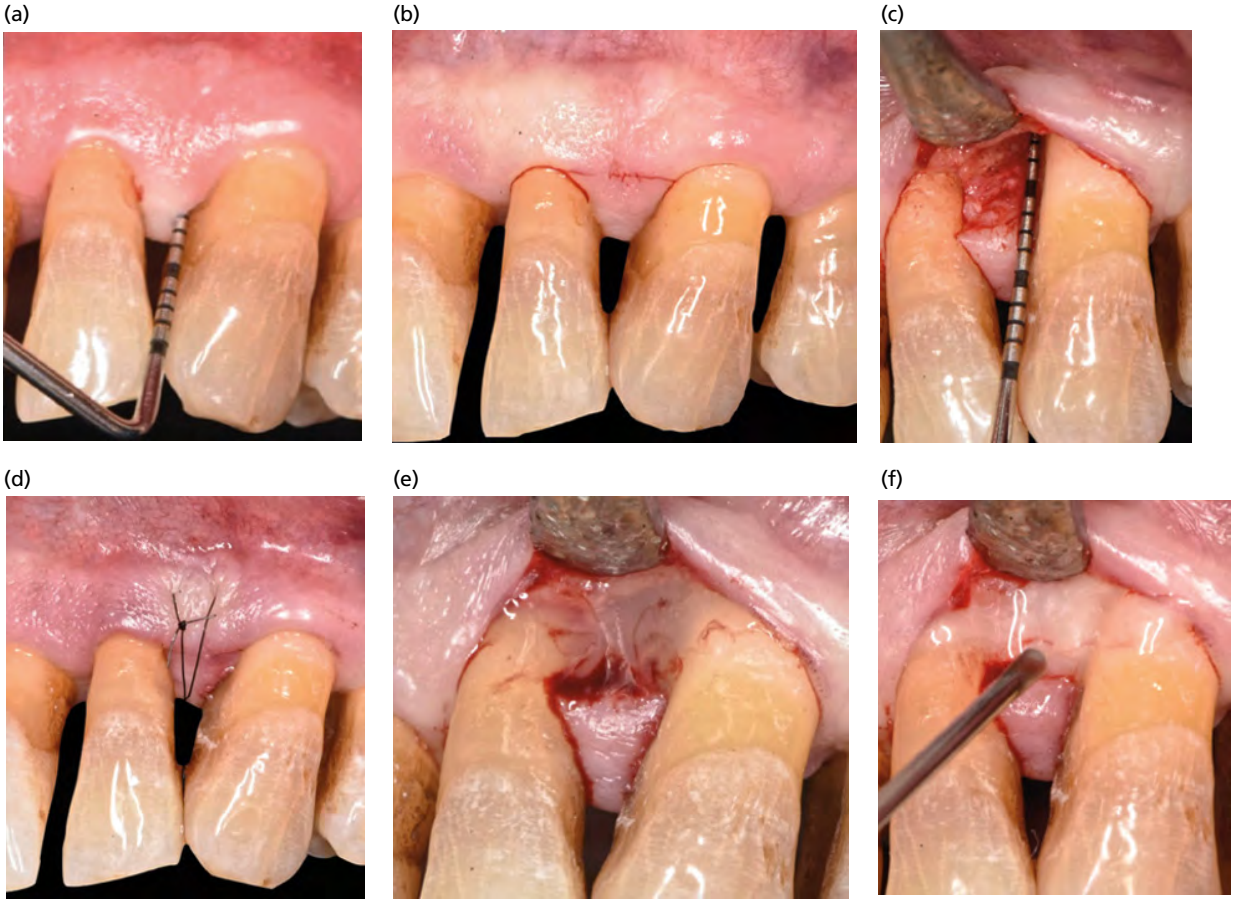

Fig. 32-64 Modified minimally invasive surgical technique. (a) Preoperative buccal view. (b) Buccal incision. (c) Flap elevation. (d) Application of EDTA. (e) Application of amelogenins. (f) Suture.

Outcomes of surgical periodontal therapy

Histological healing

Gingivectomy

Within a few days following excision of the inflamed gingival soft tissues coronal to the base of the periodontal pocket, epithelial cells start to migrate over the wound surface. The epithelialization of the gingivectomy wound is usually complete within 7–14 days following surgery (Engler *et al*. 1966; Stahl *et al*. 1968). During the following weeks, a new dentogingival unit is formed (Fig. 32-65). The fibroblasts in the supra-alveolar tissue adjacent to the tooth surface proliferate (Waerhaug 1955) and new connective tissue is laid down. If the wound healing occurs in the vicinity of a plaque-free tooth surface, a free gingival unit will form which has all the characteristics of a normal free gingiva (Hamp *et al*. 1975). The height of the newly formed free gingival unit may vary not only between different parts of the dentition, but also from one tooth surface to another due primarily to anatomic factors.

The re-establishment of a new, free gingival unit by coronal regrowth of tissue from the line of the "gingivectomy" incision implies that sites with so-called "zero pockets" only occasionally occur following gingivectomy. Complete healing of the gingivectomy wound takes 4–5 weeks, although from clinical inspection of the surface of the gingiva, it may appear to be healed after approximately 14 days (Ramfjord *et al*. 1966). Minor remodeling of the alveolar bone crest may also occur postoperatively.

Apically positioned flap

Following osseous surgery for elimination of bony defects and the establishment of "physiologic contours" and repositioning of the soft tissue flaps to the level of the alveolar bone, healing will occur primarily by first intention, especially in areas where proper soft tissue coverage of the alveolar bone has been obtained. During the initial phase of healing, bone resorption of varying degrees almost always occurs in the crestal area of the alveolar bone (Fig. 32-66) (Ramfjord & Costich 1968). The extent of the reduction of the alveolar bone height resulting from this resorption is related to the thickness of the bone in each specific site (Wood *et al*. 1972; Karring *et al*. 1975).

During the phase of tissue regeneration and maturation, a new dentogingival unit will form by coronal growth of the connective tissue. This regrowth occurs in a manner similar to that which characterizes healing following gingivectomy.

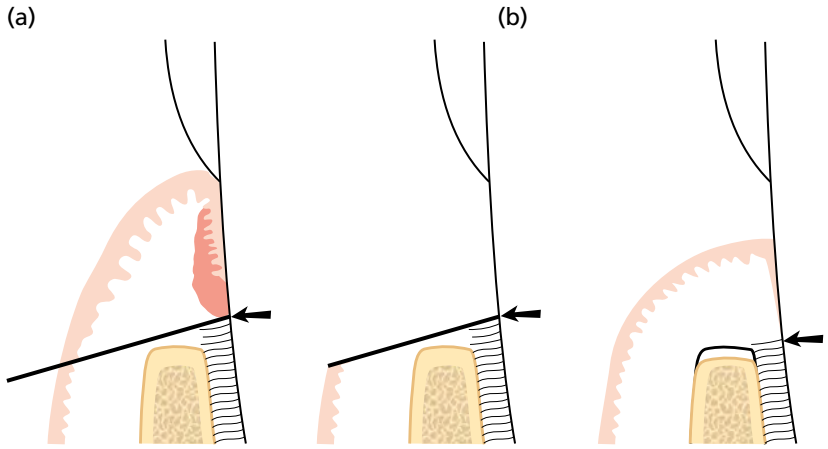

Fig. 32-65 Gingivectomy. Dimensional changes as a result of therapy. (a) Preoperative dimensions and position of the incision line. Black line indicates the location of the primary incision, that is the suprabony pocket is eliminated with the gingivectomy technique; before and after excision of the soft tissue corresponding to the depth of the periodontal pocket. (b) Dimensions following proper healing. Minor resorption of the alveolar bone crest as well as some loss of connective tissue attachment may occur during the healing. The arrows indicate the coronal position of the connective tissue attachment to the root.

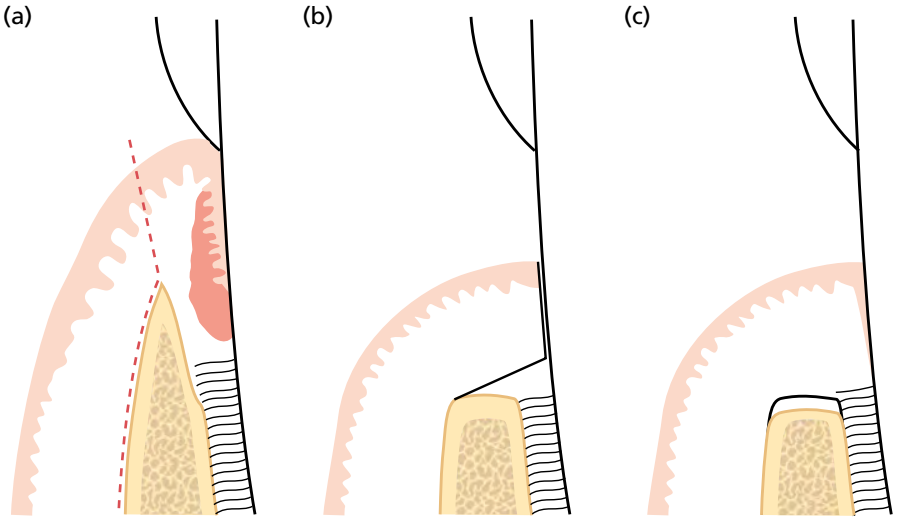

Fig. 32-66 Apically positioned flap. Dimensional changes. (a) Preoperative dimensions. The dashed line indicates the border of the elevated mucoperiosteal flap. (b) Bone recontouring has been completed and the flap repositioned to cover the alveolar bone. (c) Dimensions following healing. Minor resorption of the marginal alveolar bone has occurred as well as some loss of connective tissue attachment.

Modified Widman flap

If a "modified Widman flap" procedure is carried out in an area with a deep infrabony lesion, bone repair may occur within the boundaries of the lesion (Rosling *et al*. 1976; Polson & Heijl 1978). However, crestal bone resorption is also seen. The amount of bone fill obtained is dependent upon (1) the anatomy of the osseous defect (e.g. a three-walled infrabony defect often provides a better mold for bone repair than two-or one-walled defects), (2) the amount of crestal bone resorption, and (3) the extent of chronic inflammation, which may occupy the area of healing. Interposed between the regenerated bone tissue and the root surface, a long junctional epithelium is always found (Fig. 32-67) (Caton & Zander 1976; Caton *et al*. 1980), which is also noted after the modified Kirkland flap procedure. The apical cells of the newly formed junctional epithelium are found at a level on the root that closely coincides with the presurgical attachment level.

Soft tissue recession will take place during the healing phase following a modified Widman flap procedure. Although the major apical shift in the position of the soft tissue margin will occur during the first 6 months following the surgical treatment (Lindhe *et al*. 1987), the soft tissue recession may often continue for >1 year. Factors influencing the degree of soft tissue recession as well as the time period for soft tissue remodeling include the initial height and thickness of the supracrestal flap tissue and the amount of crestal bone resorption.

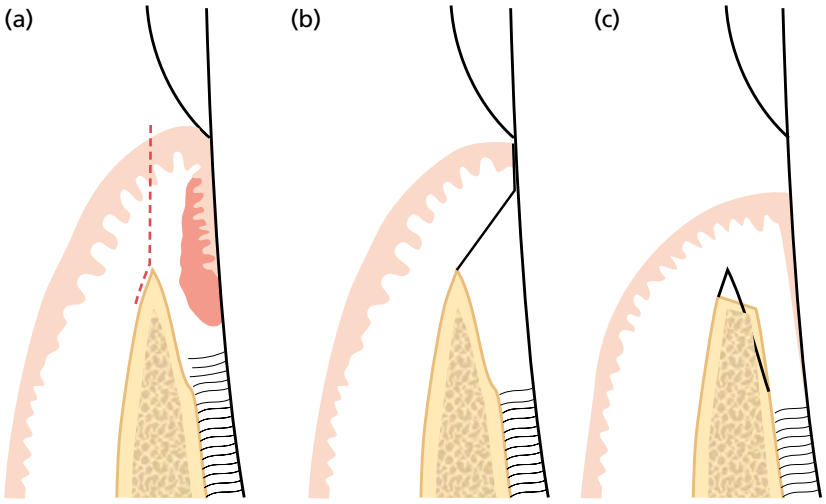

Fig. 32-67 Modified Widman flap. Dimensional changes. (a) Preoperative dimensions. The dashed line indicates the border of the elevated mucoperiosteal flap. (b) Surgery (including curettage of the angular bone defect) is completed with the mucoperiosteal flap repositioned as close as possible to its presurgical position. (c) Dimensions following healing. Osseous repair as well as some crestal bone resorption can be expected during healing with the establishment of a "long" junctional epithelium interposed between the regenerated bone tissue and the root surface. Apical displacement of the soft tissue margin has occurred.

Clinical outcomes of surgical periodontal therapy

Surgical periodontal treatment must be seen within the context of a sequential step of treatments in which the surgical options might not be needed in all cases (Graziani *et al*. 2017). To evaluate the performance of surgical interventions it is necessary to highlight the fact that the majority of the long-term studies are derived from iconic studies of the 1970s and 1980s. These pioneering contributions to the understanding of the relative importance of the surgical component of periodontal therapy were generated by the classic longitudinal studies of the Michigan group (Ramfjord and co-workers) and the Gothenburg group (Lindhe and co-workers). Subsequently, several other clinical research centers contributed important data regarding the efficacy of surgical access therapy in comparison to non-surgical periodontal therapy. Nevertheless, some limited information is available in comparing surgical intervention towards repeated surgical instrumentation, that is a second session of non-surgical root instrumentation that should represent the alternative treatment to surgery within the flow of steps of the treatment of periodontitis stage I–III (Sanz *et al*. 2020).

The performance of periodontal surgical treatment is moreover influenced by the bone anatomy associated with the residual pockets and thus recent systematic reviews and meta-analysis will be analyzed (Graziani *et al*. 2012, 2014, 2015; Sanz-Sanchez 2020).

Tooth survival

The amount of tooth loss is the most relevant criterion in an evaluation of the relative importance of surgical periodontal therapy in the overall treatment of periodontal disease. Overall tooth retention after surgery is high if appropriate supportive treatment is provided as shown in a systematic review taking into account long-term results of periodontal surgery on teeth associated with intrabony defects (Graziani *et al*. 2012). Twenty years after 15 patients were treated with an access flap (control group), two patients lost one tooth each (Cortellini *et al*. 2017). When comparing periodontal surgery with repetition of non-surgical instrumentation in residual pockets of 7 mm, more tooth retention was seen in the former in a 13-year follow-up period (0.6 teeth lost versus 1.6, respectively) (Serino *et al*. 2001).

Plaque and gingival inflammation

The most commonly used outcome criteria in clinical research have been resolution of gingivitis (BoP), PPD reduction, and clinical attachment level change. However, with regard to post-treatment plaque accumulation and gingivitis resolution, there is no evidence to suggest that differences exist between non-surgical or surgical treatment or between various surgical procedures.

Probing pocket depth reduction

Periodontal surgical therapy is remarkably effective in reducing PPD. It generally creates greater short-term reduction of probing depth than non-surgically performed scaling and root planing (Sanch-Sanchez *et al* 2020) which are significantly more pronounced in deeper pockets. In moderately deep pockets differences are noted only in the short term. Overall, the differences tend to become less apparent in the long-term follow-ups (over 12 months).

All surgical procedures result in a decrease in PPDs, with greater reduction occurring at the initially deeper sites (Knowles *et al*. 1979; Lindhe *et al*. 1984; Ramfjord *et al*. 1987; Kaldahl *et al*. 1996; Becker

et al. 2001). Flap surgery with bone recontouring (pocket elimination surgery)/resection of the soft tissue component usually results in the most pronounced short-term pocket reduction, whereas the differences tend to disappear 36 months after surgery (Polak *et al*. 2020).

Conservative periodontal surgery, that is, surgical periodontal therapy with no intentional anatomical corrections, results in a reduction of approximately 3 mm in residual pockets associated with intrabony defects, which is confirmed in long-term studies and shows a reduction of 40% in the initial probing depth. In residual pockets associated with suprabony defects or furcation the extent of the reduction is approximately 1.5 mm at 12 and 6 months postoperatively respectively.

Clinical attachment level change

In sites with shallow initial probing depth, both short- and long-term data demonstrate that surgery creates a greater loss of clinical attachment than non-surgical treatment, whereas in sites with initially deep pockets (≥7 mm), a greater gain of clinical attachment is generally obtained (Knowles *et al*. 1979; Lindhe *et al*. 1984; Ramfjord *et al*. 1987; Kaldahl *et al*. 1996; Becker *et al*. 2001).

Based on data generated from a clinical trial comparing non-surgical and surgical (modified Widman flap) approaches to root debridement, Lindhe *et al*. (1982b) developed the concept of *critical probing depth* (CPD) in relation to clinical attachment level change. For each treatment approach, the clinical attachment change was plotted against the initial pocket depth and regression lines were calculated (Fig. 32-68). The

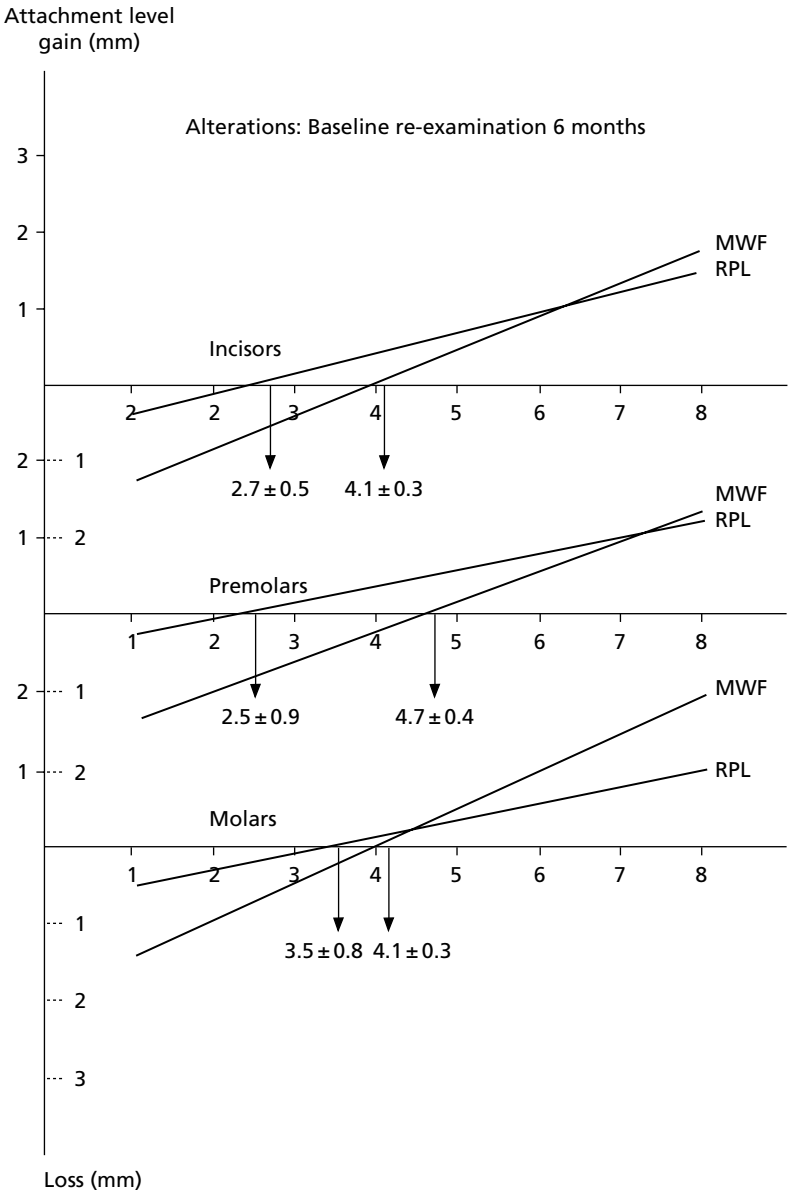

Fig. 32-68 Gain and loss of clinical attachment (y axis) at incisors, premolars, and molars, calculated from measurements taken prior to and 6 months after treatment. The non-surgical approach (RPL) consistently yielded lower critical probing depth values than the surgical approach. RPL, scaling and root planing; MWF, modified Widman flap surgery. (Source: Data from Lindhe *et al*. 1982a. Reproduced with permission from John Wiley & Sons.)

point where the regression line crossed the horizontal axis (initial probing depth) was defined as the CPD, that is, the level of pocket depth below which clinical attachment loss would occur as the result of the treatment procedure performed.

The CPD was consistently found to be greater for the surgical approach than for the non-surgical treatment. Furthermore, at incisors and premolars, the surgical therapy showed superior outcome only when the initial probing depth was >6–7 mm, while at molars the corresponding cut-off point was 4.5 mm. The interpretation of the latter finding is that, in the molar tooth regions, the surgical approach to root debridement offers advantages over the non-surgical approach.

When comparing clinical attachment levels following various types of surgery, either no difference was found between therapies, or flap surgery without osseous/tissue resection produced a greater gain, especially in shallow sites (Polak *et al*. 2020). In addition, there was no difference in the longitudinal maintenance of clinical attachment levels between sites treated non-surgically and those treated surgically, with or without osseous resection (Fig. 32-69).

In residual pockets associated with intrabony defects, surgical therapy resulted in an attachment gain of approximately 2 mm in the long-term. Interestingly, an important flap-dependent gradient indicating that papilla preservation flaps and minimally invasive flaps determined a higher extent of attachment gains compared with conventional open flap debridement in such defects was noted (Graziani *et al*. 2012). In residual pockets associated with suprabony defects and furcation defects, the extent of the gain is modest at around 0.5 mm (Graziani *et al*. 2014, 2015).

Gingival recession

Gingival recession is an inevitable consequence of periodontal therapy. Because it occurs primarily as a result of resolution of the inflammation in the periodontal tissues, it is seen both following non-surgical and surgical therapy. Irrespective of treatment modality used, initially deeper pocket sites will experience more pronounced signs of recession of the gingival margin than sites with shallow initial probing depths (Badersten *et al*. 1984; Lindhe *et al*. 1987; Becker *et al*. 2001) (Fig. 32-69). A general finding in short-term follow-up studies of periodontal therapy is that non-surgically performed scaling and root planing causes less gingival recession than surgical therapy, and that surgical treatment involving osseous and soft tissue resection results in the most pronounced recession (Polak *et al*. 2020). In general, surgical root

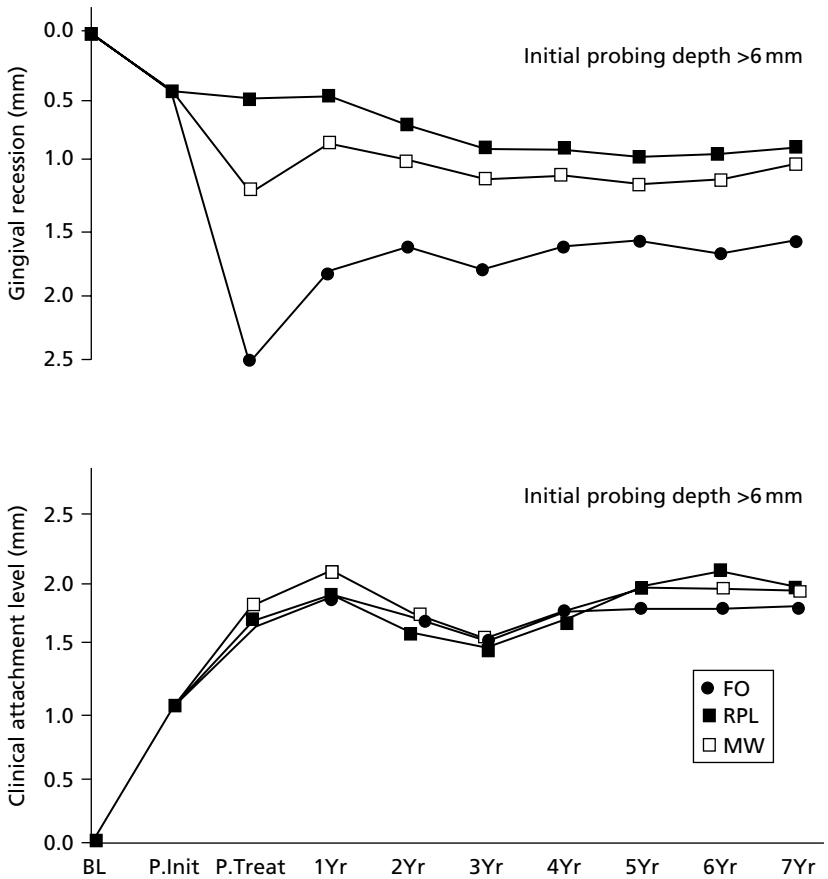

Fig. 32-69 Longitudinal changes over 7 years in recession (top) and clinical attachment levels (bottom) at sites with an initial probing pocket depth of >6 mm following three different periodontal treatment modalities. BL, baseline; FO, flap and osseous surgery; MWF, modified Widman flap procedure; RPL, scaling and root planing. (Source: Data from Kaldahl *et al*. 1996. Reproduced with permission from John Wiley & Sons.)

instrumentation without tissue resection determines approximately 1 mm of recession 12 months after surgery of residual pockets associated with intrabony, suprabony, and furcation defects.

However, data obtained from long-term studies reveal that the initial differences seen in amount of recession between various treatment modalities diminish over time caused by a coronal rebound of the soft tissue margin following surgical treatment (Kaldahl *et al*. 1996; Becker *et al*. 2001) (Fig. 32-67). Lindhe and Nyman (1980) found that after an apically repositioned flap procedure, the buccal gingival margin shifted to a more coronal position (by about 1 mm) during 10–11 years of maintenance. In interdental areas denuded following surgery, van der Velden (1982) found an up growth of around 4 mm of gingival tissue 3 years after surgery, while no significant change in attachment levels was observed. A similar finding was reported by Pontoriero and Carnevale (2001) 1 year after an apically positioned flap procedure for crown lengthening.

Bone fill in angular bone defects

The potential for bone formation in angular defects following surgical access therapy has been demonstrated in a number of studies. Rosling *et al*. (1976) studied the healing of two- and three-wall angular bone defects following a modified Widman flap procedure, including careful curettage of the bone defect and proper root debridement, in 24 patients with multiple osseous defects. Following active treatment, patients assigned to the test group received supportive periodontal care once every 2 weeks for a 2-year period, while the patients in the control group were only recalled once a year for prophylaxis. Re-examination carried out 2 years after therapy demonstrated that the patients who had been subjected to the intensive professional tooth-cleaning regimen had experienced a mean gain of clinical attachment in the angular bone defects amounting to 3.5 mm. Measurements performed on radiographs revealed a marginal bone loss of 0.4 mm, but the remaining portion of the original bone defect (2.8 mm) was refilled with bone (Fig. 32-70)

Similar healing results were reported by Polson and Heijl (1978). They treated 15 defects (two- and three-wall) in nine patients using a modified Widman flap procedure. Following curettage of the bone defect and root planing, the flaps were closed to achieve complete soft tissue coverage of the defect area. All patients were enrolled in a professional tooth-cleaning program. The healing was evaluated at a re-entry operation 6–8 months after the initial surgery. Eleven of the 15 defects had resolved completely. The healing was characterized by a combination of coronal bone regeneration (77% of the initial depth of the defects) and marginal bone resorption (18%). The authors concluded that intrabony defects might predictably remodel after surgical debridement and establishment of optimal plaque control. The results from the studies referred to demonstrate that a significant bone fill may be obtained in two- and three-wall intrabony defects at single-rooted teeth, provided the postoperative supportive care is of very high quality. Two reviews (Laurell *et al*. 1998; Lang 2000), focusing on the outcome of surgical access therapy in angular bone defects, gave additional information regarding expected bone regeneration in angular defects following open-flap debridement (modified Widman flap). In the review by Laurell *et al*. (1998), 13 studies were included, representing a total of 278 treated defects with a mean depth of 4.1 mm. The weighted mean bone fill in the angular defects amounted to 1.1 mm. Lang (2000) reported an analysis of 15 studies providing data generated from

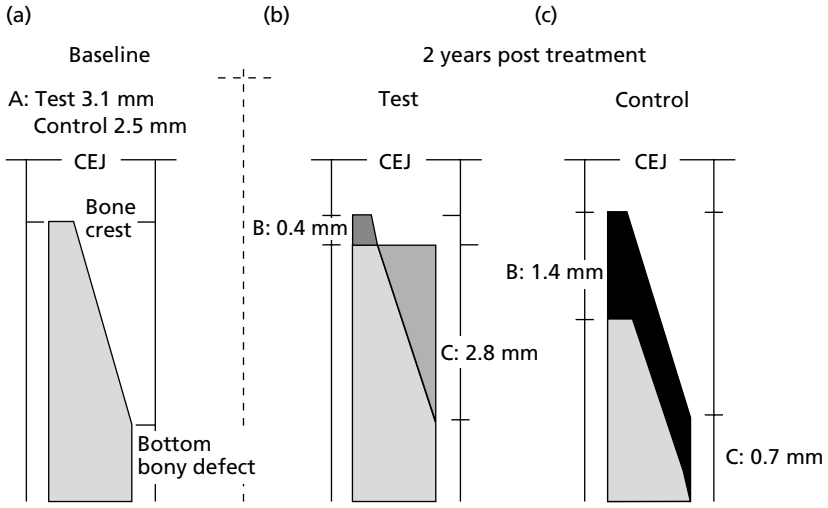

Fig. 32-70 Alterations in the level of the marginal bone crest and the level of the bottom of the bone defects in the test and control groups of the study by Rosling *et al*. (1976a). (a) Distance A denotes the depth of the bone defects at the initial examination; test group 3.1 mm, control 2.5 mm. (b, c) Distance B denotes resorption of the alveolar crest, which amounted to 0.4 mm in the test patients (b) and 1.4 mm in the controls (c). Distance C denotes gain or loss of bone in the apical portion of the defect. There was a refill of bone in the test patients (b) amounting to 2.8 mm, whereas a further 0.7 mm loss of bone occurred in the control patients (c). CEJ, cementoenamel junction. (Source: Data from Rosling *et al*. 1976a. Reproduced with permission from John Wiley & Sons.)

radiographic assessments of the healing of 523 angular bone defects. The analysis yielded a weighted mean of 1.5 mm of bone gain. This data was further confirmed by a recent meta-analysis indicating an average bone fill was 1 mm (Graziani *et al*. 2012).

Factors affecting clinical healing

Periodontal surgical treatment shows heterogenous healing influenced and explained by numerous factors that a clinician should consider when planning an intervention because many of these factors may be changed by the clinician in order to improve the overall surgical prognosis.

Patient factors

Plaque levels

Plaque levels influence healing of surgical debridement significantly. In a landmark study, patients in the test group received, after surgical debridement of intrabony defects, repeated oral hygiene instructions and professional tooth cleaning once every 2 weeks during the postoperative period (Rosling *et al*. 1976). The patients maintained the surgically reduced pocket depth throughout the 2-year follow-up period and important clinical attachment level gains and bone fill were observed for most of the surgical procedures evaluated (Fig. 32-69). Interestingly, the control group that was assessed and polished only once a year (i.e. with high plaque score), showed a significant and important deterioration of clinical attachment level and bone levels.

In a secondary study of a multicenter trial assessing surgical treatment of intrabony defects, the total bacteriological count and the presence of bacteria of the red complex was associated with a lower probability of obtaining important gains of clinical attachment (Heitz-Mayfield *et al*. 2006). The fact that the standard of postoperative oral hygiene is decisive for the outcome of surgical pocket therapy is further underlined by data from a 5-year longitudinal study by Lindhe *et al*. (1984) which showed that patients with a high standard of infection control maintained clinical attachment levels and probing depth reductions following treatment more consistently than patients with poor plaque control. On the other hand, professional tooth cleaning, including subgingival scaling every 3 months, may partly compensate for the negative effects of variations in self-performed plaque control (Ramfjord *et al*. 1982; Isidor & Karring 1986).

Gingival inflammation

The overall level of inflammation influences the outcome of surgical debridement of intrabony defects in terms of attachment gain when full mouth bleeding scores reach >12% (Tonetti *et al*. 1996). Therefore, careful decontamination and reduction of inflammation is needed before surgery.

Smoking

Smoking, despite not being a contraindication for surgery, has an important negative impact on the outcome after periodontal surgery, as shown by the negative influence on both PPD reduction and clinical attachment levels (Labriola *et al*. 2005). Smoking does lessen the impact in both outcomes 6 months after surgery. The chance of obtaining a postsurgical pocket reduction of >3 mm is nearly three times lower in patients who smoke (Scabbia *et al*. 2010).

Local factors

Type of periodontal defect

Periodontal defects are classically divided in intrabony, suprabony, and inter-radicular defects. Most knowledge is derived from the prolific literature on intrabony defects. Conservative surgical debridement of an intrabony defect determines a clinical attachment gain of approximately 1.5 mm and a probing depth reduction of 3 mm, 12 months after surgery (Graziani *et al*. 2012).

Suprabony defects do not heal as well compared with healing achieved after surgical debridement of intrabony defects with a 1.4 probing depth reduction and 0.5 mm of clinical attachment gain (Graziani *et al*. 2014).

Furcation defects also show important reductions in clinical healing if compared with intrabony defects. A meta-analysis analyzing the control group of trials in which periodontal regeneration was applied indicated that the average CAL gain of degree II mandibular furcation was 0.5 mm 6 months after debridement and a PPD reduction of 1.4 mm. This highlights the complexity of surgical access in furcation defects (Graziani *et al*. 2015).

Periodontal defect morphology

The morphology of the defect has important repercussions for healing after surgery. When a residual pocket is associated with an intrabony defect, some factors such as the number of walls of the defect, and the depth and width of the defect, influence significantly the surgical outcome. The deeper the intrabony component the larger is the postsurgical clinical attachment gain in access flaps (Cortellini *et al*. 1998). Three-wall intrabony defects have a 269% higher chance of showing a clinical attachment gain of at least 3 mm than a 1-wall defect after surgical debridement (Tonetti *et al*. 2002). Moreover, the wider the defect, the lower the healing.

Clinician factors

Experience and surgical dexterity

Clinical experience and capabilities have an obvious impact on healing. In a multicenter trial, clinicians operating on identical periodontal defects at baseline with the same surgical access showed a difference of more than 1 mm of clinical attachment gain (Tonetti *et al*. 1998).

Flap choice

The evolution of flap design contributed significantly to the clinical outcome after surgical debridement. The performance of access flaps in intrabony defects changed abruptly within 10 years, indicating an increase in performance of control sites (access flap) of 1 mm between 1996 and 2006 (Tu *et al*. 2008). This has been further confirmed in a meta-analysis indicating that if conservation of the papillary area during surgery is performed, a higher postsurgical clinical attachment gain is achieved (Graziani *et al*. 2012). Papilla preservation flaps appear to improve clinical attachment gain compared with conventional surgery, and also appear to be effective for suprabony defects (Graziani *et al*. 2014). This can be explained by the fact that the choice of papilla preservation flaps increase vascularization, as noted in laser flow doppler studies, which results in improved primary closure and better protection from postsurgical bacterial contamination in the wound (Retzepi *et al*. 2007).

Conclusion

Surgical periodontal therapy is an essential component in the treatment of periodontitis. A clinician must bear in mind that surgery is, however, a specific step of the sequential steps in treatment and is not a single/unique tool for disease resolution. In fact, surgery might not always be required. Knowledge acquired in clinical trials that evaluated the different periodontal regenerative techniques made important developments possible. When advanced flaps were used in the control groups (i.e. without regenerative materials), the performance was superior to the use of conventional flaps. Clearly, some important information, such as the performance of surgical interventions versus non-surgical re-treatment in terms of long-term tooth survival, are still scarce and some decisions are still based on the classic studies from the 1970s. Nevertheless, refined and technique-sensitive periodontal surgical treatment is without doubt a requirement in the armamentarium of a periodontist.

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Chapter 33

Treatment of Furcation-Involved Teeth

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Anatomy

Periodontitis-related bone resorption in multirooted teeth is associated with a very unique anatomical sequela: the exposure of the root separation areas ('furcations') to microbial colonization. The anatomy of the furcation, with concavities, enamel projections, and ridges, often below the gingival margin, favor further microbial accumulation leading to periodontal disease progression and eventually tooth loss. In other words, the periodontal pathogenic process is often 'amplified' in furcation regions, owing to their unique anatomy.

'Periodontal furcation involvement' is defined as destruction of periodontal attachment and bone in the root separation area. This affects maxillary first premolars (normally two-rooted), maxillary molars (normally 3-rooted), and mandibular molars (normally 2-rooted). However, variations in the number of roots exist, and sometimes other teeth such as second premolars or canines may also be affected by furcation involvement (Joseph *et al*. 1996). The 'root complex', defined as the portion of a tooth located apical to the cementoenamel junction, in multirooted teeth is divided into 'root trunk' (undivided region of the root) and 'root cones' (Fig. 33-1). The 'furcation entrance' is the area between the undivided and divided part of the roots, while the 'furcation fornix' is the most coronal portion of the furcation area (Fig. 33-2). 'Degree of separation' is defined as the angle of separation between root cones, while 'divergence' is the distance between two roots. The 'coefficient of separation' is the proportion between length of root cones and length of root complex (Fig. 33-3).

The topography of the furcation area of maxillary and mandibular molars was described in detail in 1988 by Svärdström and Wennström, who showed a complex anatomy consisting of ridges, peaks, and pits (Svärdström & Wennström 1988). First and second maxillary molars generally have three roots (mesiobuccal, distobuccal, and palatal). The distobuccal and palatal roots are usually inclined distally and palatally respectively, while the mesiobuccal root is vertical. The mesiobuccal root has a pronounced

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

concavity in its distal surface, giving it a characteristic hour-glass shape. Out of the three potential furcation entrances in maxillary molars, the mesial is on average 3 mm apical to the cementoenamel junction, while the buccal is 3.5 mm and the distal 5 mm from the cementoenamel junction (Abrams & Trachtenberg 1974). Around 40% of maxillary first premolars have buccal and palatal root cones, and due to a long root trunk, the furcation entrance is on average 8 mm apical to the cementoenamel junction. Mandibular molars usually have two root cones (mesial and distal). The latter is smaller, usually circular in section, and inclined distally, while the mesial has an hour-glass shape and a more pronounced distal concavity (Svärdström & Wennström 1988). The entrance to the furcation region has been measured by several authors in extracted teeth and found to be <1 mm in the majority of molars and <0.75 mm in around half of examined molars (Bower 1979; Chiu *et al*. 1991; Hou *et al*. 1994, 1997) (Fig. 33-4). When compared with the standard width of curettes (0.75–1.0 mm), it is clear how plaque and calculus removal can be particularly challenging in furcation-involved molars (dos Santos *et al*. 2009).

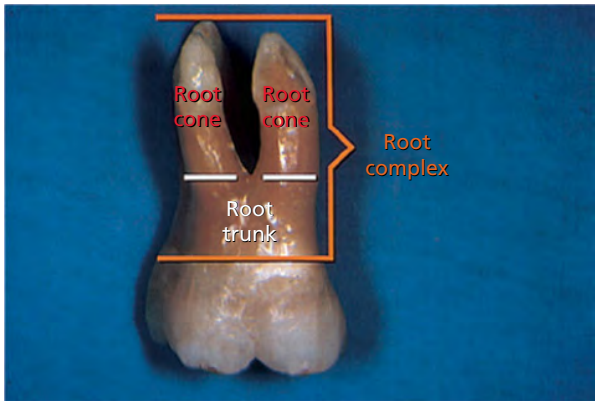

Fig. 33-1 Root complex of a maxillary molar. The root complex is separated into one undivided region (the root trunk) and one divided region (the root cones).

Bifurcation ridges consisting of dentine and/or cementum are found in over half of furcation areas (Everett *et al*. 1958; Burch & Hulen 1974; Bower 1979; Dunlap & Gher 1985; Hou & Tsai 1997) and are divided into two types: buccolingual and mesiodistal or intermediate (IBR) (Everett *et al*. 1958). IBR have been associated with progression of the furcation defect (Gher & Vernino 1980; Hou & Tsai 1997).

Cervical enamel projections are also often found in molars (Masters & Hoskins 1964), especially in Asian populations (Lim *et al*. 2016) (Fig. 33-5). They facilitate plaque accumulation and prevent connective

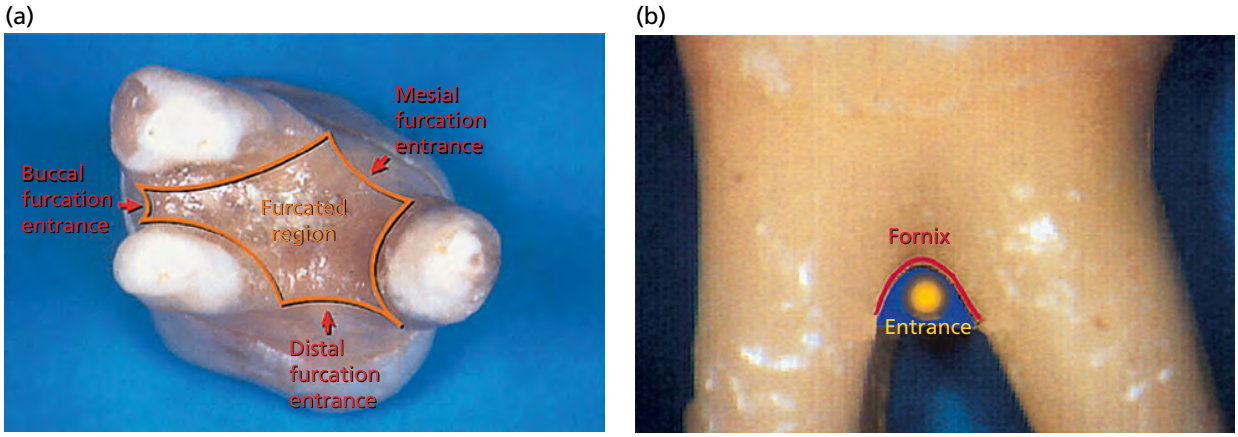

Fig. 33-2 (a) Apical-occlusal view of a maxillary molar where the three root cones make up the furcated region and the three furcation entrances. (b) A buccal view of the furcation entrance and of its roof.

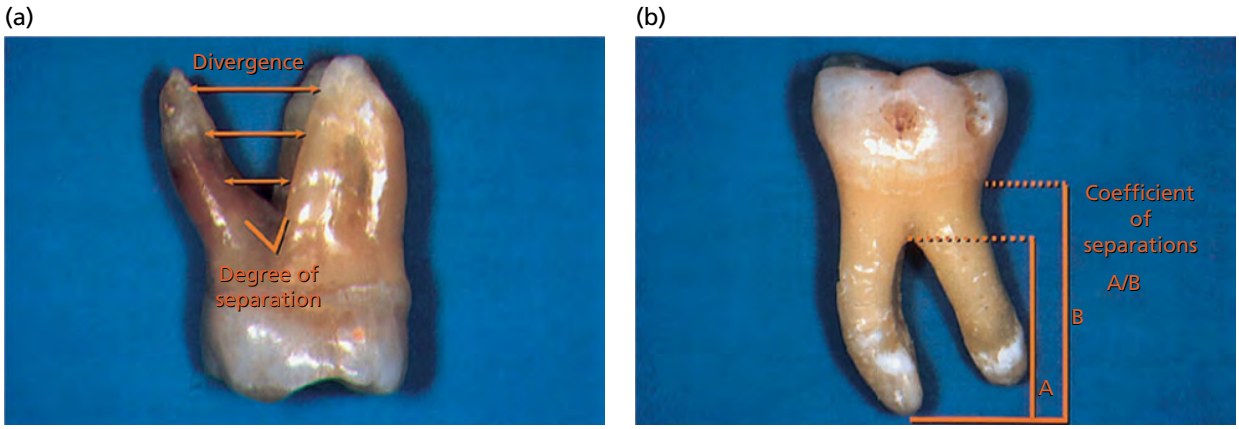

Fig. 33-3 (a) The angle (degree) of separation and the divergence between the mesiobuccal and the palatal roots of a maxillary molar. (b) The coefficient of separation (A/B) of the illustrated mandibular molar is 0.8 (A = 8 mm, B = 10 mm).

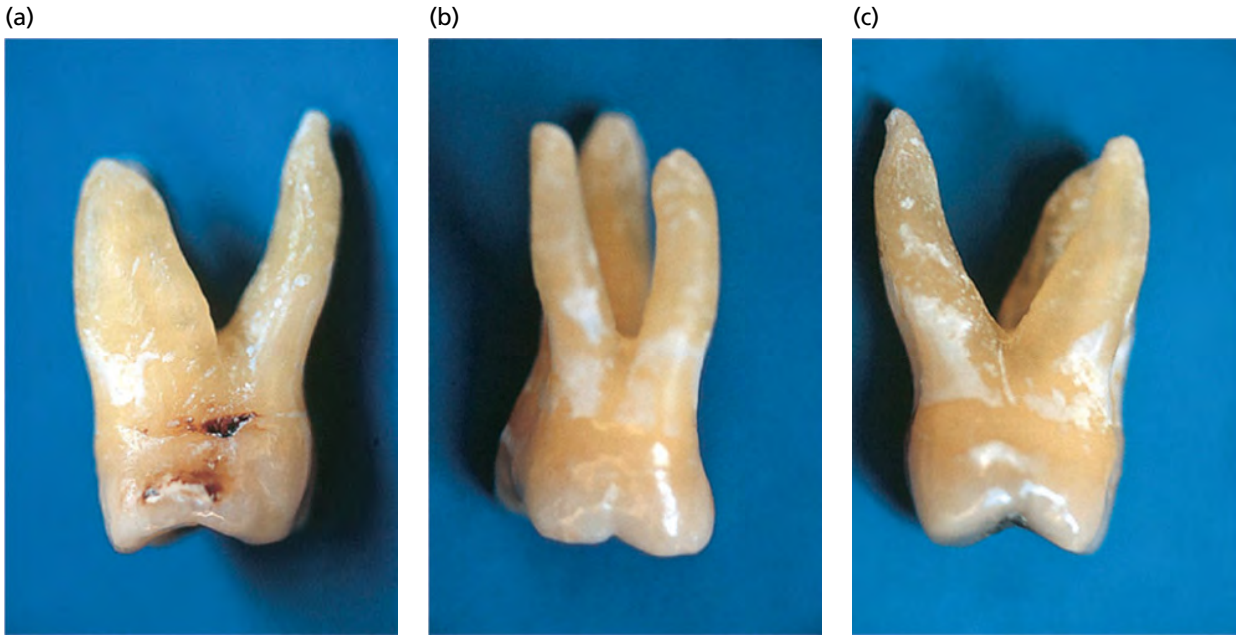

Fig. 33-4 Furcation entrances: (a) mesial; (b) buccal; (c) distal; and the position of the roots of a maxillary molar.

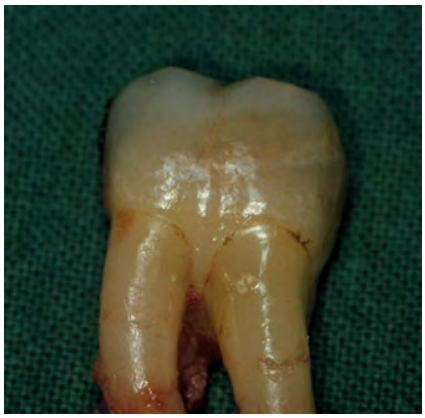

Fig. 33-5 Cervical enamel projection on extracted lower right first molar; grade III (reaching furcation entrance area; Masters & Hoskins 1964). (Source: Eickholz and Hausmann 1998.)

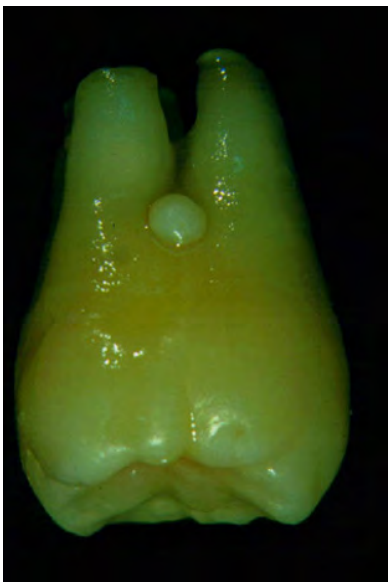

Fig. 33-6 Macroscopic image of an enamel pearl on an extracted molar. (Source: Courtesy of Prof. Dr. H.-K. Albers.)

tissue attachment, thus contributing to the aetiology of furcation lesions (Carnevale *et al*. 1995; Leknes 1997; Al-Shammari *et al*. 2001; Bhusari *et al*. 2013).

Enamel pearls are ectopic globules consisting mostly of enamel and often containing a core of dentine, which adhere to the root surface and particularly to the furcation area (Fig. 33-6). They affect a range of 1–10% of molars in different studies (Moskow & Canut 1990) and are thought to affect attachment and potentially contribute to periodontal furcation pathology.

Diagnosis of furcation involvement

Clinical diagnosis of furcation involvement

Furcation entrances do not lay open in untreated periodontal patients. In most cases they are covered by gingiva. Thus, furcation involvement (FI) cannot be seen by the naked eye but must be probed below the gingival margin. The bizarre anatomy of furcations (Schroeder & Scherle 1987), their curved course, and the fact that furcation entrances of maxillary premolars and molars open into interproximal spaces, require the use of particular curved furcation probes for furcation diagnosis (e.g. Nabers probe) (Fig. 33-7). The probe is placed onto the tooth surface coronally of the gingival margin at the site where a furcation entrance is expected (e.g. lingual of a mandibular molar). The probe is then pushed apically, gently displacing the gingiva in zig-zag movements until the bottom of the sulcus or pocket is reached. If the probe does fall into a pit horizontally, this indicates an FI in most cases (Eickholz & Walter 2018).

Straight rigid periodontal probes (e.g. PCPUNC15) are inappropriate for furcation diagnosis because

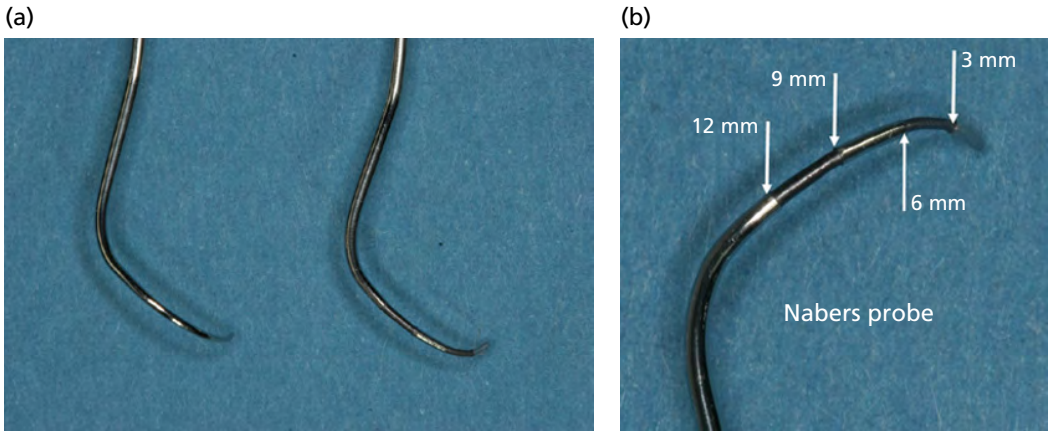

Fig. 33-7 Curved furcation probes. (a) Nabers probes (left, without markings; right, with markings). (b) Markings in 3 mm steps up to 12 mm. (Source: Eickholz & Walter 2018.)

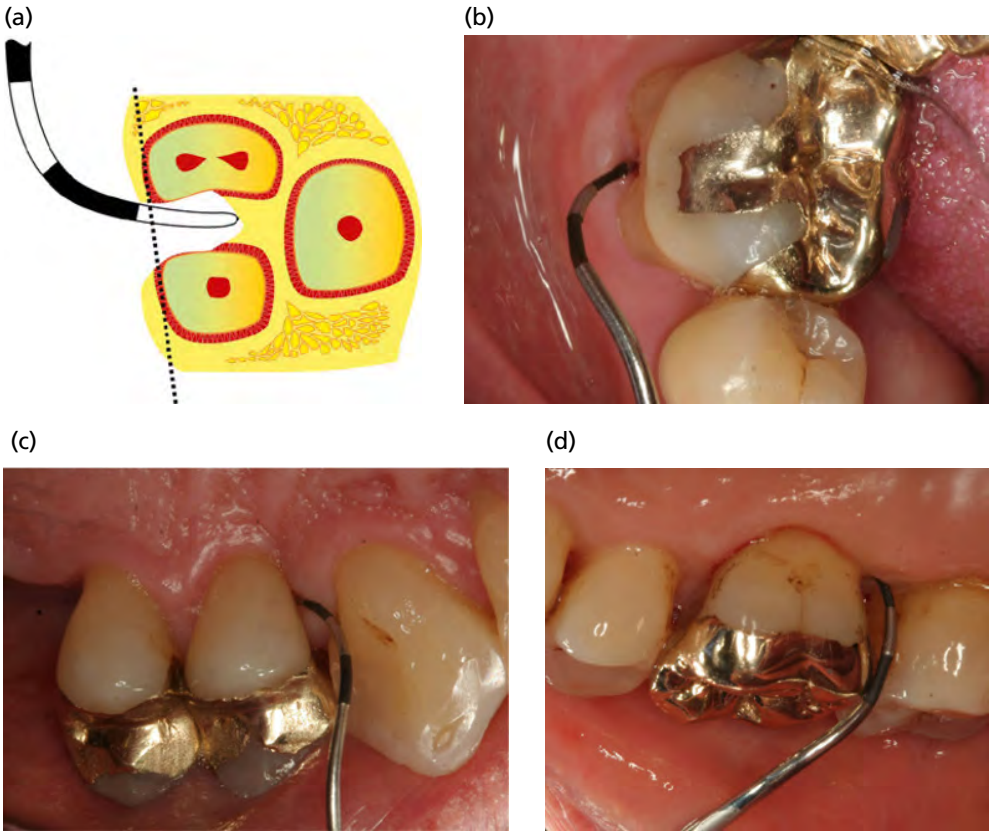

Fig. 33-8 Furcation involvement degree I (Table 33-1) (Eickholz & Staehle 1994; Eickholz & Walter, 2018): horizontal loss of periodontal tissue support up to 3 mm. (a) Schematic (maxillary molar, buccal furcation entrance): horizontal probing/clinical attachment level 2.5 mm (Eickholz & Walter 2018). (b) Buccal tooth 46: the probe does not penetrate more than 3 mm between the two buccal roots. (Source: Eickholz & Walter 2018.) (c) Mesial tooth 24 with neighboring tooth. (Source: Eickholz & Walter 2018.) (d) Distolingual tooth 16 with neighboring tooth. (Source: Eickholz & Walter 2018.)

they fail to follow the curved course of most furcations and can lead to an underestimate of the extent of the FI (Eickholz & Kim 1998).

Classification of furcation involvement

Once an FI has been located, assessing its severity is important. Severity of FI is assessed by probing the furcation in a horizontal direction using a rigid curved probe (e.g. Nabers probe) and measuring the distance from the probe tip to a virtual tangent to the root convexities adjacent to the furcation (Fig. 33-8). Measuring this distance allows assessment of different degrees of FI or the amount of horizontal attachment loss in millimeters (horizontal probing/clinical attachment level: PAL-H/HCAL) (Fig. 33-8). Whereas assessment of the continuous variable horizontal attachment loss provides information on small

changes in interradicular tissues (as they are relevant after regenerative therapy), the classification of interradicular tissue destruction into the *degree/class* of FI provides sufficient information for a prognosis to be given and therapy decisions to be made for the multirooted tooth (Eickholz & Walter 2018).

There are only minor differences in the classifications of FI. The classification by Glickman (1953) provides mainly vague criteria to distinguish classes of FI and also considers radiographic information, which is known to be of low reliability (Glickmann 1953; Ammons & Harrington 2006). The criteria of the Hamp *et al*. (1975) classification are based on clinical measurements (threshold: PAL-H = 3 mm) (Hamp *et al*. 1975).

Degrees III and IV of the Glickman classification describe two severity grades, where the desmodontal fibers are detached from the furcation fornix/dome throughout the complete diameter of the tooth, that is, horizontal "through-and-through" destruction of the periodontal tissue in the furcation (degree III according to Hamp *et al*. 1975; Eickholz & Walter 2018).

The criteria to assign a class III (Hamp *et al*. 1975) to a furcation also have been modified. To assign a class III, Graetz *et al*. (2014) required the tip of the furcation probe to be visible (Nabers) at the opposite furcation. For all other cases of deep, but not completely penetrating horizontal probing, a class II was assigned (Graetz *et al*. 2014). When horizontal probing is more than 6 mm, but does not completely penetrate to the opposite furcation entrance, Walter *et al*. (2009) created a degree II–III (Walter *et al*. 2009; Eickholz & Walter 2018).

Distinction between class II and class III furcation involvement

The distinction between class II (Hamp *et al*. 1975) and through-and-through furcation (class III) is of decisive significance for both prognosis and choice of therapy (Fig. 33-9):

1. Molars with class III furcation defects have a worse long-term prognosis than class II lesions (McGuire & Nunn 1996; Dannewitz *et al*. 2006; Salvi *et al*. 2014; Graetz *et al*. 2015; Dannewitz *et al*. 2016).
2. Whereas buccal and lingual class II lesions can be improved by regenerative therapy, through-and-through furcations do not benefit from regenerative treatment (Sanz *et al*. 2015; Jepsen *et al*. 2020a).

A furcation probe cannot be completely pushed through the whole involved furcation area, particularly from an interproximally located furcation entrance in the presence of adjacent teeth. Nevertheless, hard and soft tissue may be detached from the furcation fornix (i.e. FI class III). Graetz *et al*. (2014) would classify this situation as class II. Walter *et al*. (2009) would classify this situation as class II-III. In these cases, it is recommended that Ammons and Harrington (2006) should be followed: in cases where the clinician may not even be able to pass a periodontal probe completely through the furcation because of interference with the bifurcational ridges or facial/lingual bony margins, the buccal and lingual probing dimensions may be added. If a cumulative probing measurement is obtained that is equal or greater than the buccal/lingual dimension of the tooth at the furcation orifice, the furcation is rated class III (Table 33-1; Fig. 33-10c, d). Thus, underestimation of FI as observed by Walter *et al*. (2009) and Graetz *et al*. (2014) can be avoided (Eickholz & Walter 2018).

The vertical dimension of furcation involvement

The key difficulty in FI is accessing horizontal niches between the roots of multirooted teeth. Thus, the classifications referred to previously primarily consider the horizontal component of attachment/bone loss.

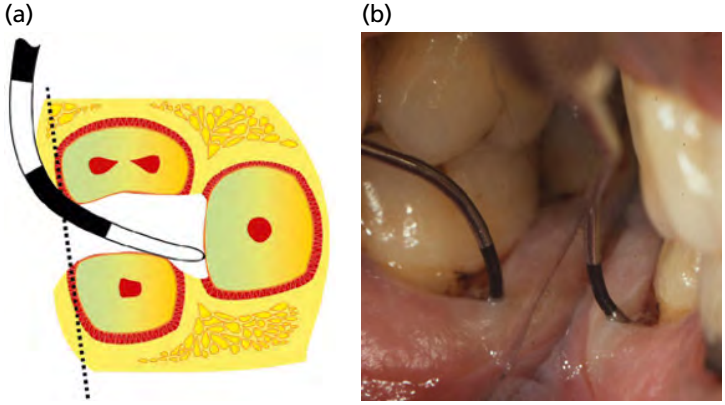

Fig. 33-9 Furcation involvement degree II (Table 33-1) (Hamp *et al*. 1975; Eickholz & Walter, 2018): horizontal loss of support exceeding 3 mm, but not encompassing the total width of the furcation area. (a) Schematic (maxillary molar, buccal furcation entrance): horizontal probing/clinical attachment level 5 mm (Eickholz & Walter 2018). (b) Tooth 47: the 9 mm marking is at the gingival margin. However, the 6 mm marking is at the height of the virtual tangent placed to the roots adjacent to the furcation. (Source: Nibali 2018.)

Table 33-1 Recommended classification of furcation involvement (Sources: Hamp *et al*. 1975; Eickholz & Staehle 1994; Ammons & Harrington 2006; Eickholz & Walter 2018).

Class 0	No furcation involvement
Class I	Horizontal loss of periodontal tissue support up to 3 mm (Eickholz & Staehle 1994) (Fig. 33-8)
Class II	Horizontal loss of support exceeding 3 mm, but not encompassing the total width of the furcation area (Hamp *et al*. 1975) (Fig. 33-9)
Class III	Horizontal "through-and-through" destruction of the periodontal tissue in the furcation. In early class III involvement the opening may be filled with soft tissue and may not be visible. The clinician may not even be able to pass a periodontal probe completely through the furcation because of interference with the bifurcational ridges or facial/lingual bony margins. However, if the clinician adds the buccal and lingual probing dimensions and obtains a cumulative probing measurement that is equal or greater than the buccal/lingual dimension of the tooth at the furcation orifice, the clinician must conclude that a class III furcation exists (Ammons & Harrington 2006) (Fig. 33-10).

However, it is plausible that in addition to horizontal attachment/bone loss, vertical attachment/bone loss in the furcation area plays a role. It has been demonstrated that survival of molars after furcation therapy does not only depend on baseline FI but also on baseline bone loss (Dannewitz *et al*. 2006; Park *et al*. 2009). Thus, a subclassification was proposed that measures the probeable vertical depth from the roof of the furcation apically: (1) subclass A indicates a probeable vertical depth of 1–3 mm, (2) subclass B of 4–6 mm, and (3) subclass C of ≥7 mm. Furcations would thus be classified as IA, IB, IC, IIA, IIB, IIC and IIIA, IIIB, IIIC (Tarnow & Fletcher 1984).

Radiographic diagnosis of furcation involvement

In general, radiographs provide information on the translucency to x-rays of different tissues. The more dense a tissue is (e.g. compact bone), the less translucent it is for x-rays. Thus, both two- and three-dimensional radiographic images primarily provide information on bone in contrast to soft tissue. However, information on connective tissue attachment is also important in diagnosis of FI. Thus, radiographs do tell a substantial part of but not the whole story about FI. This is particularly true after

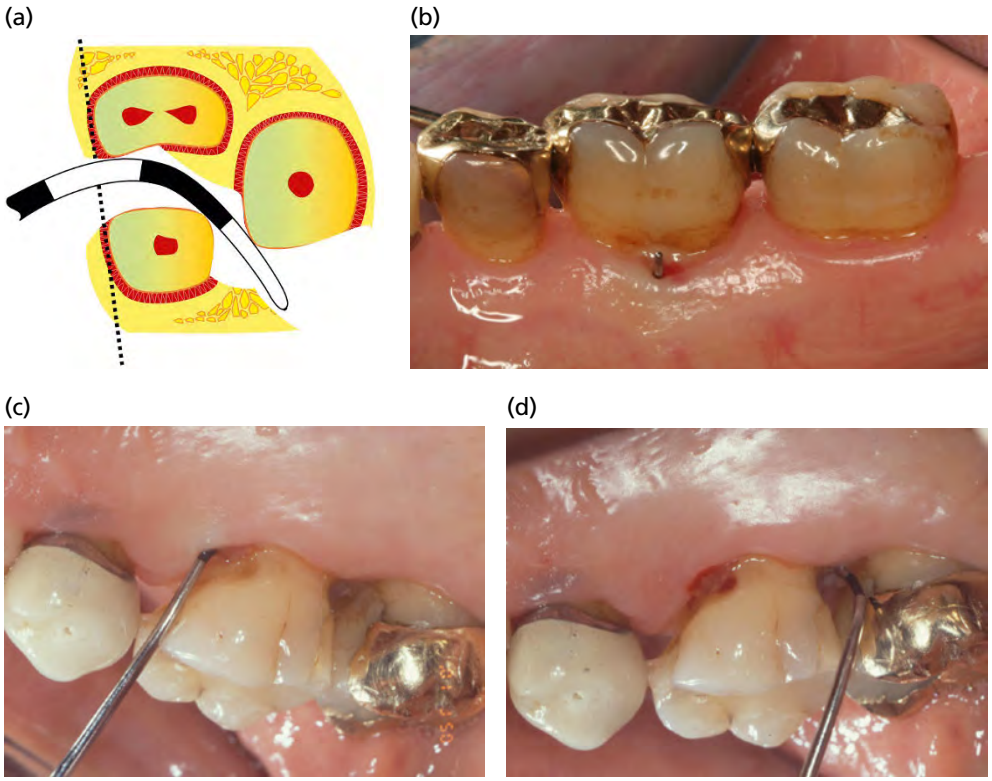

Fig. 33-10 Furcation involvement degree III (Table 33-1) (Ammons & Harrington 2006; Eickholz & Walter 2018): horizontal "through-and-through" destruction of the periodontal tissue in the furcation. (a) Schematic (maxillary molar, buccal to interproximal furcation entrance) (Eickholz & Walter 2018). (b) Tooth 46 (lingual view). (Source: Eickholz & Walter 2018.) (c) Furcation probing at tooth 16 (Eickholz, 2010a): from mesiolingual: probing (PAL-H)/clinical horizontal attachment loss (CAL-H) = 9 mm. (d) Furcation probing at tooth 16 (see part c) (Eickholz 2010a): from distolingual: probing (PAL-H)/clinical horizontal attachment loss (CAL-H) = 6 mm. In tooth 16 the PAL-H/CAL-H measurements add up to 15 mm. At the furcation entrances tooth 16 has a width less than 15 mm. Thus the furcation is through-and-through (degree III; Table 33-1).

regenerative treatment, where new connective tissue attachment may be possible without new bone formation within a furcation (Eickholz & Walter 2018).

Reliable diagnosis of FI is not provided by two-dimensional radiographic techniques (projection radiography, periapical and panoramic radiographs) (Topoll *et al*. 1988). For maxillary premolars the furcation channel is oriented perpendicularly to the central beam. Thus, FI in maxillary premolars cannot be visualized using projection geometry. In three-rooted maxillary molars the furcation channel between the mesio- and distolingual furcation entrance also runs parallel to the plane of the radiographic film or sensor and perpendicular to the central beam. The buccal furcation entrance is in most cases overlapped by the lingual root. Thus, in maxillary molars, two-dimensional radiographs only provide very limited information on interradicular bone. Only in mandibular molars is the furcation channel located perpendicularly to the plane of the film/sensor and parallel to the central beam. Thus, under conditions of orthoradial projection, interradicular bone may be assessed in mandibular molars. However, radiographs only provide information on resorption or density of bone. Reduced bone density may be because of periodontal destruction or reduced bone density caused by loose spongeous structure. Thus, conventional radiographs may only provide hints for a suspicion of FI. This suspicion has to be confirmed or rejected by furcation probing using a curved probe (Eickholz & Walter 2018).

Additionally, radiographs may provide information to judge whether a buccal or lingual class II furcation may benefit from regenerative therapy. In molars with class II FI, a long root trunk, a furcation fornix located coronally to the adjacent interproximal alveolar crest, and a wide furcation are associated with less favorable horizontal attachment gain after guided tissue regeneration (Horwitz *et al*. 2004).

Three-dimensional radiography

Because conventional two-dimensional radiographic imaging may have some clinically relevant drawbacks, it might be useful to analyze distinct clinical situations, particularly in maxillary molar teeth, with a three-dimensional diagnostic approach (Laky *et al*. 2013; Walter *et al*. 2016). Cone beam computed tomography (CBCT) has been validated *in vivo* for the assessment of FI of maxillary molars (Walter *et al*. 2016). CBCT data were found to be accurate in assessing the amount of periodontal tissue loss and in classifying the class of FI in maxillary molars (Walter *et al*. 2009; Walter *et al*. 2010; Walter *et al*. 2016). In addition, the three-dimensional images revealed several findings, such as the surrounding bony support of each maxillary molar root, fusion or proximity of roots, periapical lesions, root-perforations, and/or missing bony walls (Walter *et al*. 2009). The clinical relevance of these radiographic data was analysed regarding the decision-making process for resective or non-resective therapies. These treatment options were classified according to their invasiveness (GoI, graduation of invasiveness): (1) GoI 0, supportive periodontal treatment (SPT); (2) GoI 1, open flap debridement with/without gingivectomy or apically repositioned flap and/or tunneling; (3) GoI 2, root separation; (4) GoI 3, amputation/trisection of a root (with/without root separation or tunnel preparation; (4) GoI 4, amputation/trisection of two roots; and (6) GoI 5, extraction of the entire tooth. They range from minimally invasive SPT to maximally invasive extraction and implant restoration. Significant discrepancies between conventional and CBCT-based treatment approaches were found in most situations, which possibly necessitates intrasurgical changes in the treatment plan in those cases where no CBCT is available (Eickholz & Walter 2018).

However, the findings from a cost analysis indicated the need for a critical appraisal of CBCT applications in upper molars (Walter *et al*. 2012). In most cases with clinically-based GoI ≤1, CBCT imaging seems to have no or only a minor impact on economic benefit and reduces treatment time only slightly, if at all. With more invasive clinically based treatment decisions (>GoI 1), however, the benefits of using CBCT were greater, probably because the indication for tooth extraction is clarified. On the one hand, a straightforward tooth extraction followed by implant placement and restoration is feasible, thereby avoiding explorative periodontal surgeries when the tooth is not maintainable. On the other hand, unnecessary tooth extractions and implant placement in sites where teeth would be maintainable may be avoided. Moreover, root canal treatments in sites planned for GoI 2, 3, or 4 may be prevented, as CBCT revealed morphological variations such as root proximities or root fusions, which precluded the clinically based resective treatment planning (Eickholz & Walter 2018).

The main goal of diagnostic radiology is to keep the radiation dose "as low as reasonably achievable" (ALARA), and this should also be a prerequisite for adequate CBCT application in dentistry, since increased radiation in the dental office may potentially cause malignancies, including thyroid cancer or intracranial meningioma (Hallquist & Nasman 2001; Longstreth *et al*. 2004; Hujoel *et al*. 2006). The potential risks associated with additional radiation exposure are only justified in single cases and have to be evaluated in each individual situation.

Furcations and risk of tooth loss

For the reasons described, plaque removal inside the furcation area is a rather daunting and difficult task, both for the clinician and for patients. It is therefore

plausible to assume that teeth affected by FI, being more exposed to the microbial challenge, will develop periodontal progression more rapidly and will have a higher risk of tooth loss.

Unfortunately, few studies have systematically investigated the relative contribution of FI to tooth loss in untreated populations. A 13-year longitudinal study on a sample of 221 staff members of a Swedish industrial company not receiving a specific periodontal treatment protocol used radiographic mandibular molar interradicular bone destruction for furcation diagnosis, in the absence of clinical data. Only 1.1–2.7% of the molars had bone loss ≥50% of the root trunk. During the follow-up period, bone loss in the furcation area increased from 18% to 32%, and 9% of molars with FI were lost (Bjorn & Hort 1982). A larger study examined a population of 1897 subjects as part of the Study of Health in Pomerania (SHIP) (Nibali *et al*. 2017). All subjects had half-mouth periodontal examinations, including FI measurements with a straight probe in one upper and one lower molar at baseline (total 3267 molars). Fewer than a third of participants reported having had some form of unspecified 'gum treatment' throughout the course of the observational period. In total, 375 subjects (19.8%) lost molars during the follow-up period. As expected, there was a gradient increase in tooth loss prevalence for molars with increasing FI class (respectively 5.6%, 12.7%, 34.0%, and 55.6% of molars without FI, class I FI, class II FI, and class III FI). A strong statistically significant association between FI and tooth loss was detected. The calculated incidence rate ratios (IRR) for molar loss were:

- 1.73 (95% CI = 1.34–2.23, P <0.001) for class I FI compared with no FI at baseline
- 3.88 (95% CI = 2.94–5.11, P <0.001) for class II-–III compared with no FI at baseline.

These results were confirmed in subanalysis of the 72% of subjects who had no periodontal treatment during the course of the study (who could more genuinely be considered 'untreated') (Nibali *et al*. 2017).

Treatment options

The data in the previous section stress the importance of treating molars with FI, in order to avoid tooth loss, which results in the worsening of quality of life for patients. Previous chapters of this book have clearly explained that the mainstay of periodontal treatment consist of patient motivation, oral hygiene instructions, and supra- and subgingival tooth debridement. Furcations are no different. Every effort needs to be made to remove deposits from inside the furcation areas successfully, in order to achieve satisfactory outcomes, with reduction of pocket depths and bleeding on probing, and ideally also of the degree of the FI (horizontal and vertical). However, several studies have shown that removal of subgingival deposits, especially in the furcation area, is challenging and the expected response is not as favorable as in non-furcation sites.

Non-surgical treatment

Both professional root surface debridement and self-performed oral hygiene are very challenging in furcation-involved teeth. This is due to limited access to the usually small furcation entrances (see previously) and to deep difficult-to-reach root concavities present in interradicular areas (Bower 1979; Booker & Loughlin 1985; Eschler & Rapley 1991). Studies have clearly shown that complete plaque and calculus removal in the furcation region is unrealistic (Matia *et al*. 1986; Parashis *et al*. 1993; Kocher *et al*. 1998a,b; Jepsen *et al*. 2011), even for experienced operators (Fleischer *et al*. 1989). Ultrasonic scalers have been shown to be more effective than hand instruments in narrow and deep furcation areas, due to their smaller tips (Matia *et al*. 1986; Leon & Vogel 1987; Sugaya *et al*. 2002). Diamond-coated ultrasonic and sonic scaler tips can also be effective but are more aggressive, removing cementum and dentine (Kocher & Plagmann 1999). Therefore, it is no surprise that studies showed that sites with FI responded consistently less favorably than non-furcated sites to subgingival debridement in terms of pocket depth reduction, clinical attachment gain, and risk of reverting to baseline status (Nordland *et al*. 1987; Loos *et al*. 1988, 1989). These difficulties can be partially overcome by an open-flap approach for furcation debridement (Matia *et al*. 1986; Fleischer *et al*. 1989), but also with the introduction of stronger and thinner curettes and ultrasonic tips, with widths <0.7 mm. Slimline furcation-customized ultrasonic tips and micro-mini curettes are therefore recommended for professional furcation debridement. With the correct use of these newer tools, clinical and radiographic resolution of the furcation lesion may be possible in some cases even following non-surgical therapy only (Fig. 33-11).

Good oral hygiene is crucial for the short- and long-term success of furcation treatment. However, the evidence for efficacy of self-performed oral hygiene tools in the furcation region is very limited. A study suggested that a pointed-end tufted powered brush is more effective than a small-head powered toothbrush in removing plaque in furcal areas (Bader & Williams 1997). For interproximal furcations, we can assume that interdental brushes are more effective than floss, as shown in studies not specific to furcation lesions (Kiger *et al*. 1991). Particularly demanding oral hygiene routines are required for patients to clean class III furcations. However, this has been shown to be achievable under the right circumstances (Hellden *et al*. 1989).

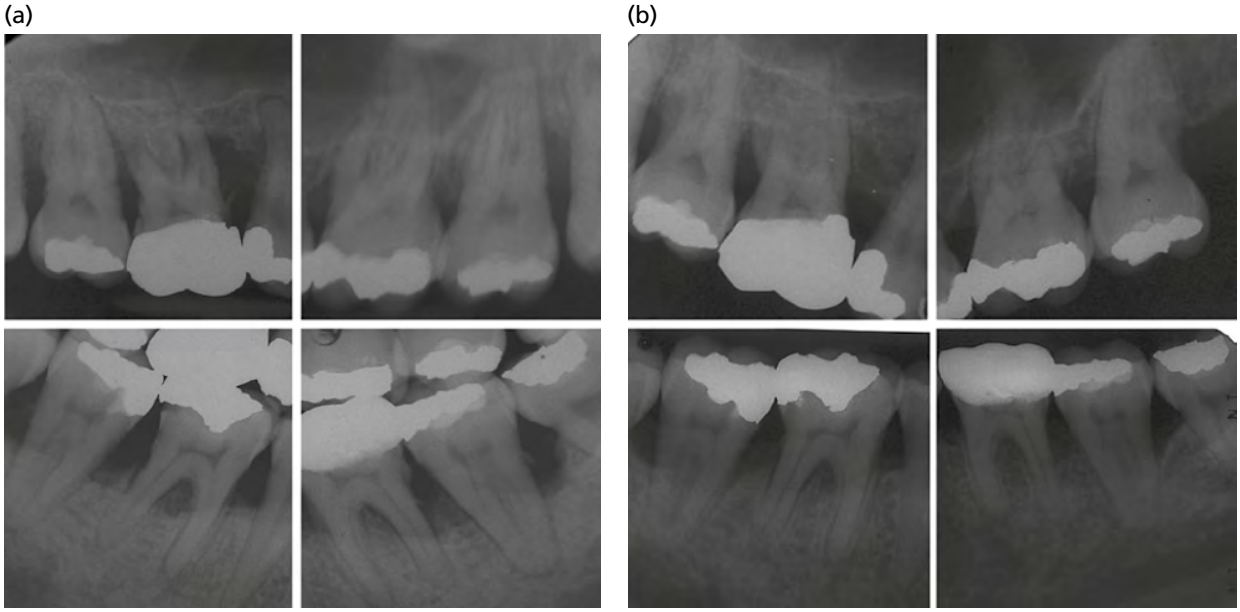

Fig. 33-11 (a) Periapical radiographs of molars of a female 32-year-old aggressive periodontitis patient at periodontal diagnosis. Radiolucency inside the furcation areas is visible, particularly for teeth 16 and 17 (both class II clinical furcation involvement [FI] diagnosis), teeth 26 and 27 (class I FI), tooth 36 (class I FI), and tooth 46 (class II FI), often associated with intrabony defects. (b) Periapical radiographs of the same molars 1 year after initial periodontal therapy (oral hygiene instructions and supra- and subgingival debridement with adjunctive systemic antibiotics and extraction of tooth 28), showing radiographic bone fill in furcation defects and intrabony defects, associated with clinical reduction of FI classes (now only class I for teeth 16 and 17, teeth 26 and 27, and tooth 46).

Corrective surgery in furcation defects

Different surgical strategies are available to address the problem of FI. Access flap surgery aims to improve instrumentation of the furcation area (root surfaces, roof of furcation, osseous lesion) under direct vision (open flap debridement). The elimination of the furcation defect is another option. This can be achieved by removal of the involved root(s) using resective approaches. Alternatively, periodontal tissues that have been destroyed by periodontitis can be regenerated, thereby decreasing the lesion.

Access flap surgery /open flap debridement

Complete removal of subgingival deposits is more difficult in molars than in single-rooted teeth (Brayer *et al*. 1989; Fleischer *et al*. 1989). Thus, after non-surgical treatment, multirooted teeth in many cases exhibit persisting pockets and require additional open flap debridement. Class I FI results in a minor deterioration of prognosis compared with class II and III FI (Nibali *et al*. 2016). Thus, in class I FI there is no need to improve the horizontal component of FI by regenerative treatment. Up to now there is no evidence that the horizontal component of through-and-through FI (class III) may benefit from regenerative treatment (Pontoriero *et al*. 1989; Pontoriero & Lindhe 1995; Jepsen *et al*. 2020a). However, substantial long-term survival of molars with class III FI has been reported after only non-surgical and open flap debridement (OFD) (Dommisch *et al*. 2020).

The clinical performance of access flap surgery (OFD) in the treatment of class II furcation defects has been evaluated (Graziani *et al*. 2015). Based on prospective data of the control groups of randomized clinical trials, most of them with 6 months' duration, the following outcomes could be established: furcation closure after OFD was never reported, mean horizontal bone level (HBL) gain was almost imperceptible, mean horizontal clinical attachment level (HCAL) gain amounted to 1 mm, mean vertical clinical attachment level (VCAL) gain to 0.5 mm, and mean probing pocket depth (PPD) reduction to 1.4 mm. Thus, surgical debridement of class II furcation defects can result in a modest improvement in clinical parameters. However no change in furcation status by horizontal bone fill can be expected.

Resective furcation surgery of furcation defects

Several studies report that molars with class I FI compared with molars without FI have a fair long-term prognosis. However, molars with class II and III have increased long-term tooth loss rates compared with molars without or class I FI. Further, different survival rates according to class of FI, in particular with differences between class II and III, are reported (McGuire & Nunn 1996; Salvi *et al*. 2014; Graetz *et al*. 2015; Dannewitz *et al*. 2016). Under favorable conditions class II FI may be closed or transferred to class I FI by regenerative therapy (regenerative furcation therapy) (Jepsen *et al*. 2020a). Thus, multirooted teeth with class II (unfavorable conditions) and in particular class III FI are the targets of resective treatment.

Resective furcation therapy basically follows two strategies:

1. Elimination of the niche created by FI by removal of roots.
2. Providing access for individual and professional hygiene to the involved furcation.

Further treatment of FI is often required in strategically important teeth that contribute to chewing capability, maintaining the complete or a shortened dental arch (Fig. 33-12) and supporting fixed or removable dental prostheses (Fig. 33-13).

Currently, a root canal treatment and filling is required for all techniques where roots are resected or teeth are separated. If these techniques are to be used, it must be considered that additional treatment (root canal treatment and filling) may result in additional complications. Thus, if a satisfactory root canal filling already exists, this may facilitate the decision for resective furcation therapy. Whereas attempts to keep the pulp of resected teeth vital using calcium hydroxide failed (Haskell & Stanley 1982), a case series using metal trioxide aggregate (MTA) reported promising results for up to 1 year (Tahmooressi *et al*. 2016). Recently, a case series demonstrated the possibility of maintaining severely furcation-involved molars by vital root resection for up to 7 years. Teeth treated were maxillary molars affected by double/triple class II or single/double class III FI and advanced bone loss around one root. Molars were treated with deep pulpotomy using a calcium silicate-based cement before the affected root was removed. All teeth remained vital and presented with healthy and stable periodontal conditions. The authors concluded that root canal therapy and its associated costs and complications can thus be avoided and further trials are warranted (Jepsen *et al*. 2020b).

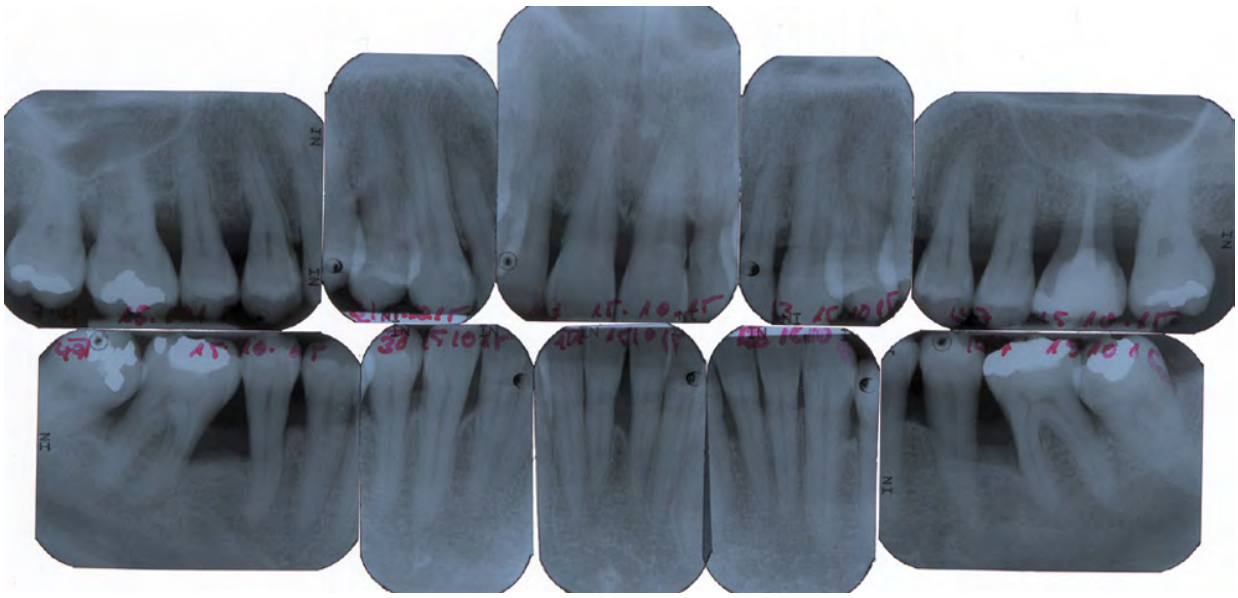

Fig. 33-12 A 41-year-old female, 17 years after active periodontal treatment with trisection of left first maxillary molar (tooth 26) (both buccal roots removed with the respective parts of the crown).

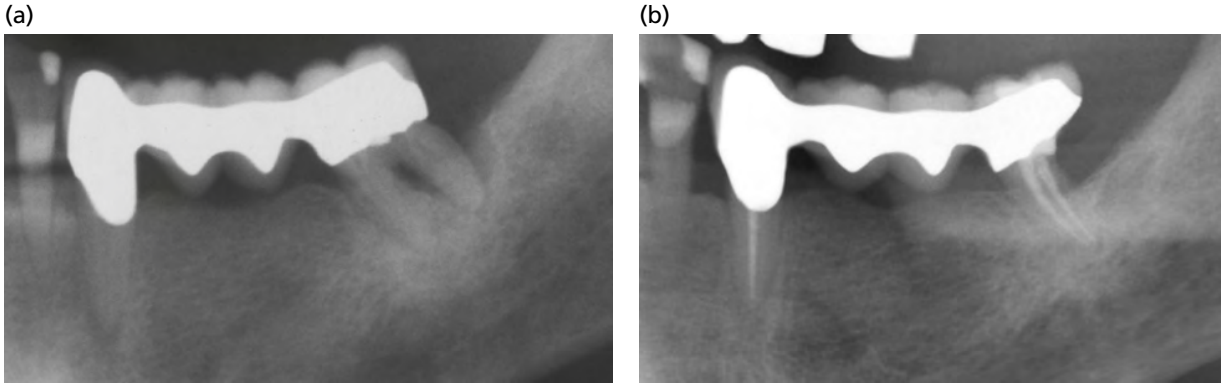

Fig. 33-13 Root resection/amputation at left first mandibular molar (tooth 36) (Eickholz 2010b). (a) Prior to root canal treatment and filling: bridge from left mandibular canine (tooth 33) to left first mandibular molar (tooth 36): both teeth are avital and show periapical radiolucencies. Periodontal-endodontic lesion at the distal root of left first mandibular molar. (b) Thirteen years after endodontic treatment and resection/amputation of distal root of left first mandibular molar. The bridge was retained.
(Source: Eickholz 2010b.)

Root resection/amputation

Root resection (also called root amputation) describes the removal of a root of a multirooted tooth under retention of the respective part of the crown. Root resection is mainly used in maxillary molars to remove one of three roots (Fig. 33-14a–h). When luxating the root to be removed, the molar unit to be retained must not be used for support (Fig. 33-14f), because the molar unit to be retained also may be luxated, which will result postsurgically in increasing mobility and, frequently, tooth loss.

In a maxillary molar resection of one root this leaves approximately 70% of the roots to support 100% of the crown. From a statics point of view, this allows retention of the whole crown and occlusal surface, respectively, without risking overload and fracture. Due to static considerations, roots of mandibular molars are rarely resected. Root resection in a /amputation mandibular molar with two roots would result in 50% of roots left with 100% of the crown, with a strong leverage causing a high risk for fracture. However, in cases where the mandibular molar scheduled for root resection is connected by a crown block or a bridge to neighboring teeth, the leverage of eccentric occlusal forces is compensated (Fig. 33-13). Resecting a root that is creating FI eliminates the respective furcation and the FI. This eliminates the niche and thereby the persisting infection.

If the tooth scheduled for resection has been restored by adhesive composite techniques after root canal treatment, the root canal of the root to be resected should be enlarged in the coronal third and filled by composite material using dentine adhesive (total etch and bond) (Fig. 33-14d). When cutting the root, the root canal is already obliterated by composite avoiding additional restorative measures (Fig. 33-14e).

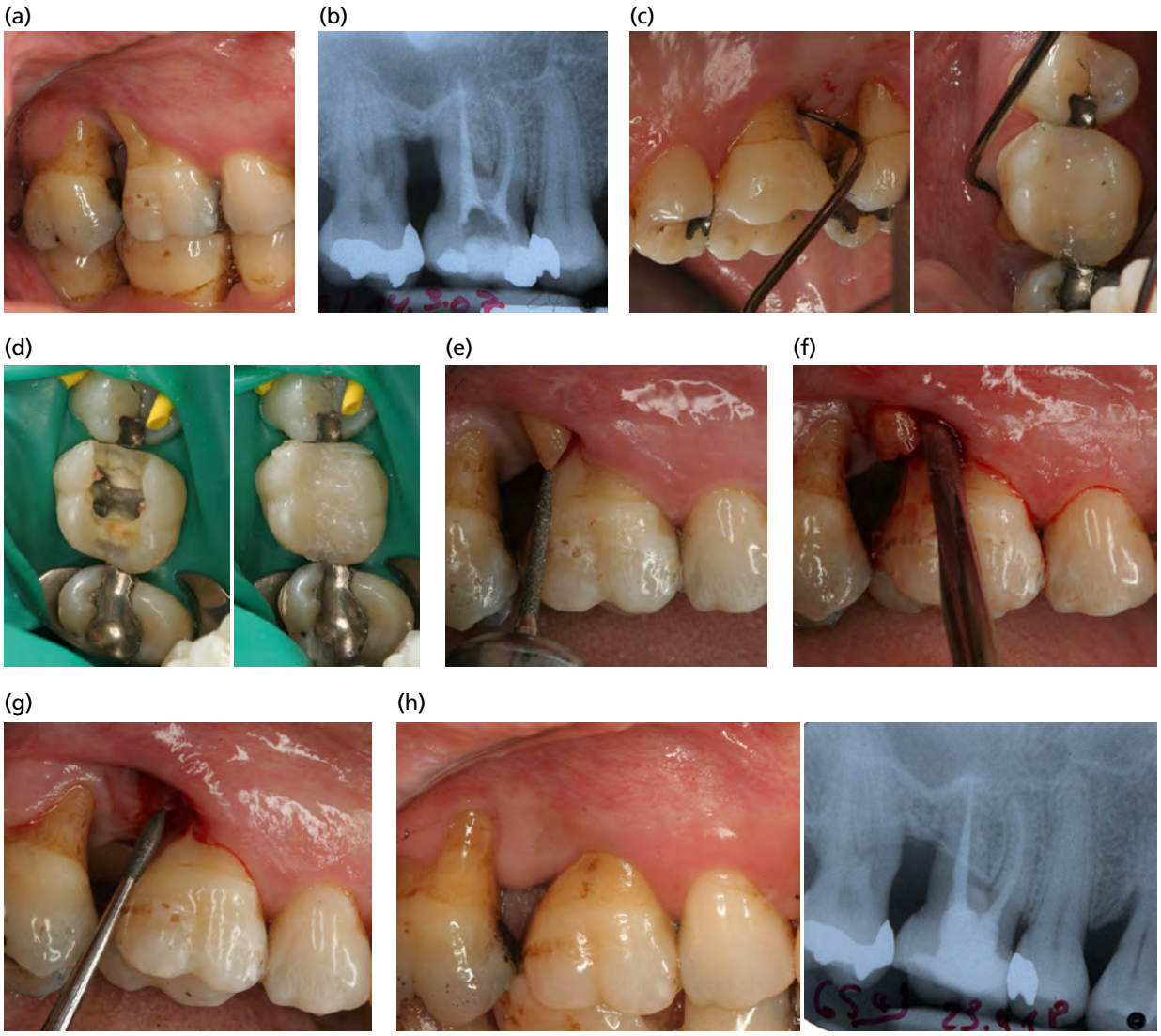

Fig. 33-14 Root resection/amputation at right first maxillary molar (tooth 16) (clinical) (Fig. 3-3a–g) (Eickholz, 2010b). (a) Buccal clinical view. (b) Radiograph. (c) Furcation involvement from buccal to distobuccal entrance. (d) Excavation of coronal third of the distobuccal root and restoration of the crown in total etch total bond technique. (e) Cutting the distobuccal root with a diamond bur. The root canal of the distobuccal root is cut in the coronal third where it is filled with composite material. (f) Luxating the root to be removed; the lever should not be supported by the tooth unit that is to be retained. (g) Smoothening of the separation surface with fine-grained diamond bur. (h) Long-term outcome: clinical view and radiograph (11 years after root resection/amputation). (Source: Eickholz 2010b.)

Hemisection and trisection

Hemisection is the simultaneous removal of a root with the respective part of the crown from a two-rooted tooth (mandibular molar). Trisection is the respective technique in maxillary molars (removal of one or two roots with the respective part of the crown from a three-rooted tooth). Hemisection is the resective technique of choice in teeth that beyond FI exhibit a defect substantially deteriorating the prognosis of one root compared with the other, for example obliterated root canal (Fig. 33-15a), deep bony defect, or apical periodontitis. The tooth is not separated centrally above the furcation but slightly laterally within the root to be removed (Fig. 33-15c). This avoids damage to the root to be retained. Hemisection in many cases creates a gap that may require prosthodontic treatment (Fig. 33-15d–f). However, if there are respective antagonists and the patient is neither functionally nor aesthetically compromised, gaps in the posterior region may be kept.

Restoration of resected molars

Until the 1980s, restorative treatment after root resection followed the paradigm that retention had to be created by root canal posts and teeth had to be stabilized by crown work. The assumption was that root canal filled teeth would become brittle and after root resection the retained tooth units would become instable. At that time, direct restorative materials that allow adhesive connection to enamel and dentine were not available. Providing space for root canal posts requires debridement of more dentine from the root canals than for pure disinfection and filling. This additional debridement of the root canal leads to substantial loss of hard tissues. This may contribute to high rates of long-term failure of resective furcation treatment due to root fractures (18%) compared with periodontal reasons (10%) (Langer *et al*. 1981). Currently, adhesive composite restoration techniques facilitate stabilization of dental hard tissues by direct restorations (Figs. 33-12, 33-14). Avoiding the dogmatic use of root posts may help to reduce the total failure rate (Carnevale *et al*. 1998).

Root separation

Root amputation, hemisection, and trisection entail removal of one or two roots from multirooted teeth to eliminate the respective furcation and FI (Eickholz 2010b). If one of the roots that generates a furcation is compromised by, for example, severe vertical bone loss, an endodontic lesion, root fracture, root perforation, or a fractured root canal instrument, this may support the decision to remove the respective root. However, which procedure may be used if all roots generating a furcation and neighboring an FI have sufficient bony support and have equal prognosis? In such cases the strategy of making the FI niche accessible to individual oral hygiene measures is applied.

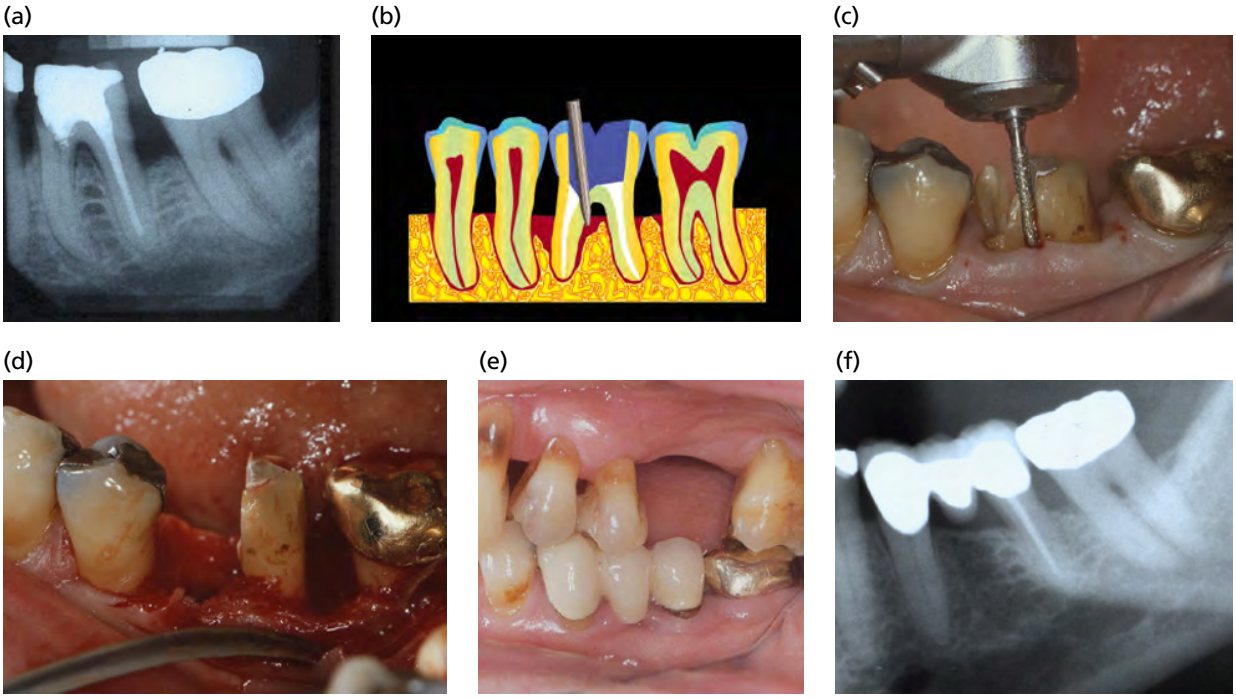

Fig. 33-15 Hemisection at left first mandibular molar (tooth 36). (a) Radiograph after root canal filling. The mesial root canals are obliterated and cannot be debrided. (Source: Eickholz 2011.) (b) Schematic: left first mandibular molar with degree III furcation involvement and infrabony defect at mesial root. Separation of mesial root paramedian of furcation within the root to be removed avoiding damage to the root to be retained. (c) Separation of mesial root. Left second molar exhibits degree III furcation involvement and, thus, is not an appropriate bridge abutment. (Source: Eickholz 2011.) (d) After removal of mesial root. (Source: Eickholz 2011.) (e) Restoration according to traditional paradigm: bridge from distal root of tooth 36 to tooth 35 (clinical view 11 years after surgery). (Source: Eickholz 2011.) (f) Radiograph 11 years after surgery (detail from panoramic radiograph); left second molar still in place despite degree III furcation involvement. (Source: Eickholz 2011.)

In class II and III furcation defects created by two roots with equally good periodontal support and prognosis the furcation niche may be made accessible for individual oral hygiene measures by a so-called root separation (Fig. 33-16). Therefore, a two- or three-rooted tooth is separated into two or three single-rooted tooth units (Fig. 33-16). In contrast to hemisection/trisection for root separation, the roots are separated centrally above the furcation fornix (Fig. 33-16c), because two roots in the mandible and three roots in the maxilla should be retained and, thus, must not be damaged. The furcation is transformed to an interproximal space that can be accessed more easily for individual hygiene measures. Because the grinding bur to separate the roots has a defined diameter that creates a gap between the separated roots (Fig. 33-16c), the interproximal contact has to be recreated restoratively after surgery (Fig. 33-16d–f).

Tunneling

Whereas up-to-date root canal treatment and filling are prerequisites for root resection, hemisection, trisection, and root separation, the tunneling procedure allows the patient access to the furcation area to keep teeth vital. The technique is appropriate particularly for mandibular molars with a mesial and distal root and a buccal and lingual furcation entrance (Fig. 33-17a). Although tunneling maxillary molars is possible in principal, its success depends on the patient's dexterity when using interdental brushes. Opposite each furcation entrance there is a root blocking the straight passage of the brush. In mandibular molars with severe class III FI and a short root trunk, small interdental brushes may pass through the furcation because of already receding gingiva as a result of non-surgical subgingival instrumentation. However, in many cases the channel created by the FI is too narrow or narrowed lingually by a bony wall. In these cases a flap is raised (apically repositioned flap) (Fig. 33-17b, c). After revealing the bone and the furcation defect, interradicular bone is reduced using bone files (Schluger and Sugarman files) sufficiently to facilitate access of interdental brushes after healing (Fig. 33-17b–d). As a rule of thumb, the tunnel should be able to accommodate a Schluger file without edging (Fig. 33-17c). Using rotating instruments carries the risk of irreversibly damaging the root surfaces within the furcation and generating predilection sites for root caries. Finally, the flap is repositioned apically by interradicular and interdental periosteal sutures (Fig. 33-17e). A periodontal dressing should be applied to keep the soft tissues apically and to prevent reclosure of the tunnel. A space holder may keep the tunnel open; a piece of gauze can be used (Fig. 33-17f–h) – the suture is fixed at one end of the gauze (Fig. 33-17f). The periodontal dressing is mixed and one half applied to the gauze (Fig. 33-17g). The needle is then pushed through the tunnel and the gauze, loaded with the dressing, is carefully pulled into the tunnel (Fig. 33-17h). Overhangs should be reduced. However, to facilitate removal 1 week after tunneling at the time of suture removal, the gauze should not be cut too short. The other half of the

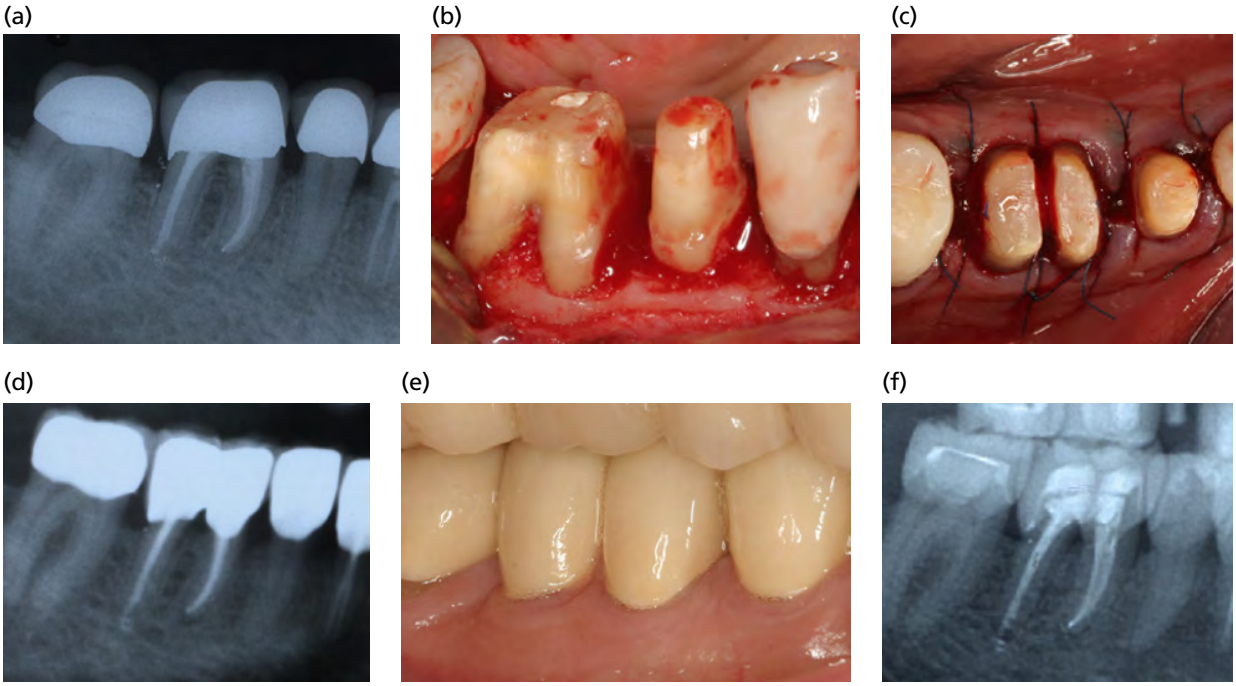

Fig. 33-16 Root separation at right first molar (tooth 46). Buccal degree II and lingual degree I furcation involvement, short root trunk, crown to be replaced. (a) Radiograph after root canal filling. (b) Full thickness flap and surgical crown lengthening. (c) Periosteal suture after root separation (apically repositioned flap). (d) Radiograph 10 months after root separation and temporary crown (detail of panoramic radiograph). (e) Clinical view 12 months after root separation. (f) Radiograph 50 months after root separation and definite crown (detail of panoramic radiograph).

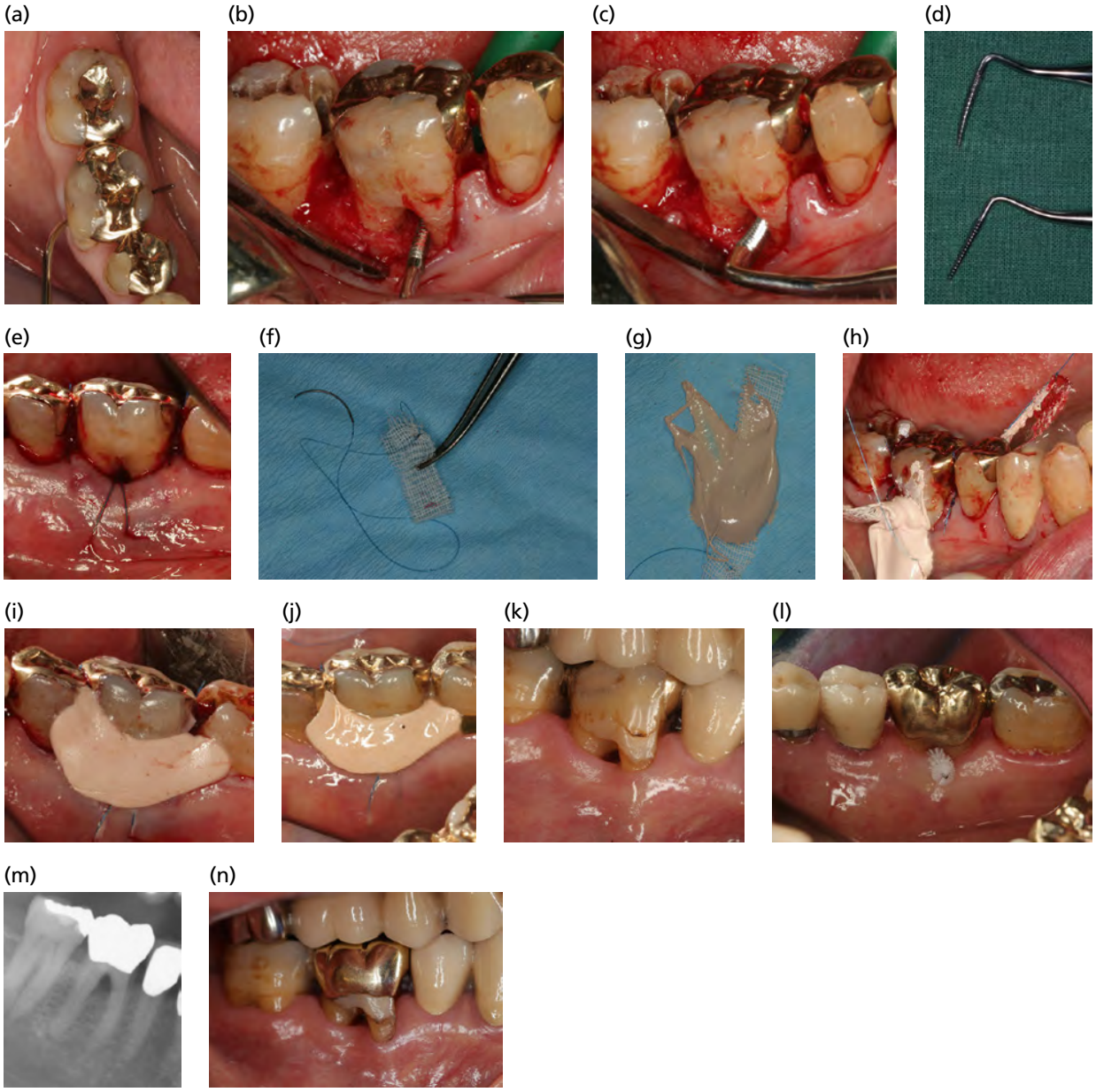

Fig. 33-17 Tunneling of right first mandibular molar (tooth 46). (a) Degree III furcation involvement (occlusal view of Fig. 33-10b). (b) After full thickness flap interradicular ostectomy using Sugarman file. (c) Ostectomy using Schluger file. (d) Sugarman (below) and Schluger (above) ostectomy files. (e) Intrafurcal periosteal suture (apically repositioned flap). (f) Fixing suture to gauze. (g) Putting one half of periodontal dressing onto gauze. (h) Pulling the gauze loaded with periodontal dressing into the tunnel. (i) Fixing the other half of periodontal dressing to buccal and lingual furcation entrances (lingual view). (j) Six days after tunneling. Periodontal dressing still in place. (k) One year after tunneling (buccal view). (l) Two years after tunneling (lingual view with interdental brush). (m) Radiograph 3 years after tunneling (detail from panoramic radiograph). (n) Five years after tunneling (buccal view).

periodontal dressing has now become putty and is placed to the buccal and lingual area of the gingival margin (Fig. 33-17i, j). Another technique is to pull and fix an elastic ligature (e.g. Wedjet®) into the furcation (Müller *et al*. 2017).

In the mandible, tunneling has the same indication as root separation. However, tunneling does not require root canal treatment and filling. Tunneling is particularly beneficial for retaining existing and functioning crown and bridge work without damaging restorations, which may occur during root canal treatment.

The aim of tunneling is not elimination of the furcation but facilitating access for a patient's oral hygiene (Fig. 33-17k–n). For tunneling the respective roots should be spread sufficiently and the furcation fornix should be located coronally (short root trunk) to facilitate interradicular professional debridement and individual cleaning. Root caries within the tunnel is the most dreaded complication of this technique (Fig. 33-18). Restoration of such caries is practically impossible. The only putative solutions to this problem are root separation, root resection, trisection/hemisection, or extraction. Patients are advised to

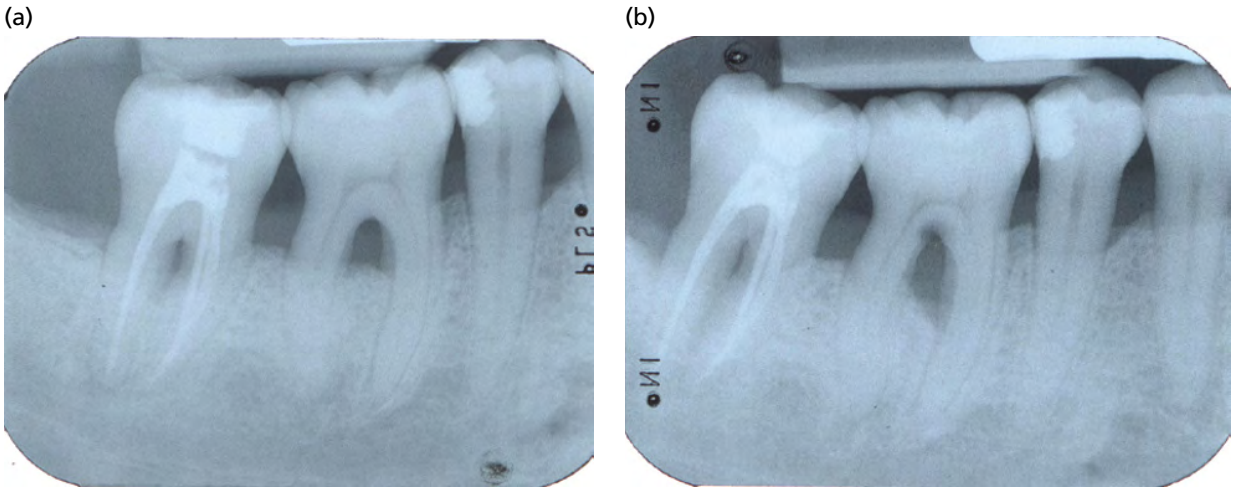

Fig. 33-18 Tunneling of right first and second mandibular molar (teeth 46 und 47). (a) Two months after tunneling. (b) Fifty-six months after tunneling: root caries developed within the furcation fornix of the first molar. Additionally, breakdown of periodontal bone has occurred in the furcation. (Source: Eickholz 2011.)

clean the tunnel meticulously and to apply fluorides on a daily basis into the tunnel to prevent caries. This requirement should be communicated to patients prior to surgery.

Combination of resective techniques

In maxillary molars with class III FI affecting all three furcation entrances, one root may be resected and tunneling performed for the remaining two roots. Alternatively, after resection of one root, the remaining roots may be separated. However, use of such combinations may not be successful. It is important to make sure that there is enough intact periodontium to support the remaining tooth unit (at least 50% remaining bone height) (Park *et al*. 2009).

Prognosis of resective furcation treatment

A recent systematic review evaluated the effect of resective surgical periodontal therapy (root amputation or resection, root separation, tunnel preparation) in periodontitis patients exhibiting class II and III FI and its benefit when compared with non-surgical treatment or open flap debridement. One prospective and six retrospective cohort studies and case series were included, reporting 667 patients contributing 2021 teeth with class II or III FI. Data were highly heterogeneous regarding follow-up and distribution of FI. A total of 1515 teeth survived 4–30.8 years after therapy. Survival ranged from 38% to 94.4% (root amputation or resection, root separation), 62% to 67% (tunnel preparation), 63% to 85% (OFD), and 68% to 80% (scaling and root planing, SRP). Overall, any treatment provided better results for class II than class III FI (Dommisch *et al*. 2020).

In addition to the class of FI prior to therapy and type of restoration, the amount of periodontal support that remains after surgery seems to play a decisive role for prognosis. Teeth with class III FI and little bone loss (Fig. 33-12) or little FI and severe bone loss on average have a good prognosis, whereas multirooted teeth with class III FI and severe bone loss are less suitable for resective surgery (Dannewitz *et al*. 2006). This observation is supported by another group that reports better long-term prognosis in retained tooth units with at least 50% remaining bony support in relation to root length (Park *et al*. 2009).

If performed early enough, root resection, trisection, hemisection, and root separation provide survival rates >90% 10 years after treatment (Carnevale *et al*. 1998). Hemisection of the distal root of mandibular molars provides the worst success rate (75%). Resective surgery facilitates long-term success that is similar to endosseous implants that were inserted in the molar region (>90%) (Fugazzotto 2001). A recent structured review reported that 294 patients contributing 468 teeth lost a total of 105 teeth treated by root amputation or resection, and root separation for class II or III FI (survival 77%). Overall, treatment provided better results for class II FI than class III (Dommisch *et al*. 2020).

After tunneling of seven multirooted teeth (six mandibular molars, one maxillary premolar) and reporting caries within the tunnel 5 years after surgery, this technique had a bad reputation (Hamp *et al*. 1975). A recent structured review revealed that seven of 19 teeth treated by tunnel preparation were lost (survival 63%) (Dommisch *et al*. 2020). Very recent observational studies report slightly better survival rates: in a prospective case series of 32 patients contributing 42 molars with class III FI, 69% survival 5 years after tunnel preparation was observed (Rudiger *et al*. 2019). A retrospective cohort following 102 molars with class III FI in 62 patients at least 5 years after tunnel preparation reported 70% survival with regular SPT positively influencing survival (Nibali *et al*. 2019).

With respect to the heterogeneity of included studies, the lack of randomized controlled trials, and based on the evidence aggregated in this systematic analysis of recent/timely studies on resective surgical periodontal therapy (root amputation or resection,

root separation, tunnel preparation) in class II or III FI, an additional benefit of resective surgery compared with SRP or OFD in class II or III FI cannot be stated. However, in terms of elimination of periodontal inflammation, adjunctive surgical measures (root separation, root resection, tunnel preparation) may be yet justified. A careful case selection with respect to residual circular attachment is strongly suggested (Dommisch *et al*. 2020).

Extraction or palliative furcation treatment

In severely furcation-involved teeth without strategic significance (third molar or second molar in complete dentition or in the presence of the prognostically more favorable first molar), it is questionable whether root canal treatment, surgery, and restorative treatment is worth the effort. In such cases, removal of these teeth may be the most reasonable solution.

However, to surgically treat or extract teeth that are severely affected by FI is difficult to justify to patients who do not feel any pain or discomfort. From the patients' point of view, these teeth still function. If there is no need for new prosthodontic rehabilitation, which includes the FI-affected teeth, what can be offered to the patient? Class II and III FI-affected teeth may be treated with prolonging or palliative treatment: subgingival scaling and an access flap, and be maintained by regular SPT with frequent subgingival re-instrumentation and/or local subgingival antimicrobials. The aim is to slow down progression of periodontal destruction and to prevent loss of the respective tooth in the short and intermediate term. Survival rates after SRP and OFD ranged from 85% to 45% (Dommisch *et al*. 2020).

However, regular SPT is of paramount importance if resective or palliative furcation treatment is to be successful and be stabilized in the long term.

Regenerative surgery of furcation defects

Various surgical regenerative techniques have been proposed for the treatment of furcation defects of periodontitis-affected teeth and, over the past 30 years, they have been evaluated by a large number of clinical trials. Among the techniques, the most frequently described are guided tissue regeneration (GTR), using either resorbable (GTR-res) or non-resorbable (GTR-nonres) membranes, bone replacement grafts (autografts, allografts or xenografts) (BRG), bioactive agents such as enamel matrix derivative (EMD), platelet-derived growth factor (PDGF), platelet-rich plasma, platelet-rich fibrin (PRP/PRF), and combinations of them (Sanz *et al*. 2015; Jepsen & Jepsen 2018).

Evidence from human histology

Exemplary human histology is the ultimate proof for a regenerative healing outcome and is needed to supplement the information obtained from clinical regenerative studies (Machtei 1997). Evidence for periodontal regeneration requires the histological demonstration of restored tooth-supporting tissues, including cementum, periodontal ligament, and alveolar bone over a previously diseased root surface. Even though such outcomes have been demonstrated in well-controlled experimental animal studies for a variety of treatment modalities, when reviewing the histologic evidence for periodontal regeneration in furcations, information derived from human histology was found to be limited (Laugisch *et al*. 2019). Human histology showing regeneration is available for GTR (Gottlow *et al*. 1986; Stoller *et al*. 2001). One study using a combination of GTR-res and BRG (Harris 2002) and two studies using BRG (Camelo *et al*. 2003; Nevins *et al*. 2003) observed new bone, cementum, and connective tissue attachment coronal or limited to the notch area.

Evidence from clinical trials

Outcome measures

A variety of outcome measures can be considered to assess the effectiveness of regenerative furcation therapies (Sanz *et al*. 2015; Jepsen & Jepsen 2018). From a clinical point of view, apart from demonstrated improved long-term tooth retention, complete elimination or reduction of the interradicular defect appears to be the most important outcome, based on the assumption that FI class 0 or I is associated with a decreased long-term tooth loss risk (Nibali *et al*. 2016). Thus, the main outcome variables for studies evaluating the efficacy of regenerative techniques in furcations are change of furcation status (conversion into class I or complete closure) and horizontal hard-tissue fill. As histological evidence for successful furcation regeneration is not a practical outcome variable for controlled clinical trials, changes in direct bone measurements (open measurements: horizontal probing bone level, at surgery, and during re-entry) serve as primary outcome variables for evaluating clinical success, while closed measurements such as clinical attachment level gain (horizontal/vertical probing attachment level), probing depth reduction (horizontal/vertical), and radiographic assessments may serve as secondary outcomes (Machtei 1997). Patient-reported outcomes following regenerative furcation surgery may include postoperative pain, the rate of complications, perceived benefit, and change in quality of life.

Systematic reviews

The efficacy of various regenerative approaches in furcation defects has been evaluated by several systematic reviews with or without meta-analyses

(Jepsen *et al*. 2002; Murphy & Gunsolley 2003; Reynolds *et al*. 2003; Kinaia *et al*. 2011; Chen *et al*. 2013; Avila-Ortiz *et al*. 2015; Panda *et al*. 2019; Jepsen *et al*. 2020a) and has also been addressed in comprehensive narrative reviews (Sanz *et al*. 2015; Jepsen & Jepsen 2018).

By far the most evidence is available for class II furcations (mainly in mandibular molars and to a lesser extent in maxillary buccal defects).

In these systematic reviews, GTR was shown to be significantly superior to OFD for HBL and HCAL gain, PPD reduction, and VCAL gain (Jepsen *et al*. 2002; Kinaia *et al*. 2011; Jepsen *et al*. 2020a). Regarding furcation closure in mandibular defects, the results indicated that GTR plus BRG was the most effective therapeutic approach and that GTR in combination with BRG was superior to OFD and GTR alone (Murphy & Gunsolley 2003; Chen *et al*. 2013; Jepsen *et al*. 2020a).

Based on the best available evidence, by including only randomized clinical trials of at least 12 months' duration, and using Bayesian network meta-analyses to allow for direct and indirect comparisons between various regenerative techniques, it was clearly established that furcation improvement (furcation closure or class I conversion) can be expected for the majority of class II furcation defects (Jepsen *et al*. 2020a) (Table 33-2). BRG resulted in the highest probability of being the best treatment for HBL gain. GTR plus BRG ranked as the best treatment for VCAL gain and PPD reduction.

Long-term outcomes

Long-term data following regenerative therapy in furcation defects are sparse (Figueira *et al*. 2014). Significant gains in horizontal attachment level (2.6 mm) obtained 1 year after GTR were maintained over 4 years with a slight decline at the end of year 3 (Machtei *et al*. 1996). Mean horizontal attachment level gains after the use of non-resorbable and biodegradable barriers could be maintained for 5 years (Eickholz *et al*. 2001). A 10-year follow-up of 18 teeth in nine patients revealed further stability of horizontal attachment level gains between 12 and 120 months. However, two molars were lost in one patient, and another molar lost more than 2 mm of horizontal probing attachment level (Eickholz *et al*. 2006).

Table 33-2 Furcation closure/conversion (class II to class I) after 12 months in randomized clinical trials. (Source: Jepsen *et al*. 2020a.)

Study	Treatment arms	Furcation closure	Furcation conversion
Queiroz *et al*. (2016)	EMD	0 (0%)	13 (100%) to class I
	BRG	0 (0%)	10 (71.4%) to class I
	EMD + BRG	0 (0%)	12 (85.7%) to class I
Jaiswal & Deo (2013)	OFD	0 (0%)	2 (20%) to class I
	GTR-RES + BRG+EMD	3 (30%)	7 (70%) to class I
	GTR-RES + BRG	0 (0%)	8 (80%) to class I
Santana *et al*. (2009)	OFD	0 (0%) if HCAL ≤ 2 mm	NR
	GTR-NONRES + BRG	18 (60%) if HCAL ≤ 2 mm	NR
Jepsen *et al*. (2004)	GTR-RES	3 (7%)	27 (60%) to class I
	EMD	8 (18%)	27 (60%) to class I
De Leonardis *et al*. (1999)	GTR-RES	0 (0%)	6 (50%) to class I
	GTR-RES + BRG	0 (0%)	11 (91%) to class I
de Santana *et al*. (1999)	OFD	1	NR
	GTR-NONRES + BRG	5 (33%)	NR
Garrett *et al*. (1997)	GTR-NONRES	14 (22%)	33 (52%) to class I
	GTR-RES	16 (24%)	35 (53%) to class I
Hugoson *et al*. (1995)	GTR-NONRES	4 (10%)	13 (34%) to class I
	GTR-RES	13 (34%)	11 (29%) to class I
Bouchard *et al*. (1993)	GTR-NONRES	4 (36%)	NR
	GTR-RES	2 (18%)	NR
Garrett *et al*. (1990)	BRG	9 (56%)	NR
	GTR-RES + BRG	3 (20%)	NR

Perspectives

Platelet concentrates

Growth and differentiation factor technologies have been evaluated for their potential to enhance periodontal wound healing/regeneration. Autologous platelet concentrates, such as PRP and PRF, are a source of growth factors that can be applied to the periodontal wound. The adjunctive effect of autologous platelet concentrates for the treatment of furcation defects has been evaluated in a recent systematic review with meta-analysis; significantly superior outcomes compared with open flap debridement were reported for HCAL, and VCAL gain and PPD reduction (Panda *et al*. 2019).

Combined horizontal and vertical bone loss

Little information is available so far on the outcomes of regenerative therapy in molars compromised by the presence of a combination of furcation and intrabony defects, even though such situations are frequently encountered in clinical practice. In a retrospective case series, improvements, defined as tooth retention, reduction in horizontal and vertical FI, decrease in probing depths, and increases in clinical attachment level were reported at 1 year in 100% of maxillary and 92% of mandibular molars (Cortellini *et al*. 2020). Improvements were not observed in molars with baseline hypermobility. Improvement in vertical furcation subclassification was observed in 87.5% of maxillary and in 84.6% of mandibular molars. One-year improvements could be maintained over the 3–16-year follow-up. These results were obtained in cases with an interdental peak of bone and gingival margin coronal to the furcation entrance in well-maintained and compliant subjects. Randomized controlled clinical trials with medium- to long-term follow-up are needed to confirm these findings.

Summary and conclusions

- Various regenerative approaches, including the use of (non)-resorbable barrier membranes, BRG, EMD, and their combinations, have been evaluated in class II furcation defects and have been shown to be superior compared with open flap debridement
- Treatment modalities involving BRG are associated with better performance.
- Furcation improvement (furcation closure or class I conversion) can be expected for the majority of defects.
- Adjunctive regenerative techniques lead to a significant gain of HCAL, VCAL, and reduction of PPD compared with OFD.
- No conclusions can be made for interproximal maxillary class II furcation defects because of lack of studies.

Furcation regeneration: step-by-step procedure (Jepsen & Jepsen 2018)

The suggested treatment sequence is as follows:

1. *Patient selection*. Systemic factors that limit the success of periodontal surgery, such as uncontrolled diabetes and immunocompromised status, must be considered. Poor patient compliance, inadequate oral hygiene, and smoking are the most frequent patient factors limiting the selection of this procedure. Treatment options and alternatives must be presented to the patient and the potential problems and the additional costs should be discussed. Regenerative furcation surgery should be part of a comprehensive treatment plan aiming at complete periodontal and functional rehabilitation.
2. *Tooth selection*. Adequate access to the surgical site and also for future maintenance is extremely important. Molars with class II furcations (mandibular and buccal maxillary FI) are the best candidates to be considered for a regenerative procedure. Based on the available evidence, interproximal maxillary class II furcation defects are significantly less suited, most likely due to limited access. Class III mandibular and maxillary furcations have shown various treatment responses and in general there are no significant differences in treatment outcomes comparing regenerative therapy with conventional surgery. Defect and site characteristics have been identified that have impacts on the outcomes of regenerative furcation surgery (Bowers *et al*. 2003; Horwitz *et al*. 2004; Reddy *et al*. 2015). For example, a thicker phenotype and the absence of soft-tissue recession can positively influence healing following GTR procedures. More favourable outcomes can be expected in sites in which the remaining interproximal bone height is coronal to the entrance of the furcation defect compared with those in which the bone is at or apical to the furcation entrance (Fig. 33-19). Interdental root proximity may impair proper defect debridement. Presence of a root canal filling is not a contraindication to furcation regeneration per se, provided there are no signs of apical pathology.
3. *Regenerative periodontal surgery*. The goal is to obtain sufficient access to the defect for meticulous debridement and application of the regenerative device. In the case of isolated defects, vertical releasing incisions may be used (Fig. 33-20). Alternatively, the flap can be extended laterally (Fig. 33-19). Keratinized tissues should be preserved by intrasulcular incision and the elevation of a full-thickness mucoperiostal flap. Granulation tissue will be removed and the exposed root surfaces carefully cleaned by hand instruments, power-driven scalers (optionally with diamond-coated tips), or rotary instruments. Root anomalies such as enamel projections/pearls should be removed. If EMD is part of the regenerative strategy, it is usually applied following two minutes of root conditioning with EDTA and rinsing with sterile saline. Subsequently a bone graft/substitute can be used to fill the furcation defect. Alternatively, a GTR barrier membrane can be applied, with or

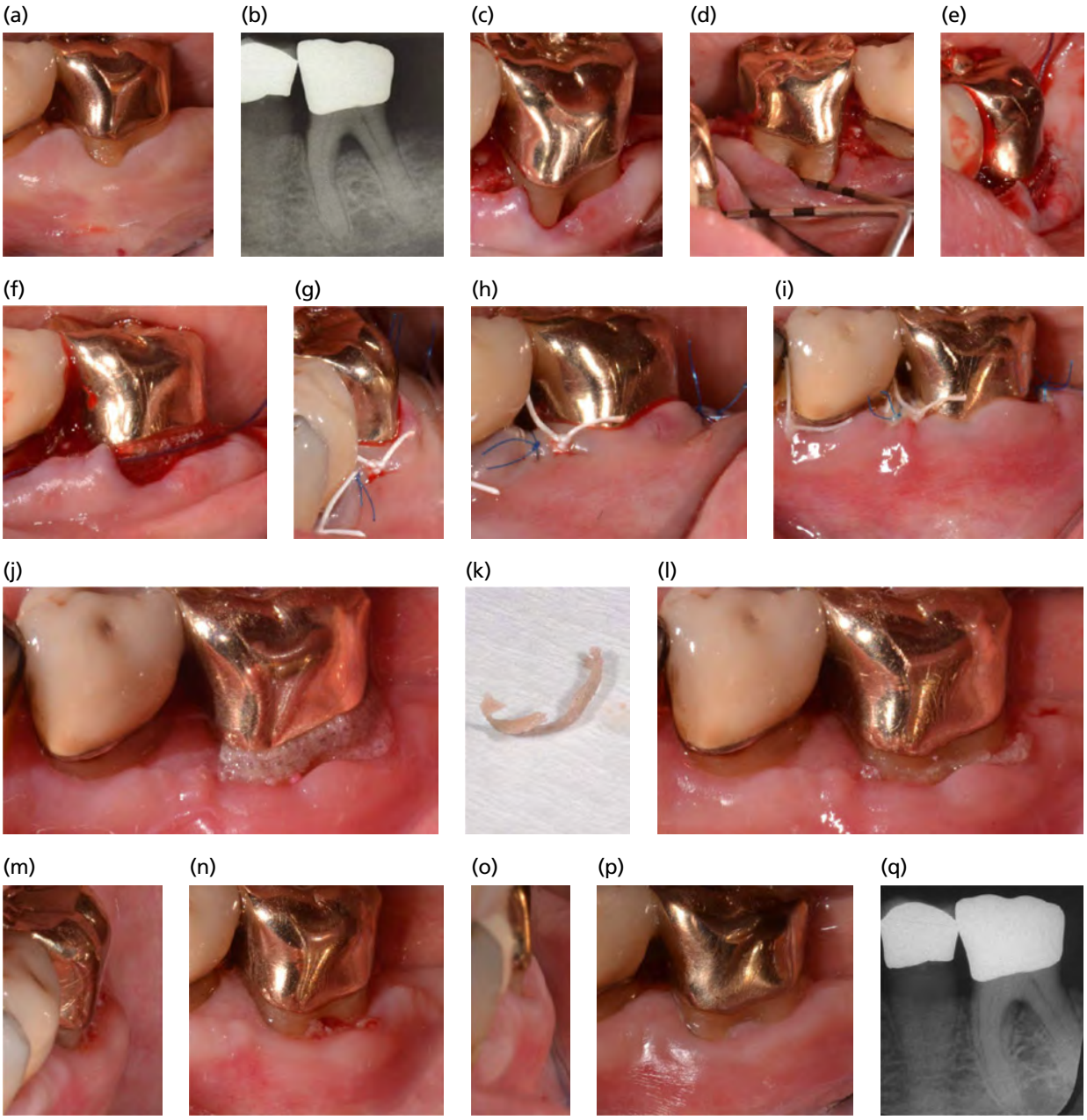

Fig. 33-19 (a) Periodontal measurements at baseline tooth 36. Probing depth mesial and distal = 2 mm, furcation class II buccally, horizontal probing depth 4 mm, recession 3 mm. (b) Radiograph of tooth 36 with visible furcation defect, adjacent bone level slightly above forcation fornix. (c) Flap elevation: intrasulcular incision/horizonal release, mucoperiostal flap, papillae de-epithelialized, periosteal split in the vestibule. Root surface debridement. (d) Horizontal probing bone level: 4 mm. (e, f) Placement of a bioresorbable matrix barrier (Guidor™ MSL-configuration, Sunstar Americas, Inc., Schaumburg, IL, USA) to facilitate guided tissue regeneration. Fixation of the barrier with integrated sling sutures. (g, h) Coronally advanced flap secured with sling and interrupted sutures. (i) One day after periodontal regenerative surgery. (j) Clinical view 3 weeks after surgery with matrix exposure. (k, l) Exposed matrix partially removed. (m, n) Five weeks after surgery. (o, p) Twelve months after surgery. Horizontal and vertical probing depths: 2 mm, recession 3 mm. (q) Radiograph taken 12 months after surgery. Almost complete radiographic bone fill in furcation area. (Source: Jepsen & Jepsen 2018.)

without an additional defect filler (Figs. 33-19, 33-20). The barrier membrane is secured by a resorbable sling suture to cover the furcation entrance and to promote wound and clot stabilization. In order to facilitate complete coverage of the barrier, the periosteum can be cut to allow for a coronal advancement of the flap. The flap is secured in a coronal position by a sling suture and interrupted sutures over the vertical releasing incisions (Fig. 33-20), or interdental sutures in the case of a laterally extended flap (Fig. 33-19). The patient is instructed to abstain from mechanical plaque removal in the surgical area for a period of up to 4 weeks. During this time, chlorhexidine rinses or topical gel applications are used. The patient returns for monitoring of healing after 1 and 2 weeks, when sutures are removed. Interdental hygiene and mechanical plaque removal are re-started after 4 weeks, and the personalized maintenance recall programme will be determined.

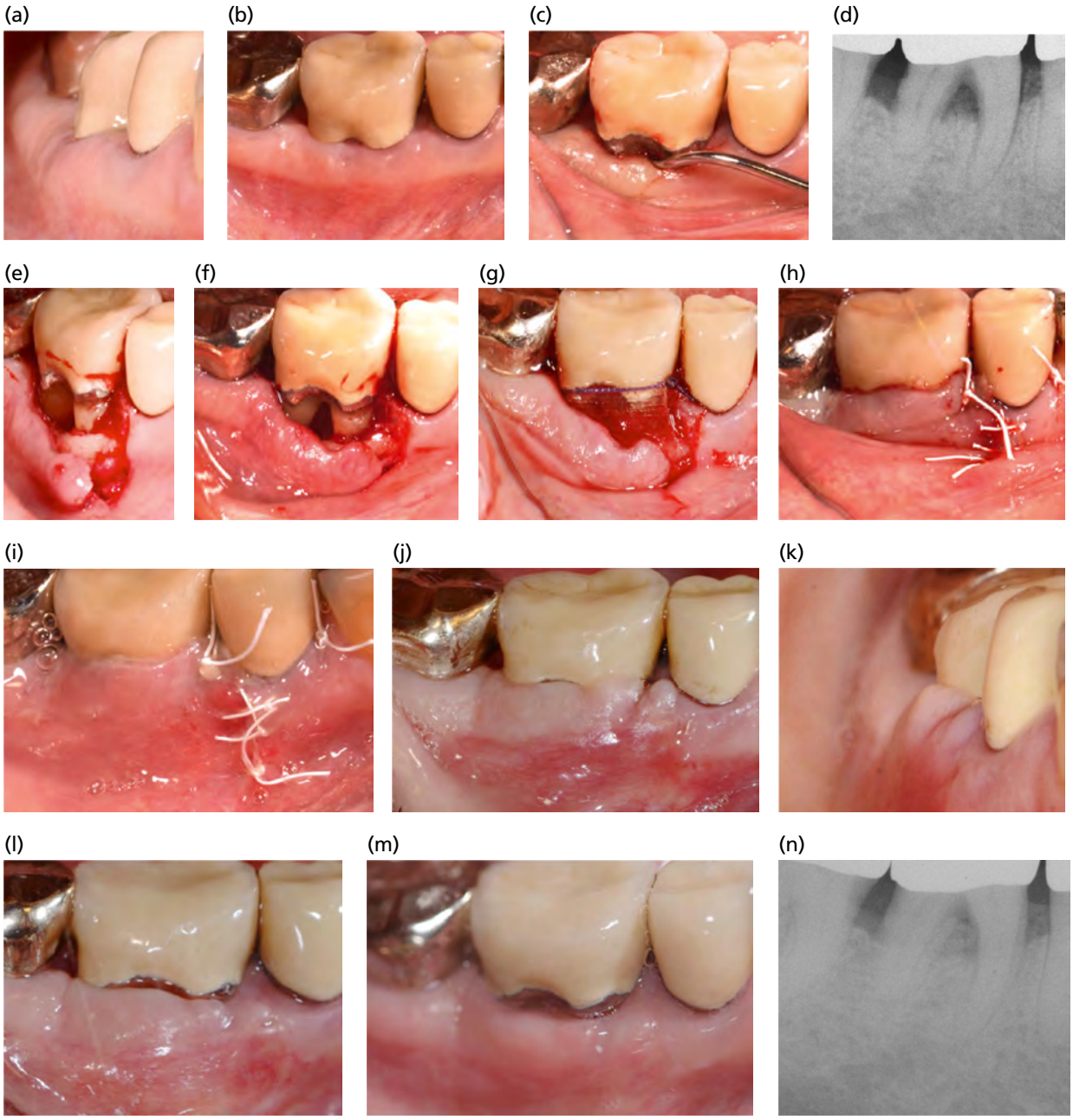

Fig. 33-20 (a, b) Periodontal measurements at baseline tooth 46. Probing depth mesial and distal: 3 mm, furcation class II. Situation 2 months after an acute abscess and mobility grade 2 treated with debridement of the accessible root surfaces and local antimicrobials. (c) Radiograph of tooth 46 with visible furcation defect, proximal bone loss to the level of the furcation and a very short distal root. (d) Horizontal probing bone level = 7 mm, crown margin reduced and polished. (e, f) Debrided root surfaces. Flap design: intrasulcular incision/vertical release mesial, mucoperiostal flap, papilla mesial de-epithelialized, periosteal split in the vestibule. The distal papilla was was left intact, but mobilized and slightly elevated by a tunneling procedure. (g) Placement of a bioresorbable matrix barrier (Guidor™ MSL-configuration) after application of a xenogeneic bone mineral into the furcation defect (Bio-Oss collagen®, Geistlich, Wolhusen, Switzerland) to facilitate guided tissue regeneration. (h) Coronally advanced minimally rotated flap secured with sling and interrupted sutures. (i) Clinical view 1 day after periodontal-regenerative surgery. (j, k) Clinical view 2 weeks after surgery. (l) Clinical view 3 months after surgery. (m) Nine months: vertical and horizontal probing depths: 2 mm. (n) Nine months: radiographic fill of the furcation defect. (Source: Jepsen & Jepsen 2018.)

Decision making (clinical recommendations) in the surgical treatment of class II and III furcation defects (Sanz et al. 2020)

- FI is no reason for tooth extraction.
- It is recommended that molars with class II and III FI and residual pockets after initial non-surgical therapy receive further periodontal therapy.
- It is recommended that mandibular molars with residual pockets associated with class II FI are treated with periodontal regenerative surgery.
- It is suggested that molars with residual pockets associated with maxillary buccal class II FI are treated with periodontal regenerative surgery.
- It is recommended that molars with residual pockets associated with mandibular and maxil-

lary class II FI are treated with periodontal regenerative surgery using EMD alone or bone-derived graft with or without resorbable membranes (Fig. 33-21).

- In maxillary interdental class II FI, non-surgical instrumentation, OFD, periodontal regeneration, root separation, or root resection may be considered.
- In maxillary class III and multiple class II FI in the same tooth, non-surgical instrumentation, OFD, tunneling, root separation, or root resection may be considered.
- In mandibular class III and multiple class II FI in the same tooth, non-surgical instrumentation, OFD, tunneling, root separation, or root resection may be considered (Fig. 33-22).

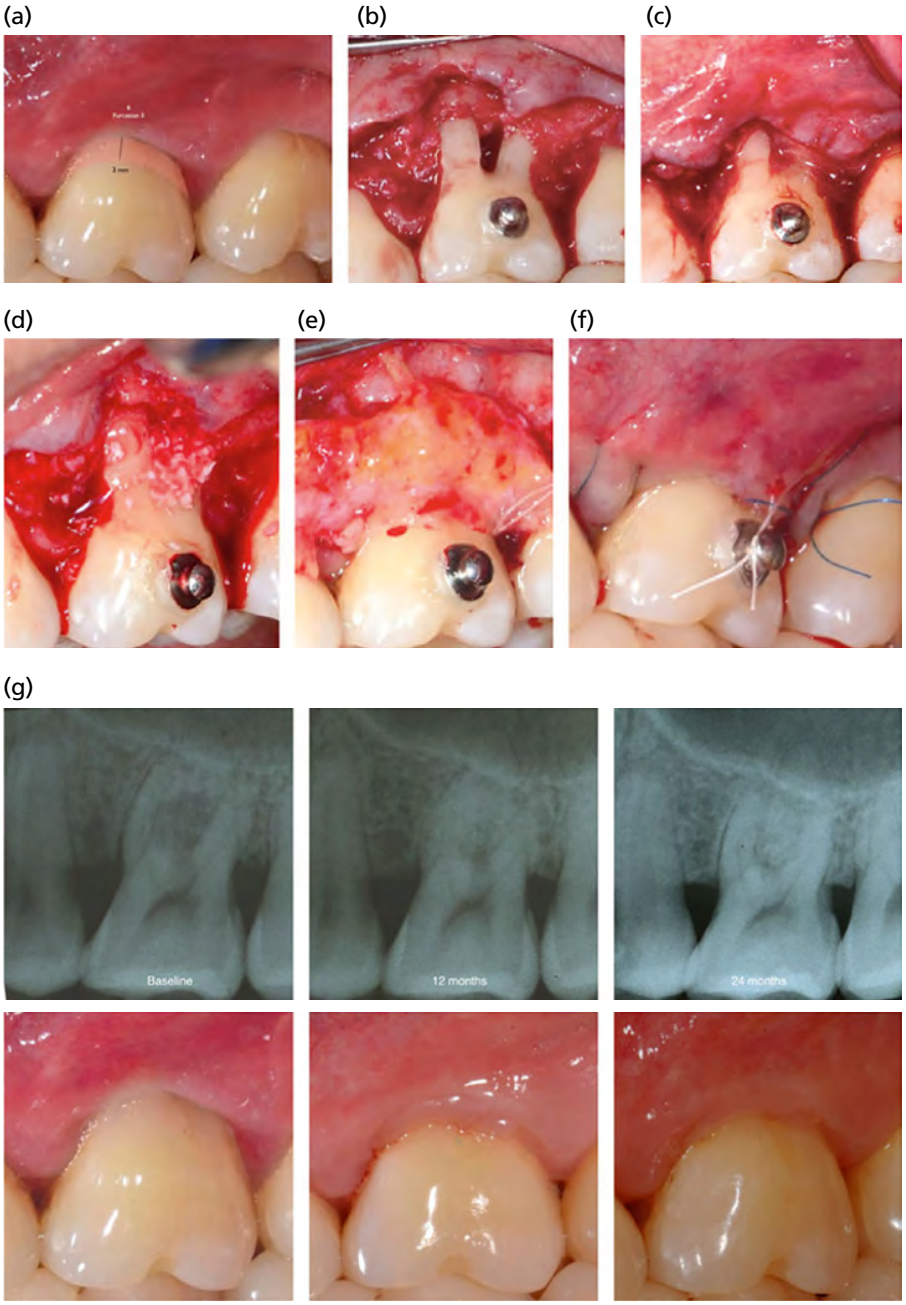

Fig. 33-21 (a) Periodontal measurements at baseline tooth 26. Recession: buccal to the cemento–enamel junction: 3 mm. Probing depth mesial = 2 mm, furcation class II; probing depth buccal = 6 mm; probing depth distal = 4 mm. Note minimal keratinized tissue at the furcation site. (b) Intraoperative view. Furcation class II (horizontal probing bone level = 6 mm), debrided root surface and cervical enamel projections removed. Placement of an orthodontic button to facilitate crown-attached sutures. Flap design: intrasulcular incision/no vertical release, mucoperiostal flap, papillae de-epithelialized, periosteal split in the vestibule. (c) Application of enamel matrix derivative after root surface conditioning with 24% EDTA for removal of the smear layer. (d) Application of xenogeneic bone mineral into the furcation defect. (e) Connective tissue graft from the palate placed onto the root surface and over the furcation area, secured by resorbable sling sutures. (f) Coronally advanced flap secured with crown-attached sutures. (g) Clinical and radiographic view at baseline, and 12 and 24 months after periodontal regenerative surgery. Complete resolution of the furcation defect and recession coverage. (Source: Sanz et al. 2015.)

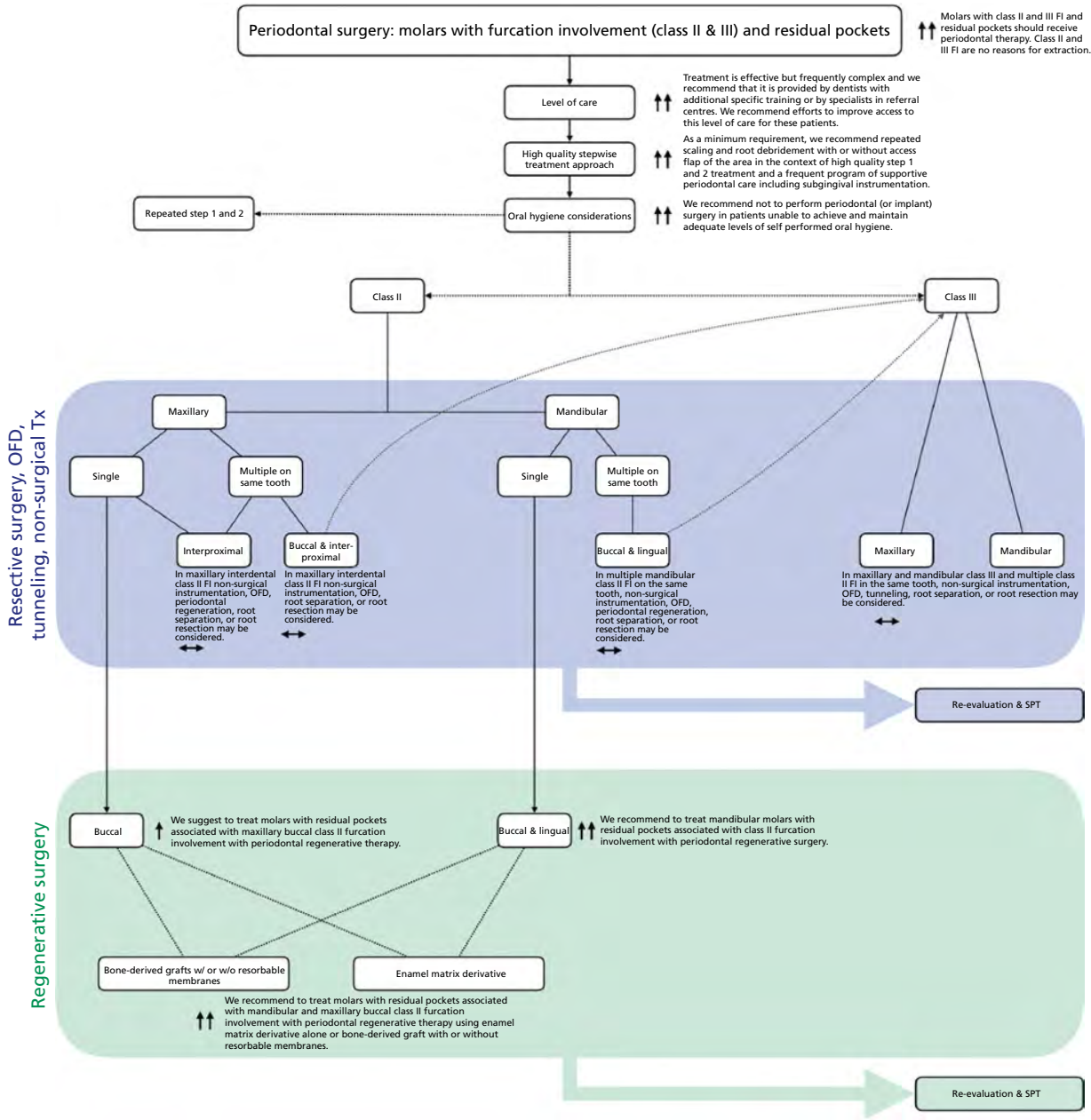

Fig. 33-22 Periodontal surgery: molars with furcation involvement class II and III and residual pockets – a decision algorithm. OFD, open-flap debridement; SPT, supportive periodontal treatment; Tx, treatment. (Source: Sanz *et al*. 2020.)

Long-term maintenance of teeth with furcation involvement

Having covered the different treatment options for molars with FI, it is important to know what to expect from these teeth long-term. Previous chapters have described how long-term longitudinal studies in periodontitis cohorts with SPT reported tooth loss of approximately 0.10 (Hirschfeld & Wasserman 1978), 0.13 (McGuire & Nunn 1986), 0.15 (Eickholz *et al*. 2008), 0.18 (McFall 1982), and up to 0.30 teeth per patient per year (Tsami *et al*. 2009). The classic study by Hirschfeld and Wasserman was perhaps the first to provide some evidence in this field. Following 600 patients during SPT for at least 15 years retrospectively (average 22 years), the authors identified three different groups of patients based on progression pattern: 'well-maintained' (the great majority), 'downhill', and 'extreme downhill'. Of 1464 teeth with FI at baseline, 460 were lost (240 of them by one-sixth of the patients who deteriorated most). Grouping together longitudinal human studies with a follow-up of at least 3 years in patients with chronic periodontitis presenting data on furcation diagnosis and tooth loss, a systematic review identified 14 papers which could be grouped together for meta-analysis (Nibali *et al*. 2016). All these studies included 'active' periodontal therapy (often including different types of surgical procedures), followed by SPT. A total of 8143 molars without FI and a total of 5772 molars with FI were included. Tooth survival ranged from 43% to 100% in the different studies and among teeth reported in these studies, the average

tooth loss/patient/year was 0.1 and 0.2 respectively for molars without and with FI (relative risk [RR] of tooth loss = 2.90, 95% CI = 2.01–4.18). Periodontal progression, endodontic complications, caries, and fractures were reported as main causes of tooth loss (Kuhrau *et al*. 1990; Haney *et al*. 1997; Yukna & Yukna 1997; McLeod *et al*. 1998; Dannewitz *et al*. 2006). The RR of tooth loss increased in parallel with follow-up time, ranging from 1.46 (95% CI = 0.99–2.15, $P = 0.06$) for studies with 5–10 years follow-up, 2.21 (95% CI = 1.79–2.74, $P < 0.0001$) for studies with 10–15 years follow-up and 4.46 (95% CI = 2.62–7.62, $P < 0.0001$) in studies with >15 years follow-up (Nibali *et al*. 2016). With the same gradient effect observed in populations without regular periodontal treatment (Nibali *et al*. 2017), 8%, 18%, and 30% of the total of teeth with furcation class I, II and III respectively were lost in the follow-up period. This resulted in a combined RR of tooth loss of:

- 1.67 (95% CI = 1.14–2.43, $P = 0.008$) for FI class II versus class I
- 1.83 (95% CI = 1.37–2.45, $P < 0.0001$) for FI class III versus class II
- 3.13 (95% CI=2.30–4.24, $P < 0.0001$) for FI class III versus class I.

Tooth loss by vertical furcation component

Retrospective analysis of 200 molars followed up for 10 years of supportive therapy after conservative periodontal surgery with limited osseous surgery showed that vertical furcation subclassification with a modification of the classification proposed by Tarnow and Fletcher (1984) was associated with a higher incidence of tooth loss for class II FI with bone loss up to the coronal third, middle third, or apical third of the root (respectively 9%, 33%, and 77% tooth loss at 10 years). In agreement with this study, similar results were observed in another retrospective cohort of 200 patients with chronic periodontitis (Tonetti *et al*. 2017), where both the horizontal and the vertical furcation components were associated with increased risk of tooth loss during SPT in a multivariable model (Nibali *et al*. 2018; Tonetti *et al*. 2017).

Although it is not possible to completely disentangle the relative contribution of PPD or bleeding on probing to tooth loss from the mere presence of FI, it is clear that FI at least doubles the risk of long-term tooth loss, and probably more when no regular periodontal treatment is carried out. This clearly highlights the importance of improving our efficacy for the treatment of FI-involved teeth. One could assume that, with improvements in regenerative treatment of FI, these figures could potentially improve in the future. However, it is already clear that in patients undergoing comprehensive periodontal treatment, most molars affected by FI respond well to periodontal treatment. It is important to highlight that, even in the presence of class III FI, only 30% of molars were lost with up to 15 years of follow-up in reviewed studies (Nibali *et al*. 2016). The importance of strict SPT for the survival of teeth affected by FI, as for periodontitis cases in general, is paramount (Pretzl *et al*. 2008; Nibali *et al*. 2019). Therefore, although data need to be gathered on other important outcomes such as oral-health related quality of life or systemic inflammation, treatment of teeth affected by FI needs to be considered an important part of periodontal care.

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Chapter 34

Non-Surgical Therapy of Peri-Implant Mucositis and Peri-Implantitis

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Introduction

Peri-implant diseases are inflammatory conditions of the tissues surrounding implants, caused by an imbalance between the peri-implant biofilm and the host response to the biofilm, resulting in dysbiosis and tissue destruction. Chapter 20 describes the histopathologic features of peri-implant mucositis and peri-implantitis, while Chapter 9 outlines the nature of peri-implant biofilms in health and disease.

Peri-implant mucositis is a reversible plaque-associated inflammatory condition of the soft tissues surrounding the implant (Salvi *et al*. 2012; Schwarz *et al*. 2018a). Clinical signs of peri-implant mucositis are bleeding on gentle probing (BoP) without loss of supporting bone. Redness and swelling of the peri-implant mucosa and increased probing depths (PDs), as compared to previous measurements, may also be observed (Heitz-Mayfield & Salvi 2018) (Fig. 34.1).

Peri-implantitis is a plaque-associated pathologic condition characterized by inflammation of the soft tissues surrounding the implant and progressive bone loss (Berglundh *et al*. 2018a). Clinical signs of peri-implantitis are BoP and radiographic bone loss in comparison to previous bone levels. Redness, swelling, suppuration, and deep PDs (≥6 mm) are commonly observed at implants diagnosed with peri-implantitis (Berglundh *et al*. 2018a,b; Schwarz *et al*. 2018b) (Fig. 34.2).

Peri-implant diseases are common conditions with an estimated patient prevalence of 43% (CI: 32%–54%) for peri-implant mucositis and 22% (CI:14%–30%) for peri-implantitis (Derks & Tomasi 2015). Peri-implant mucositis is considered to be the precursor to peri-implantitis, and non-surgical treatment of peri-implant mucositis is a prerequisite for the prevention of peri-implantitis (Jepsen *et al*. 2015). If left untreated peri-implantitis may lead to implant loss. Therefore, effective measures to treat peri-implant diseases have been a focus of attention in recent years.

It is essential that the clinician regularly monitors the peri-implant tissues, by peri-implant probing, and provides treatment of peri-implant disease at an early stage using non-surgical therapy. Distinguishing

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

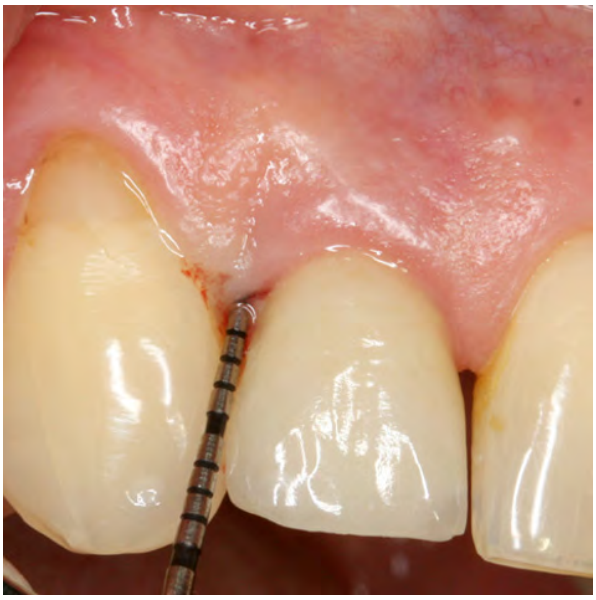

Fig 34.1 Peri-implant mucositis. Clinical signs of peri-implant mucositis with presence of bleeding on gentle probing with an increased probing depth (5 mm) compared with a previous examination. There was no loss of supporting bone.

between peri-implant mucositis and incipient peri-implantitis may be challenging. This is in part due to difficulties in evaluating radiographic bone levels at implants related to angulation and measurement error, further emphasizing the importance of regular monitoring and early intervention. Effective measures to treat peri-implant diseases require an anti-infective approach by supra- and submucosal biofilm removal with the goal of resolving inflammation and preventing disease progression.

Successful treatment of peri-implant mucositis is defined as resolution of inflammation assessed by the absence of BoP. Successful treatment of peri-implantitis is defined using composite success criteria, for example peri-implant PD of ≤5 mm, absence of bleeding or suppuration on probing, and no additional bone loss.

If peri-implant disease is detected at an early stage, non-surgical therapy may result in a successful outcome. Whereas surgical intervention is usually required for treatment of advanced peri-implantitis (see Chapter 35), non-surgical therapy should always be the first stage of treatment and includes professional biofilm removal and oral hygiene instruction (Jepsen *et al*. 2019).

Non-surgical treatment strategies include various methods of professional biofilm removal such as debridement using hand or ultrasonic instruments, air-polishing (biofilm removal using a mixture of compressed air, water, and a fine abrasive powder), or laser irradiation. Adjunctive measures such as antimicrobial photodynamic therapy (use of low-powered laser irradiation with a photosensitizer), delivery of local antimicrobial agents, or prescription of probiotics may also be used, albeit with no additional benefit. Implant surface, material, and topography may influence biofilm formation and the choice of decontamination method. This chapter outlines anti-infective non-surgical treatment strategies for peri-implant mucositis and peri-implantitis (Fig. 34.3).

Non-surgical therapy of peri-implant mucositis

Following a comprehensive examination and diagnosis, an assessment and appropriate management of modifiable risk factors/indicators (such as cigarette smoking, periodontitis, uncontrolled diabetes mellitus) should precede treatment. Figure 34.3a outlines

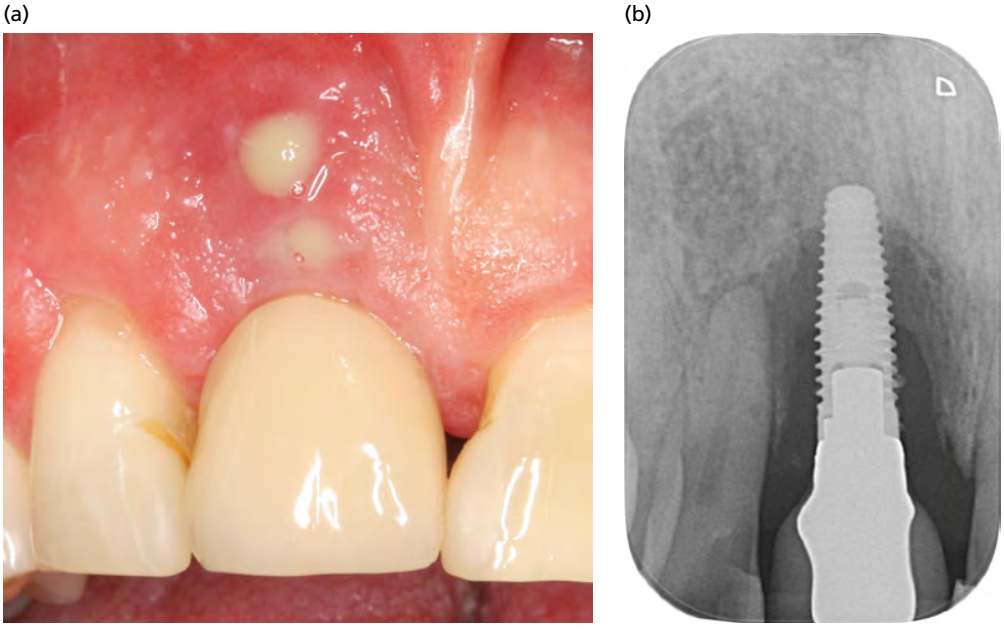

Fig 34.2 (a) Peri-implantitis. Clinical signs of peri-implantitis with suppuration on probing in addition to the presence of a draining sinus on the buccal peri-implant mucosa. Deep probing depths >8 mm. (b) A periapical radiograph of the implant shows advanced peri-implant bone loss to within 2 mm of the apex of the implant.

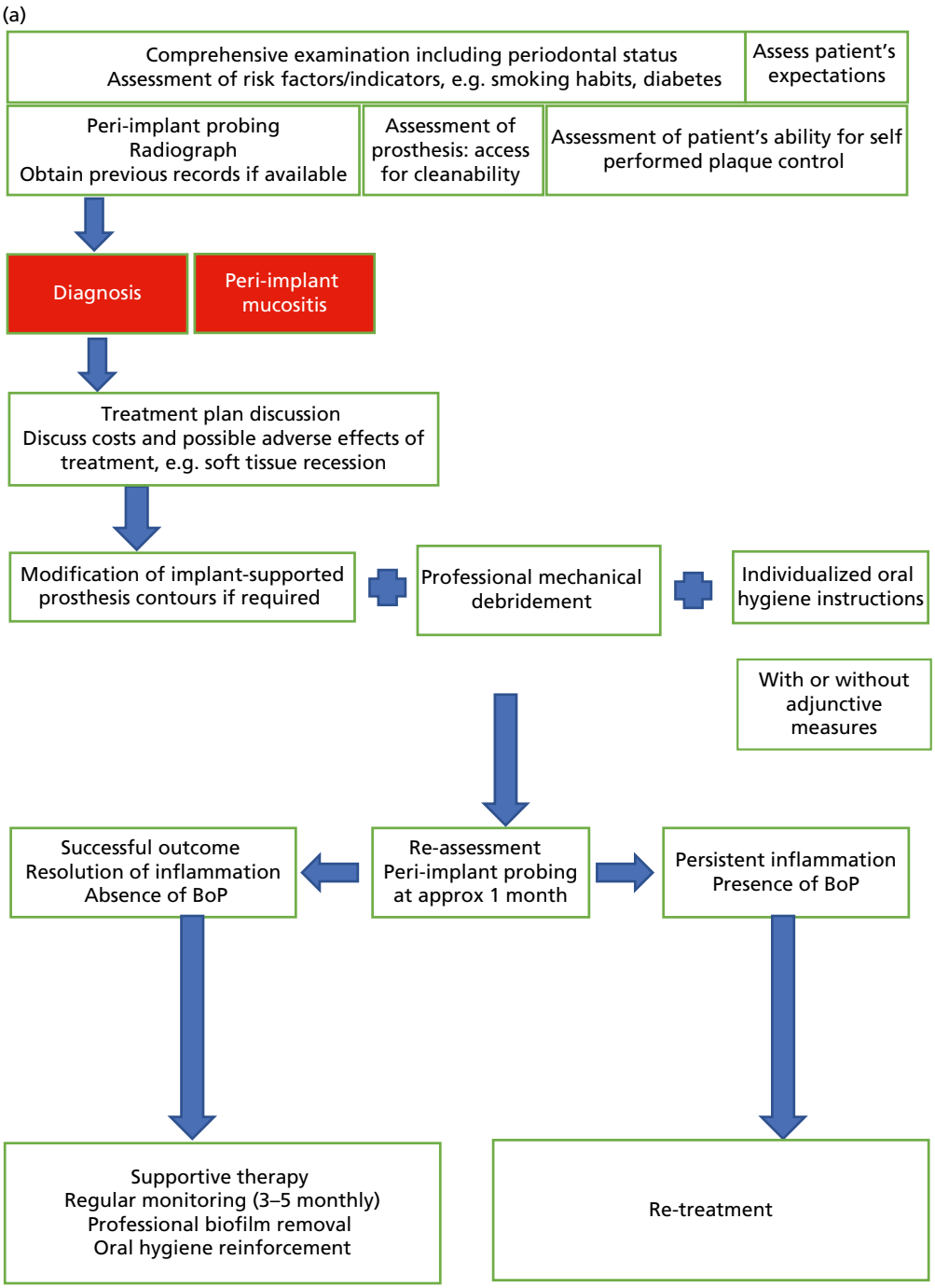

Fig 34.3 (a) Flow-chart outlining the recommended non-surgical treatment sequence for management of peri-implant mucositis.

the steps involved and treatment options available for non-surgical therapy of peri-implant mucositis.

Assessment of the implant-supported prosthesis

The contours of the implant-supported prosthesis and the position of the restoration margin relative to the peri-implant mucosal margin play an important role in the outcome of peri-implant mucositis treatment.

The prosthesis design and access for cleanability as well as the patient's ability for self-performed plaque control should be carefully assessed as part of the non-surgical phase of therapy. Modification of the contours of the prosthesis to allow adequate access for use of oral hygiene aids has been shown to improve treatment outcomes following mechanical non-surgical treatment of peri-implant mucositis (de Tapia *et al*. 2019). Furthermore, improved treatment outcomes at implants with supramucosal restorative margins have been shown following non-surgical treatment of peri-implant mucositis (Heitz-Mayfield *et al*. 2011; Chan *et al*. 2019).

Hence a careful assessment of the contours of the prosthesis and the access for biofilm removal and peri-implant monitoring is important. Modification of the prosthesis may require minor adjustments or may involve redesigning and remaking the prosthesis to eliminate plaque retentive factors and facilitate access for oral hygiene measures (Fig. 34.4). The fit of

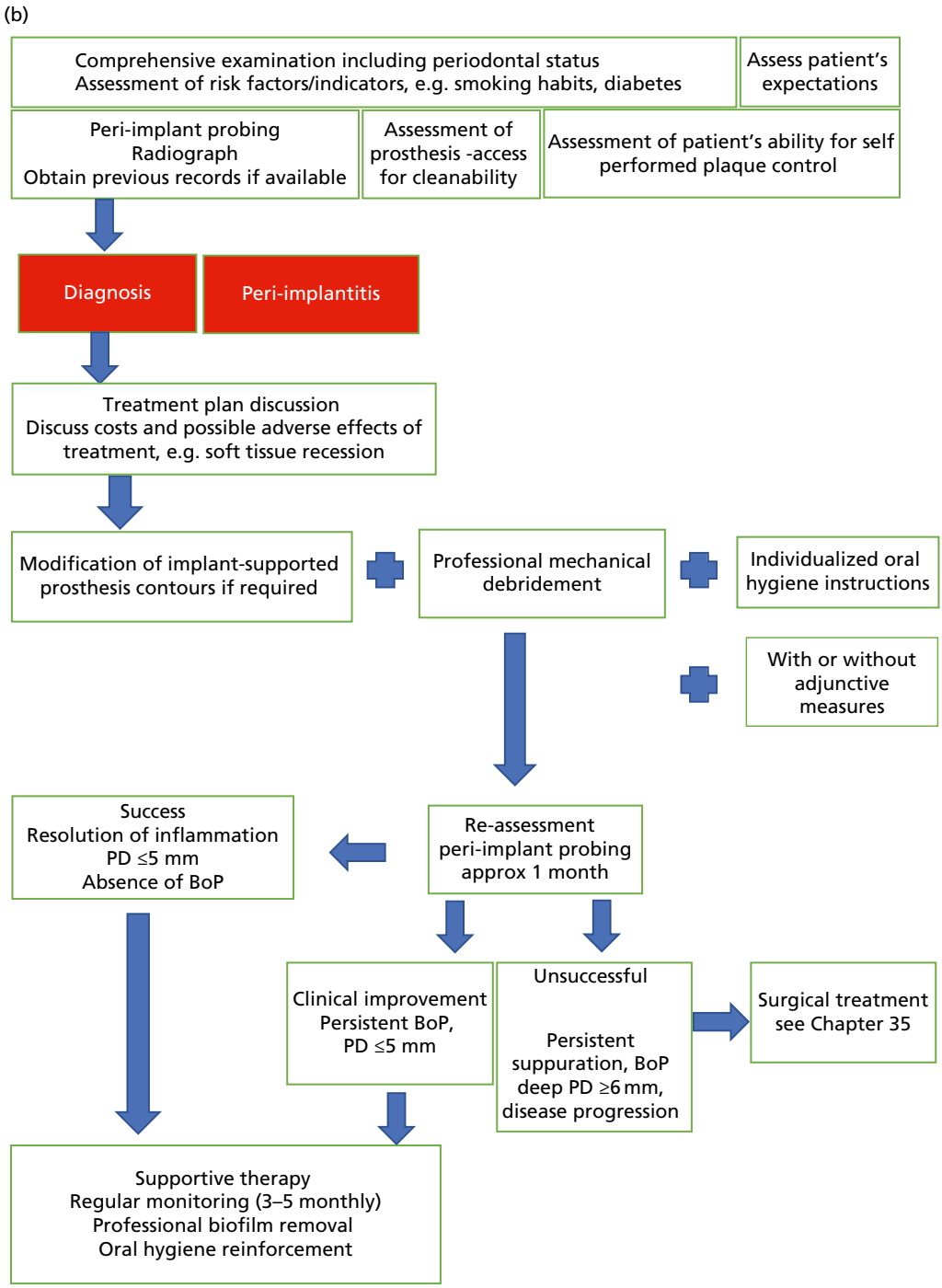

Fig 34.3 (Continued) (b) Flow-chart outlining the recommended non-surgical treatment sequence for management of peri-implantitis.

the implant-supported prosthesis and the tightness of the retention screws should also be assessed for integrity as poor fit or screws with inadequate torque may increase biofilm accumulation.

Cemented prostheses should also be carefully assessed for the presence of excess luting cement which is a risk indicator for peri-implant mucositis (Jepsen *et al*. 2015). Where presence of submucosal luting cement is detected it should be removed.

Oral hygiene measures for self-performed biofilm removal

Oral hygiene measures using either manual or powered toothbrushes are effective for self-performed biofilm removal at implant-supported prostheses (Salvi & Ramseier 2015; Allocca *et al*. 2018). Various interproximal brushes have also been evaluated and found to be effective (Chongcharoen *et al*. 2012). Selection of the appropriate oral hygiene aids, including the use of dental floss or interproximal brushes, should be tailored to suit the aptitude of each individual patient (Fig. 34.5).

Where there is minimal (<2 mm) or lack of keratinized attached peri-implant mucosa patients may have difficulty in performing oral hygiene due to discomfort when brushing (Fig. 34.6), and more frequent supportive care, or augmentation of the keratinized peri-implant mucosa, may be considered (Roccuzzo *et al*. 2016).

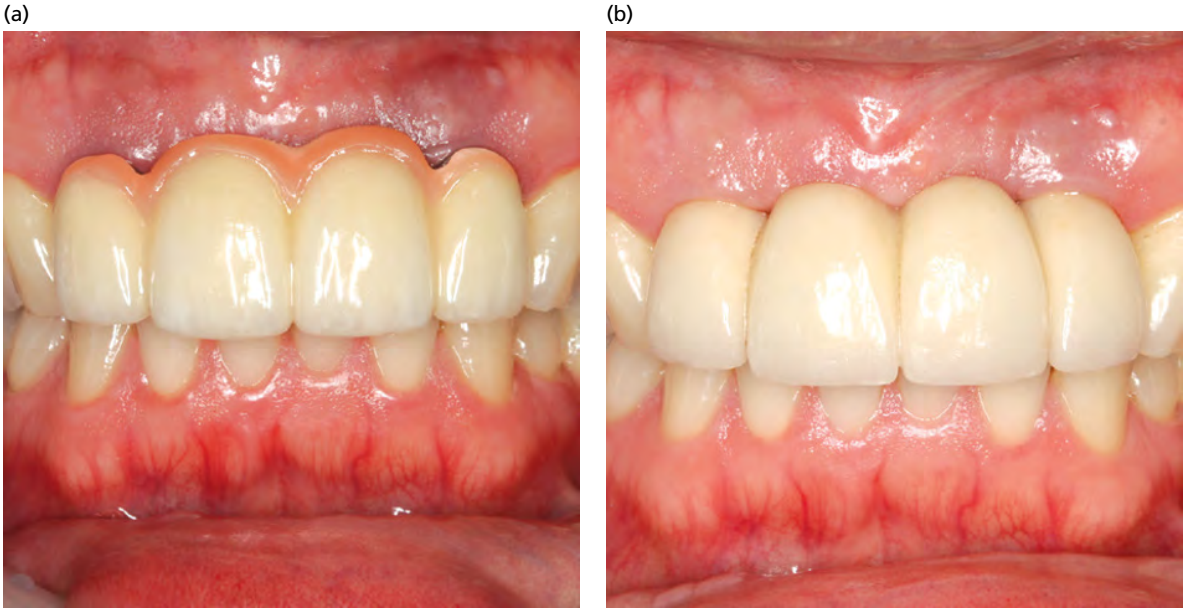

Fig 34.4 (a) Implant-supported prosthesis with inadequate access for cleanability of the implants. The labial flange of the prosthesis prevents access for biofilm removal and monitoring of the implants in position 12 and 22. (b) The implant-supported prosthesis was re-designed and remade without a labial flange to allow good access for cleanability and monitoring at the implants in position 12 and 22.

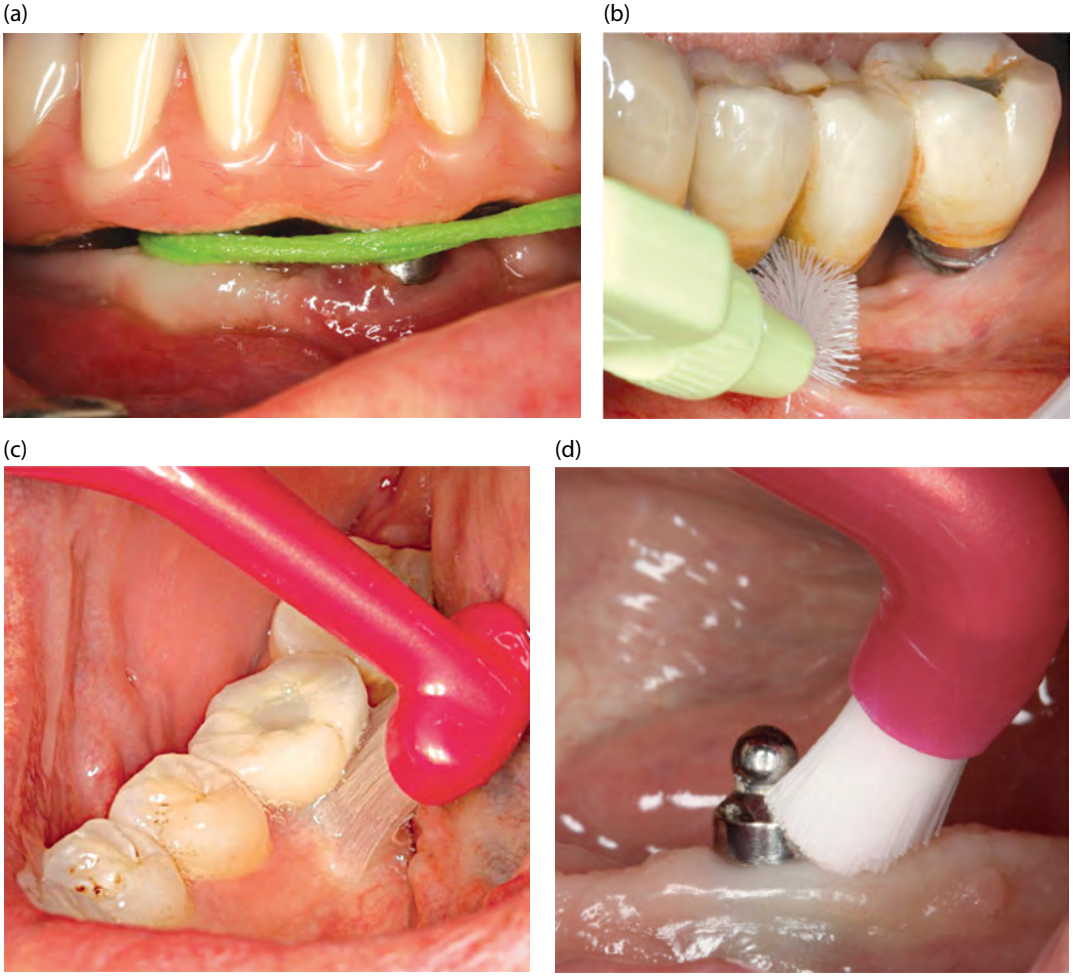

Fig. 34.5 (a) An example of dental floss used for self-performed oral hygiene at the implant-supported prosthesis. The floss is passed interproximally and used to remove biofilm deposits. (b) An example of an interproximal brush used for self-performed oral hygiene to remove biofilm at the implant. (c) An example of an angulated head toothbrush used for improved lingual access for self-performed oral hygiene to remove biofilm at the implant-prosthesis. (d) An example of a single-tuft toothbrush used for self-performed oral hygiene to remove biofilm at an implant overdenture abutment.

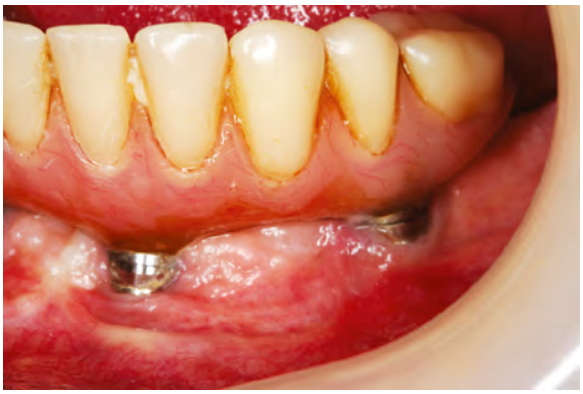

Fig. 34.6 Clinical image of two implants with minimal keratinized attached peri-implant mucosa. The patient experiences discomfort when performing oral hygiene measures at this implant.

Professional mechanical debridement (supra- and submucosal calculus and biofilm removal)

Hand instrumentation

Hand instrumentation including the use of steel, titanium, carbon-fiber or plastic curettes, and/or ultrasonic instruments with a variety of tips may be used for removal of supra- and submucosal calculus and biofilm deposits (Fig. 34.7a). Instruments which cause minimal alteration to the surface of the transmucosal components of the implant/restoration should be used. Prophylaxis using a rubber cup and polishing paste may also be used for supramucosal biofilm removal (Fig. 34.7b).

Air-polishing

Air-polishing is an alternative to hand or ultrasonic instrumentation for supra- and submucosal biofilm removal at titanium implants (Tastepe *et al*. 2012). The powders used mainly consist of either amino acid glycine, sodium bicarbonate, or erythritol and are effective in biofilm removal from machined or structured titanium and zirconia implants without causing major surface changes (Schwarz *et al*. 2009b; John *et al*. 2016) (Fig. 34.8).

A systematic review, including five studies, found that glycine powder air-polishing used as either an adjunct to hand instrumentation or as a monotherapy was as effective as hand instrumentation for peri-implant mucositis treatment (Schwarz et al. 2015a).

Adjunctive measures for peri-implant mucositis treatment

Adjunctive measures including application of local antimicrobials, diode laser irradiation, photodynamic therapy, and probiotics have been investigated. However, adjunctive measures have not been found to improve the efficacy of professionally administered mechanical biofilm removal in resolving inflammation (Table 34-1).

Adjunctive local antimicrobials/antiseptics

There is conflicting evidence regarding an additional benefit of local antimicrobials/antiseptics for peri-implant mucositis treatment. In patients diagnosed with peri-implant mucositis, delivery of 0.12% chlorhexidine gluconate solution into peri-implant pockets, after mechanical debridement using plastic curettes, was compared with the submucosal delivery of placebo solution (Menezes *et al*. 2016). In addition, the patients were prescribed a twice daily mouth rinse with a chlorhexidine or placebo solution for 2 weeks (Menezes *et al*. 2016). At the 6-month follow-up, no statistically significant difference in the number

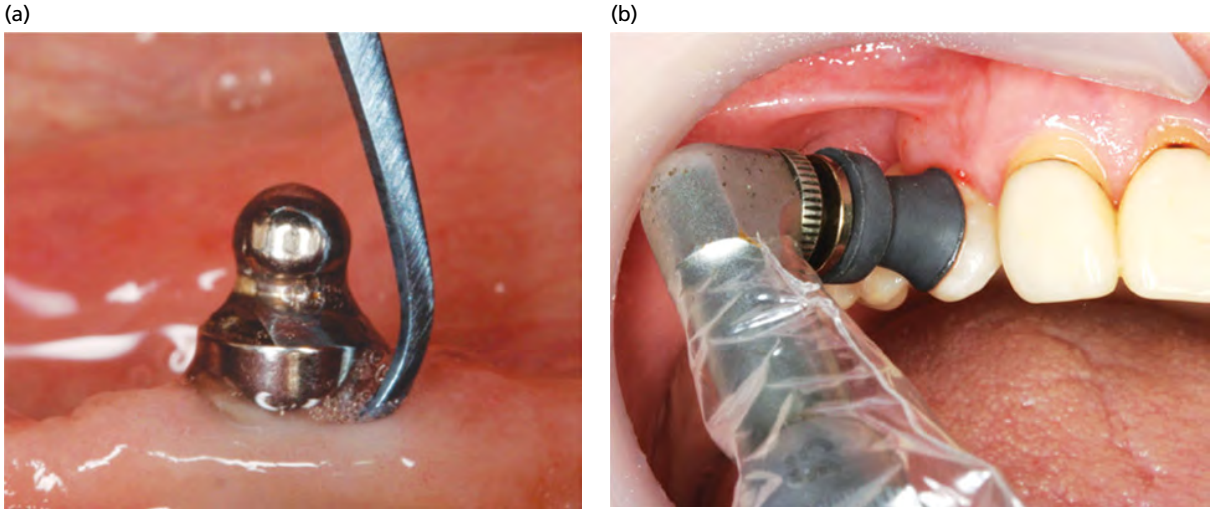

Fig. 34.7 (a) A titanium curette used to remove supra-and submucosal biofilm at an implant overdenture abutment. (b) Prophylaxis using a rubber cup and polishing paste for biofilm removal in the non-surgical treatment of peri-implant mucositis.

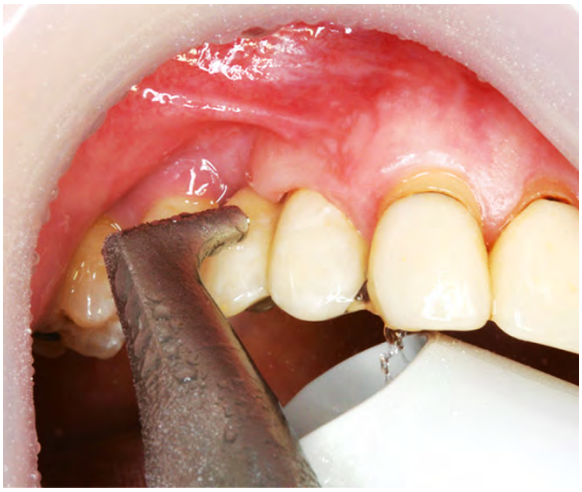

Fig. 34.8 An air-polishing device used for supra- and submucosal biofilm removal for non-surgical treatment of peri-implant mucositis.

of BoP-positive implant sites was found between the antiseptic and placebo groups (Menezes *et al*. 2016).

Heitz-Mayfield *et al*. (2011) reported in a study treating 29 peri-implant mucositis patients that non-surgical debridement using titanium curettes and self-performed plaque control was effective in treating peri-implant mucositis and that the adjunctive application of chlorhexidine digluconate gel, applied daily using a toothbrush, did not enhance treatment outcomes. At 3 months, 38% of implants treated had complete disease resolution (absence of BoP) (Heitz-Mayfield *et al*. 2011) (Table 34-1).

In contrast, Hallström *et al*. (2017) reported an additional improvement in treatment outcomes when adjunctive 0.2% chlorhexidine-containing gel was applied daily with a toothbrush. The effects of daily application of a 0.2% chlorhexidine-containing gel as a supplement to oral hygiene instructions and mechanical debridement were investigated in a 12-week randomized control trial in patients diagnosed with peri-implant mucositis (Hallström *et al*. 2017). The daily use of the chlorhexidine-containing gel resulted in statistically significantly lower BoP scores and less residual PD of ≥4 mm after 4 and 12 weeks compared with the application of a placebo gel (Hallström *et al*. 2017).

The clinical effects of a mouth-rinse containing 0.03% chlorhexidine and 0.05% cetylpyridinium chloride as an adjunct to professionally and patient-administered mechanical plaque removal was assessed in the management of peri-implant mucositis over 12 months (Pulcini *et al*. 2019). At the 12-month follow-up, twice daily rinsing with the antiseptic solution was not more effective compared with rinsing with a placebo solution. Complete resolution of BoP-positive sites was achieved in 58% of cases following rinsing with the antiseptic solution and 50% of cases following rinsing with placebo (Pulcini *et al*. 2019).

The application of a chloramine-containing gel was investigated as an adjunct to mechanical debridement in the management of patients diagnosed with peri-implant mucositis (Iorio-Siciliano *et al*. 2020). The chloramine-containing gel was applied to the implants of the test group while the control group received a placebo gel. The gels were applied five times for 30 seconds prior to mechanical ultrasonic debridement. The 6-month outcomes of this randomized clinical trial failed to show statistically significant differences in PDs and BoP scores when comparing test and control groups. Complete elimination of sites with BoP was achieved in 45% of test and 32% of control implants at 6 months (Iorio-Siciliano *et al*. 2020) (Table 34-1).

Table 34-1 Studies reporting disease resolution (absence of bleeding on probing) following treatment of peri-implant mucositis.

Author	Treatment	Study design	*n*	Follow-up	Disease resolution (absence BoP)	Comments
Heitz-Mayfield 2011	MD +/- CHX gel	RCT	29 patients	3 months	38% implants/patients	No added benefit of CHX
Schwarz 2015c	MD + CHX	Case series	17 patients 24 implants	6 months	5 of 17 patients 53% patients	Zirconia implants
John *et al*. 2017 (same as Schwarz 2015c)	MD + CHX	Case series	14 patients	Median 34 months	7 of 14 patients 50% patients	Two-piece zirconium implants
Pulcini *et al*. 2019	MD + CHX-CET MD	RCT	24 patients 22 patients	12 months	58.3% implants 50% implants	Some advantage of CHX/CET at buccal sites only
Iorio-Siciliano *et al*. 2020	MD + chloramine MD + placebo	RCT	46 patients 68 implants	6 months	45% implants 32% implants	No significant difference between groups
Aimetti 2019	MD + diode laser MD	RCT	110 patients 110 implants	3 months	35% implants 31% implants	No advantage of diode laser

BoP, bleeding on probing; CET, cetylpyridinium chloride; CHX, chlorhexidine; MD, mechanical debridement; RCT, randomized controlled trial.

Adjunctive probiotics

It has been suggested that daily oral administration of probiotic bacteria may support the formation of bacterial biofilms compatible with peri-implant health and therefore improve clinical, microbiological, and host-derived parameters when administered as adjuncts to non-surgical mechanical therapy of peri-implant mucositis. There is conflicting evidence regarding the clinical benefit of adjunctive probiotic treatment. Flichy-Fernández *et al*. (2015) reported positive effects following prophylaxis and daily oral probiotic containing *Lactobacillus reuteri* for 30 days at implants diagnosed with peri-implant mucositis. Daily oral probiotics showed an additional PD reduction of 1.09 ± 0.90 mm compared with adjunctive delivery of placebo tablets at 6 months (Flichy-Fernández *et al*. 2015). These results, however, should be interpreted with caution due to the fact that parameters reflecting changes in mucosal inflammation (i.e. BoP) were not reported.

In another study, *L. reuteri* administered for 30 days in conjunction with full-mouth mechanical debridement showed an improvement in clinical parameters at implants diagnosed with mucositis or peri-implantitis for up to 90 days (Galofre *et al*. 2018). Delivery of *L. reuteri*, however, yielded a significant decrease in the bacterial load of *Porphyromonas gingivalis* only at implants with peri-implant mucositis (Galofre *et al*. 2018).

However, outcomes from randomised controlled trials (Hallström *et al*. 2016, Pena *et al*. 2019), failed to demonstrate beneficial effects of adjunctive probiotics in the management of peri-implant mucositis. Therefore the available evidence for use of adjunctive probiotics is limited and inconclusive.

Adjunctive laser irradiation

The adjunctive use of diode (980 nm) laser irradiation for peri-implant mucositis treatment was investigated in a randomized controlled study including 220 patients, each with one implant diagnosed with peri-implant mucositis. Three months following treatment of peri-implant mucositis disease resolution (absence of BoP) was observed at 31% of the implants treated with mechanical debridement alone and 34% of implants treated by the laser in conjunction with mechanical debridement (Aimetti *et al*. 2019) (Table 34-1). Therefore, the diode laser treatment was not shown to provide any additional benefit compared with mechanical debridement (curettes and ultrasonic devices) alone.

Adjunctive antimicrobial photodynamic therapy (aPDT)

A randomized controlled trial in 54 patients who smoked with peri-implant mucositis found that antimicrobial photodynamic therapy as an adjunct to mechanical therapy resulted in additional clinical benefits, 3 months after treatment, in terms of PD reduction compared with mechanical debridement alone (Javed *et al*. 2017). The number of sites with residual BoP, however, was similar between treatment groups indicating that adjunctive aPDT has a limited benefit.

Adjunctive systemic antimicrobials

Adjunctive systemic antimicrobials are not recommended for the treatment of peri-implant mucositis because they do not provide additional clinical benefits and there is a risk of adverse effects (Hallström *et al*. 2012).

Zirconia implants

Most studies evaluating treatment of peri-implant mucositis have included titanium implants. There is limited data available regarding treatment of peri-implant mucositis at zirconia implants. One case series including 17 patients with zirconia implants diagnosed with peri-implant mucositis which were treated with mechanical debridement and local chlorhexidine application found that nine of the 17 (52.9%) patients achieved disease resolution (absence of BoP) 6 months following treatment (Schwarz *et al*. 2015c).

Conclusion

Adjunctive measures to mechanical debridement have not been found to improve the efficacy of professionally administered mechanical biofilm removal in peri-implant mucositis treatment (Schwarz *et al*. 2015b). Glycine powder air-polishing used as a monotherapy is as effective as hand instrumentation for peri-implant mucositis treatment (Schwarz et al. 2015a). Significant clinical improvements in terms of reduction in the number of sites with BoP and a reduction in PDs can be achieved following treatment of peri-implant mucositis. However, complete resolution of inflammation is not achieved in the majority of cases (Table 34-1). Therefore, regular monitoring and regular professional mechanical biofilm removal in addition to daily self-performed plaque control is considered the standard of care and should be performed to treat peri-implant mucositis and prevent progression to peri-implantitis (Fig. 34.3a).

Non-surgical therapy of peri-implantitis

Once a diagnosis of peri-implantitis has been made, treatment should proceed without delay.

In cases of incipient bone loss, non-surgical therapy may be successful in resolving peri-implantitis. However, where there is more advanced bone loss, while clinical improvements (PD and BoP reduction)

are frequently observed, non-surgical treatment alone is usually ineffective in resolving the inflammation and arresting disease progression in the majority of cases. The limitation of non-surgical treatment of peri-implantitis is related to the difficulty in accessing the implant surface due to the topography, presence of implant threads, and anatomy of the surrounding area. Surgical management (see Chapter 35) is recommended where deep PDs and bleeding and/or suppuration remain following non-surgical treatment. Non-surgical treatment should, however, be performed as a first treatment phase and prior to surgical management in order to reduce the level of inflammation and ensure that the patient's self-performed oral hygiene is optimized prior to surgery.

Non-surgical therapy of peri-implantitis (Fig. 34.3b) involves the same treatment sequence as for the treatment of peri-implant mucositis. Following a comprehensive examination and diagnosis an assessment and reduction of modifiable risk factors/indicators such as cigarette smoking, periodontitis, and uncontrolled diabetes mellitus should precede treatment. Treatment includes an assessment of cleanability and fit of the prosthesis and modification as required, followed by oral hygiene instructions and professional mechanical debridement to remove calculus and biofilm deposits. Re-evaluation at approximately 4–6 weeks following non-surgical treatment will enable the clinician to evaluate the response to treatment. Where clinical improvements are observed (reduction in PDs of ≤5 mm and resolution of BoP), the patient should be provided with a structured supportive care program which entails regular monitoring and professional removal of biofilm. If there is persistent inflammation (BoP/suppuration) with remaining deep PDs of ≥6 mm, surgical treatment (see Chapter 35) is recommended (Fig. 34.3b).

Professional mechanical debridement

Instrumentation including the use of steel, titanium, carbon-fiber, and/or ultrasonic instruments or Er:YAG laser irradiation may be used for removal of supra- and submucosal calculus and biofilm deposits. Air polishing may be used to remove non-mineralized deposits. Care should be taken when instrumenting deep peri-implant pockets, regardless of the method chosen, due to the inability to visualize the implant topography. Adjunctive measures include the use of local antimicrobials, antimicrobial photodynamic therapy, and probiotics. Cost-effectiveness and patient preference should be considered when choosing the method for non-surgical biofilm removal.

Laser irradiation

The Er:YAG (erbium-doped: yttrium, aluminium and garnet) laser is the most commonly investigated laser for peri-implantitis treatment. Its emission wavelength (2940 nm) is highly absorbed by water, allowing effective removal of non-mineralized and mineralized biofilms without damaging the implant surface or causing major thermal side effects to the adjacent tissues (Aoki *et al*. 2004) (Fig. 34.9).

The histological characteristics of wound healing following Er:YAG laser application for the non-surgical treatment of peri-implantitis have been evaluated in both experimental animal and clinical studies (Schwarz *et al*. 2009a). Non-surgical therapy using either Er:YAG laser, an ultrasonic device, or plastic curettes and local application of metronidazole gel was evaluated in an experimental animal study. After 3 months of healing, biopsies showed similar inflammatory cell infiltrates in all treatment groups with minimal re-osseointegration (new bone-to-implant contact) following non-surgical treatment (Schwarz *et al*. 2006c).

The observation that a single course of non-surgical instrumentation using an Er:YAG laser may not be effective in obtaining complete disease resolution was confirmed in a clinical study including a total of 12 patients each with one implant diagnosed with peri-implantitis (Schwarz *et al*. 2006b). Examination of tissue biopsies obtained following non-surgical treatment during subsequent open flap surgery at implant sites revealed a mixed chronic inflammatory cell infiltrate (macrophages, lymphocytes, and plasma cells) which was encapsulated by irregular bundles of fibrous connective tissue showing an increased proliferation of vascular structures (Schwarz *et al*. 2006b).

These results confirmed the findings of controlled clinical studies (Schwarz *et al*. 2005, 2006a) which compared Er:YAG laser monotherapy with mechanical debridement (plastic curettes + chlorhexidine digluconate irrigation) for the non-surgical treatment of moderate and advanced peri-implantitis lesions. After 3 and 6 months of healing, Er:YAG laser treatment revealed a significantly greater mean BoP reduction than the mechanical debridement using plastic curettes. However, at 12 months both treatment groups had a slight increase in BoP which was most pronounced at initially deep sites (PD >7 mm) (Schwarz *et al*. 2006a).

In conclusion, Er:YAG laser irradiation has not been shown to provide additional benefits in terms of disease resolution compared with mechanical debridement alone.

Air-polishing

Air-polishing using glycine powder, for removal of supra- and submucosal biofilm at implants diagnosed with peri-implantitis (Fig. 34.10), has been shown in a meta-analysis to provide a greater improvement in reduction of BoP (weighted mean BoP reduction of −23.83%; 95% CI [−47.47, −0.20]) compared with either mechanical debridement with or without local antiseptic therapy or to Er:YAG laser treatment (Schwarz *et al*. 2015a).

However, as complete disease resolution is infrequently obtained after therapy, a strict follow-up is

essential to determine the need for additional treatment (Schwarz *et al*. 2016).

Adjunctive antimicrobial photodynamic therapy (aPDT)

Adjunctive antimicrobial PDT in conjunction with mechanical debridement may represent an alternative treatment for peri-implantitis as clinical and microbiological improvements have been reported following treatment. In cases of incipient peri-implantitis (defined as PD of 4–6 mm with BoP and ≤2 mm bone loss), non-surgical mechanical debridement (titanium curettes and air-polishing with glycine powder) with adjunctive use of PDT resulted in similar clinical, microbiological, and host-derived outcomes as with the adjunctive use of minocycline microspheres (Schär *et al*. 2013; Bassetti *et al*. 2014). Complete elimination of sites with BoP was achieved in 31.6% of patients with adjunctive aPDT application at the 12-month follow-up (Table 34-2).

Although the application of aPDT has been investigated as an additional approach for decontamination of implants affected by peri-implantitis, a recent summary of available evidence reported

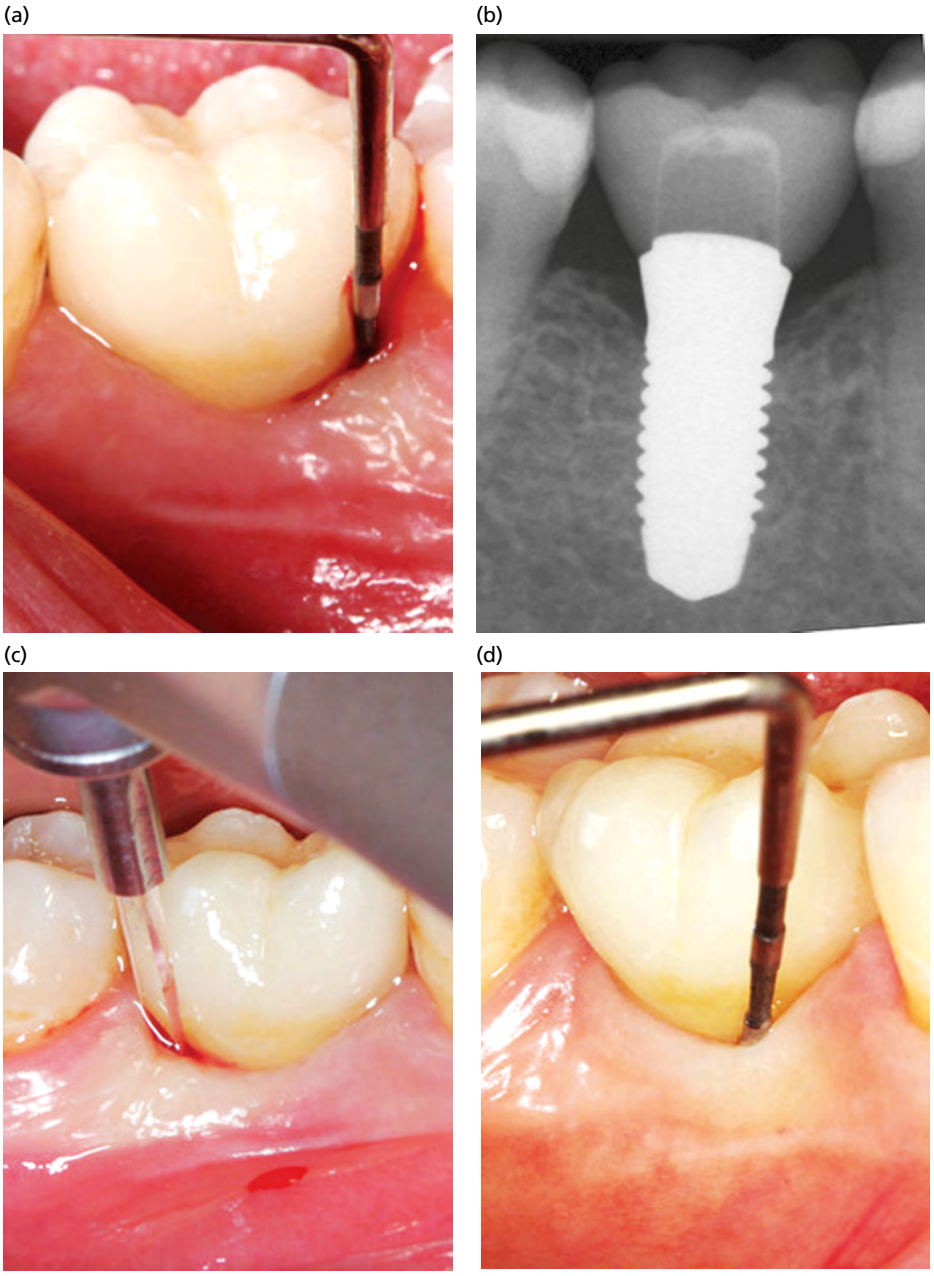

Fig. 34.9 Non-surgical treatment of incipient peri-implantitis at a zirconia implant using an Er:YAG laser. (a) Clinical signs (bleeding on probing and increased probing depth) of incipient peri-implantitis at a zirconia implant. (b) Radiographic appearance of a zirconia implant with incipient bone loss at the mesial and distal aspects. (c) Er:YAG laser application using a chisel-shaped glass fibre tip at 100 mJ/pulse (12.7 J/cm2) and 1 Hz. (d) Successful treatment outcome at 3 years with resolution of inflammation (absence of bleeding on probing) and peri-implant tissue health. (Source: John *et al*. 2017. Reproduced with permission from John Wiley & Sons, Inc.)

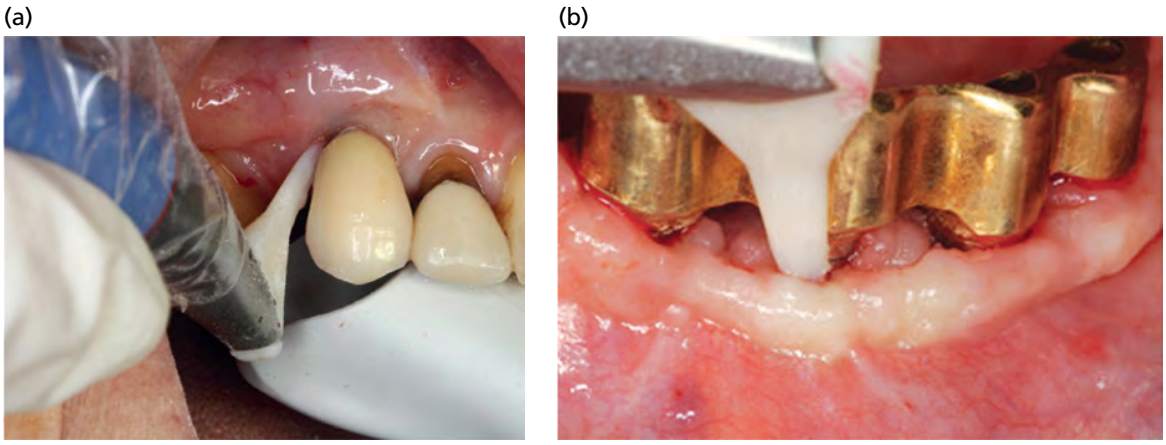

Fig. 34.10 (a) Air-polishing with glycine powder using a flexible tip, for removal of submucosal biofilm at an implant diagnosed with peri-implantitis. (b) Non-surgical treatment of peri-implantitis using an air-polishing device with a flexible tip. (Source: Sahm *et al*. 2011. Reproduced with permission from John Wiley & Sons, Inc.)

inconclusive results on its application as an adjunct to mechanical debridement alone (Chambrone *et al*. 2018).

Adjunctive local antimicrobials

Improvements in clinical and microbiological parameters have been reported following non-surgical mechanical debridement and adjunctive delivery of chlorhexidine (Machtei *et al*. 2012) and local non-resorbable and resorbable antimicrobials (Buchter *et al*. 2004; Renvert *et al*. 2004, 2006, 2008; Persson *et al*. 2006; Salvi *et al*. 2007) for treatment of peri-implantitis.

Repeated placement of chlorhexidine chips as an adjunct to non-surgical mechanical debridement was investigated in patients diagnosed with peri-implantitis, defined as a PD of 6–10 mm combined with bone loss ≥2 mm (Machtei *et al*. 2012). This randomized clinical study included seven applications of chlorhexidine chips and results indicated significant improvements in clinical parameters at 6 months (Machtei *et al*. 2012). However, absence of BoP was achieved in only 57.5% of implant sites treated with repeated chlorhexidine chip application (Machtei *et al*. 2012) (Table 34-2).

Mechanical implant surface debridement in conjunction with the placement of non-resorbable tetracycline-impregnated fibers yielded statistically significant clinical changes with respect to the reduction in mean PD from 6.0 to 4.1 mm and BoP scores after 12 months (Mombelli *et al*. 2001). The resorbable tetracycline-impregnated fibers are no longer commercially available.

The clinical and microbiological effects of locally delivered minocycline microspheres as an adjunct to non-surgical mechanical debridement using carbon fiber currettes was investigated in a case series of peri-implantitis lesions (Persson *et al*. 2006; Salvi *et al*. 2007) (Fig. 34.11). Significant reductions in levels of *Tanerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola* were observed up to 6 months (Persson *et al*. 2006). Although the results indicated significant reductions in the percentage of sites with BoP and in pocket PD over 12 months, disease resolution was not achieved in all cases and the need for additional surgical intervention could not be excluded (Salvi *et al*. 2007).

In a comparative study, the clinical adjunctive effects of repeated local delivery of minocycline microspheres was compared with that of chlorhexidine gel application in patients with peri-implantitis (Renvert *et al*. 2008). Adjunctive minocycline microsphere delivery resulted in a statistically greater reduction in PDs and number of sites with BoP compared with that of chlorhexidine gel application (Renvert *et al*. 2008).

The adjunctive clinical benefits of a chloramine-containing solution to mechanical debridement alone was also tested in a randomized clinical trial with a split-mouth design in 16 patients diagnosed with peri-implantitis (Roos-Jansaker *et al*. 2017). At the 3-month follow-up, significant reductions in BoP-positive sites and PDs were observed in both groups when compared with baseline. No statistically significant differences, however, were observed between groups indicating that non-surgical mechanical debridement alone was equally effective in the reduction of mucosal inflammation and other clinical parameters compared with non-surgical mechanical debridement with adjunctive application of chloramine (Roos-Jansaker *et al*. 2017).

Adjunctive systemic antimicrobials

A randomized placebo-controlled study did not find any clinical advantage of adjunctive systemic antimicrobials for non-surgical treatment of advanced peri-implantitis (Shibli *et al*. 2019), with only half of the patients achieving a successful treatment outcome (PD of <5 mm, no BoP, no further bone loss). Therefore, the adjunctive use of systemic

Table 34-2 Studies reporting disease resolution following non-surgical treatment of peri-implantitis.

Study	Treatment	Study design	*n*	Follow-up	Disease resolution Absence of BoP	Comments
Schwarz *et al*. 2015c	Er:YAG laser monotherapy	Case series	17 patients 21 implants	6 months	5 of 17 patients 29% Absence of BoP	Zirconia implants
Schär *et al*. 2013 (6 month) Bassetti *et al*. 2014 (12 month)	MD + AAD + LDD MD + AAD + PDT	RCT	20 patients/ implants 20 patients/ implants	6 months	MD+LDD: 15% implants MD+PDT: 30% implants Absence of BoP	Initial peri-implantitis LDD – minocycline microspheres No difference between groups Treatment repeated at 3 and 6 months at sites with BoP
Shibli *et al*. 2019	MD + placebo MD + AMX/MET	RCT	40 patients	12 months	Success: PD <5 mm, no BoP, no bone loss 50% success in both groups	Severe peri-implantitis No difference in outcome between groups

AAD, amino acid glycine powder; AMX, amoxicillin; BoP, bleeding on probing; CHX, chlorhexidine; LDD, local delivery device; MD, mechanical debridement; MET, metronidazole; PDT, photodynamic therapy; PD, probing depth; RCT, randomized controlled trial.

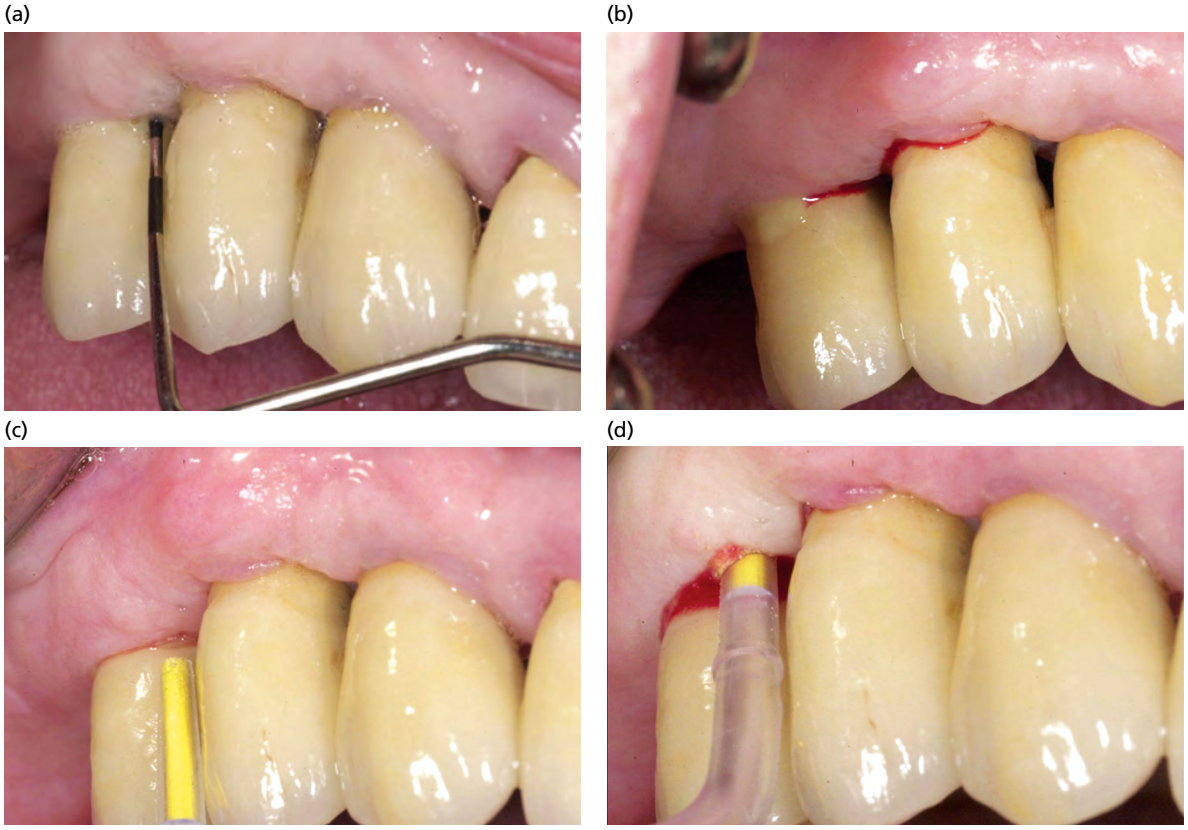

Fig. 34.11 Deep peri-implant probing depth (8 mm) associated with peri-implantitis at the implant site 15. (b) Bleeding and suppuration following probing at the implant site 15. (c) Adjunctive application of a local antimicrobial agent (minocycline microspheres) for the non-surgical treatment of peri-implantitis. Minocycline microsphere delivery tip prior to placement into the peri-implant pocket. (d) Adjunctive application of a local antimicrobial agent (minocycline microspheres) for the non-surgical treatment of peri-implantitis. Insertion of the delivery tip into the peri-implant pocket.

antimicrobials is not supported for non-surgical treatment of peri-implantitis.

Zirconia implants

There is limited data available regarding treatment of peri-implantitis at zirconia implants. In a case series, 17 patients diagnosed with peri-implantitis received treatment with Er:YAG laser monotherapy followed by supramucosal plaque removal and local pocket irrigation with chlorhexidine. At 6 months disease resolution (absence of BoP and absence of PD of ≥6 mm) was obtained in the five of 17 (29.4%) patients (Schwarz *et al*. 2015c). At 3 years, resolution of peri-implant mucositis was obtained in seven of 14 (50.0%) patients and resolution of peri-implantitis in five of 13 (38.5%) patients investigated (Fig. 34.9). Based on this limited data, it can be concluded that non-surgical treatment at zirconia implants may result in clinical improvements; however, complete disease resolution is not achieved in all cases (John *et al*. 2017).

Conclusion

Treatment of peri-implantitis requires an anti-infective approach which includes professional non-surgical mechanical removal of supra-and submucosal peri-implant biofilm and regular self-performed biofilm control. The goal of treatment is to resolve inflammation and prevent disease progression. Clinical improvements such as a reduction in the number of sites with BoP and a reduction in PDs can frequently be achieved following non-surgical treatment of peri-implantitis. However, complete resolution of inflammation is not achieved in the majority of peri-implantitis cases. Various techniques for professional mechanical debridement are available. Glycine powder air-polishing has been demonstrated to provide some advantage in BoP reduction compared with either mechanical debridement with or without local antiseptic therapy or to Er:YAG laser treatment (Schwarz *et al*. 2015b). Adjunctive measures may be used; however, no significant clinical benefit over mechanical debridement alone has been shown.

Regular monitoring of peri-implant tissues and detection of incipient peri-implantitis is essential as non-surgical therapy may be successful in treating peri-implantitis in its early stages. In more advanced stages of peri-implantitis non-surgical management is often unsuccessful in the resolution of inflammation and surgical intervention is frequently required.

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Chapter 35

Surgical Treatment of Peri-Implantitis

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Introduction and goals of surgical therapy

Peri-implantitis is characterized by inflammation in the peri-implant mucosa and loss of peri-implant bone (see Chapter 20). If left untreated, the disease may progress with further marginal bone loss and, in the end, result in implant loss. It is therefore imperative that the tissues around implants be monitored at regular intervals to identify biological complications and to treat disease at an early stage. The overall goal of treatment of peri-implantitis is to resolve inflammation in the peri-implant mucosa and to preserve supporting hard and soft tissues. The parameters to be considered in the evaluation of outcomes of treatment are reduction of bleeding on probing (BoP), reduction of probing depth (PD), and preservation or gain of crestal bone assessed in radiographs.

Peri-implantitis is typically associated with osseous defects involving the full circumference of the implant. Depending on the width of the ridge, buccal and lingual bone walls may remain, resulting in a crater-like defect. Conversely, in sites with a narrow ridge, buccal and lingual bone walls will be lost during progression of peri-implantitis. Thus, sites with peri-implantitis often present with open ("one-wall"), angular bone defects on the mesial and the distal aspects of the implant (Fig. 35-1).

In line with treatment concepts of periodontitis, a step-by-step strategy should be applied in the treatment of peri-implantitis. While non-surgical treatment procedures should be considered as an initial step in the management of the disease, data indicate that such methods may be ineffective in resolving moderate and severe forms of peri-implantitis (for details see Chapter 34). Thus, if clinical signs of pathology persist in peri-implant tissues following initial therapy, that is, BoP and/or suppuration in combination with deep pocketing, surgical therapy is required. The specific goal of surgical treatment of peri-implantitis is to obtain access to the implant surface for debridement and decontamination in order to achieve resolution of the inflammatory lesion (Lindhe & Meyle 2008). A prerequisite for surgical treatment of peri-implantitis, however, is an appropriate level of self-performed infection control.

Surgical therapy of an implant site presenting with peri-implantitis is shown in Figs. 35-2 and 35-3. Clinical signs of inflammation, PD of 7 mm in combination with BoP were detected at the initial examination (Fig. 35-2). The radiograph revealed the presence of angular bone defects. Flap elevation allowed access to the area and inflamed tissues were removed

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

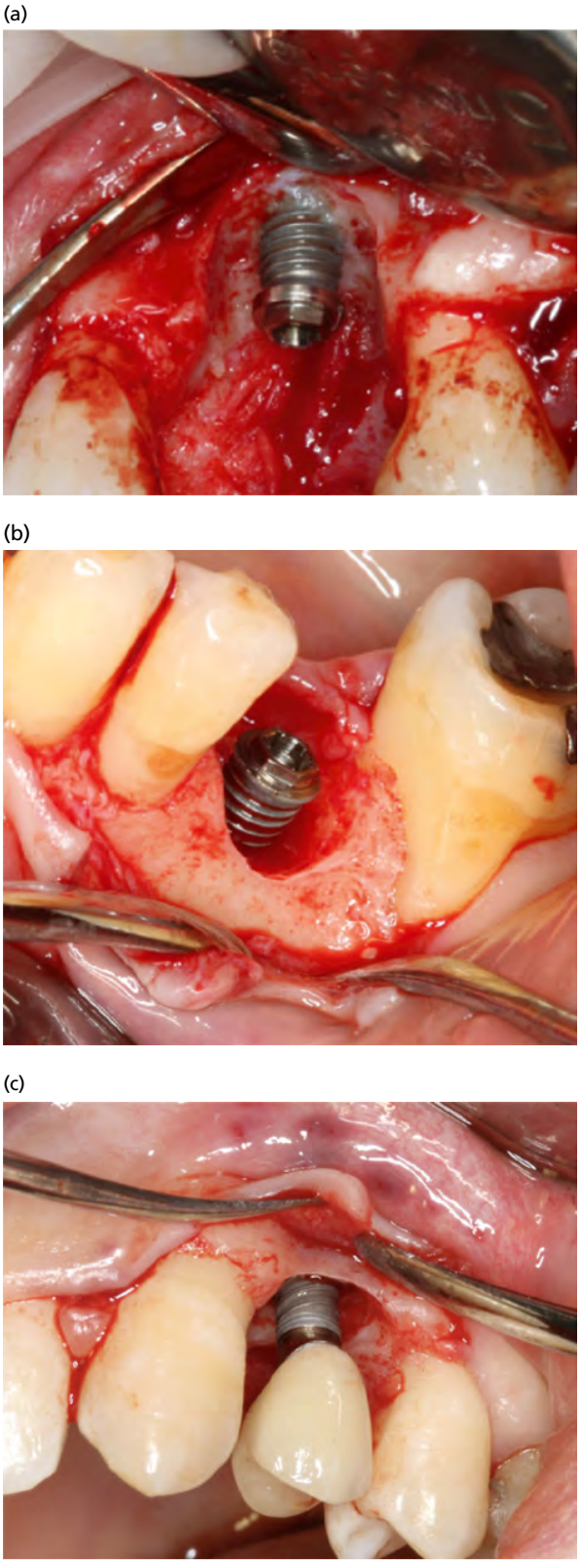

Fig. 35-1 (a) Open defects involving the buccal and palatal bone walls. (b, c) Contained peri-implant defects with largely preserved buccal and lingual/palatal bone walls.

from the defects (Fig. 35-3). Mechanical debridement of the implant surface was performed using a rotating titanium brush and small pieces of gauze soaked in saline. Flaps were replaced and sutured in their original position (access flap). A supportive therapy

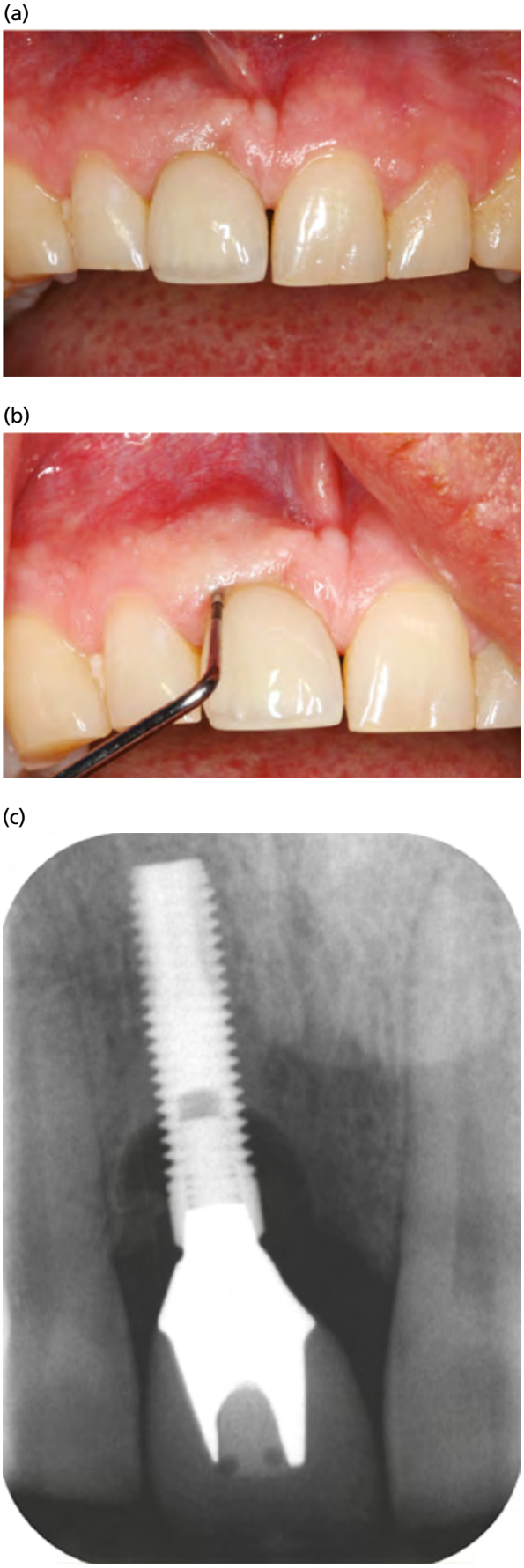

Fig. 35-2 Clinical photographs (a, b) and radiograph (c) from an implant site presenting with peri-implantitis. (b) Note the probing depth of 7 mm and the angular bone defects (c).

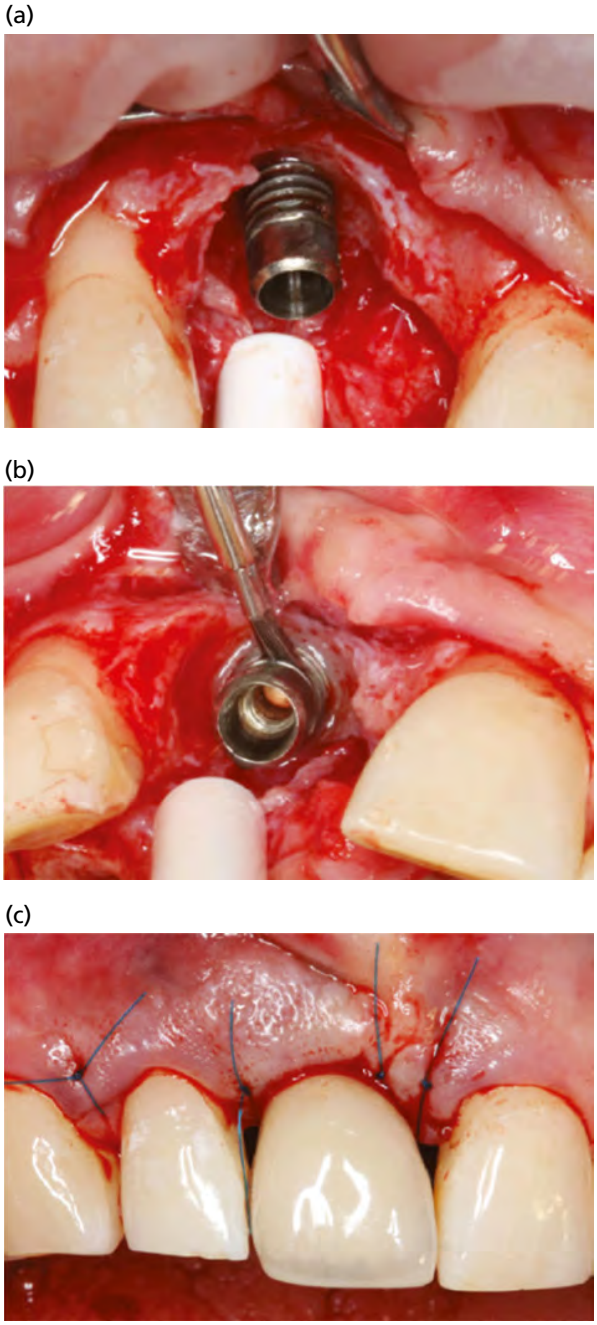

Fig. 35-3 (a) Implant site shown in Fig. 35-2 after flap elevation and removal of inflamed tissues. Note the absence of the buccal bone wall. (b) Decontamination of the implant surface was performed using a rotating titanium brush under saline irrigation. (c) Flaps were replaced and sutured.

program with supervised infection control was subsequently provided.

At the 12-month follow-up after surgery, PD was reduced and clinical signs of inflammation were absent (Fig. 35-4).

Implant surface decontamination

One of the greatest challenges in the treatment of peri-implantitis is implant surface decontamination. As illustrated in the scanning electron micrographs in Fig. 35-5, the target surface of an implant affected by peri-implantitis exhibits a complex biofilm with microorganisms residing in compartments resulting from different implant surface modifications. Although the removal of the biofilm is a prerequisite for achieving the goal of resolution of the peri-implantitis lesion, complete elimination of biofilm appears to be difficult. Results from preclinical and clinical studies, however, have demonstrated that resolution of peri-implantitis lesions can indeed occur following implant surface decontamination using a mechanical approach.

Evidence of complete resolution of peri-implantitis lesions following mechanical debridement was presented in a preclinical study by Albouy *et al*. (2011). Experimental peri-implantitis around different types of implants was produced according to techniques previously described (Lindhe *et al*. 1992) (see Chapter 20). The surgical therapy was carried out without adjunctive use of systemic antibiotics or local antimicrobial agents. The histologic examination of biopsies obtained at 6 months after surgery revealed complete resolution of the lesions at most implant sites. In another preclinical evaluation, Almohandes *et al*. (2019) used the same decontamination protocol in the treatment of experimentally induced peri-implantitis and, after healing, consistently observed re-osseointegration at previously contaminated surfaces (Fig. 35-6).

The feasibility of treatment of peri-implantitis through surgical decontamination of implant surfaces using gauzes soaked in saline has been evaluated clinically. At a 12-month examination following surgical therapy of peri-implantitis in 24 patients, Heitz-Mayfield *et al*. (2012) reported that a significant reduction of PD, BoP, and suppuration had occurred. While 47% of the implant sites exhibited complete resolution of disease, 92% of the sites showed stable crestal bone levels or bone gain. In a retrospective evaluation, 2–11 years following surgical therapy of peri-implantitis, Berglundh *et al*. (2018) found that 71% of all implant sites displayed stable bone levels and that clinical signs of inflammation were reduced. The adjunctive use of a local antiseptic to the surgical decontamination protocol has been evaluated in controlled studies but not been found beneficial. Thus, in a study including 100 subjects, Carcuac *et al*. (2016) found that the local administration of the antiseptic agent (0.2% solution of chlorhexidine digluconate) did not improve 1-year outcomes when compared with the use of saline alone. De Waal *et al*. (2015) compared two different concentrations of chlorhexidine solutions (0.12% versus 2%) as part of the surgical treatment of peri-implantitis in 44 subjects. While 1-year outcomes were in line with other reports in terms of PD reductions and absence of additional bone loss, no relevant differences between study groups were observed. Taken together, there is currently a lack of evidence suggesting the benefit of the adjunctive use of antiseptic or antimicrobial agents in the surgical decontamination of implant surfaces.

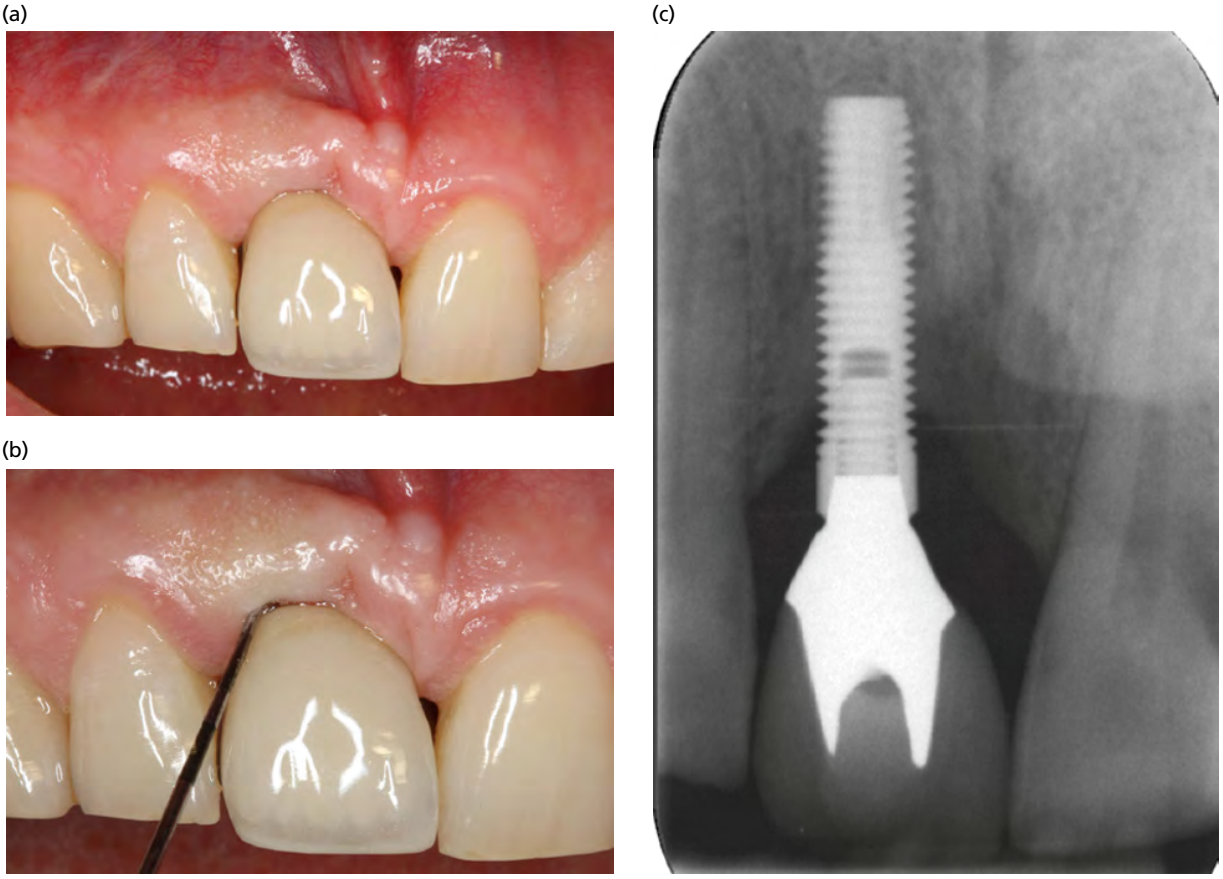

Fig. 35-4 Implant site shown in Figs. 35-2 and 35-3 at 12 months after surgical therapy. (a, b) Note the reduced probing depth and absence of clinical signs of inflammation. (c) The radiograph indicates some fill of the bone defects relative to baseline.

Data from preclinical and clinical evaluations of other methods of decontamination, including air abrasive devices and lasers are limited. The effect of rotating or oscillating titanium brushes on implant surfaces and on postsurgical outcomes has been assessed in *in vitro;* and in clinical studies. Thus, Cha *et al*. (2019) observed that, while instrumentation with an ultrasonic metal instrument resulted in pronounced alterations of the micro- and macrostructure of the implant surface, rotating titanium brushes were able to access all parts of the threaded area without causing major structural damage. Clinical efficacy of the concept was evaluated by Tapia *et al*. (2019), who supplemented surgical decontamination with an oscillating titanium brush in a test group including 15 subjects. Clinical and radiographic outcomes at 12 months were superior to findings from the control group, in which decontamination was performed by the use of a plastic ultrasonic scaler, only. In contrast, there is a lack of data, preclinical or clinical, demonstrating benefits of the use of air abrasives or lasers for surface decontamination during surgical treatment of peri-implantitis.

Aggressive mechanical techniques, often referred to as "implantoplasty", have been suggested to achieve implant surface decontamination. Such procedures have included grinding of the implant surface and removal of threads from the titanium cylinder together with polishing of rough implant surfaces. Results from one study with a 3-year follow-up after surgical therapy indicated some benefit when using such "implant-resective techniques" on titanium plasma-sprayed (TPS) surface implants (Romeo *et al*. 2007). In this context, however, the risks involved in implant grinding procedures – potential damage to the peri-implant bone caused by overheating as well as spreading of metal particles – must be considered.

The outcome of decontamination procedures during surgical treatment of peri-implantitis is influenced by implant surface characteristics. Thus, data presented in preclinical studies by Albouy *et al*. (2011), Carcuac *et al*. (2015), and Almohandes *et al*. (2019) revealed that the resolution of experimental peri-implantitis lesions was influenced by implant surface characteristics, consistently favoring turned or less complex surfaces. Results presented in clinical studies support the concept that the response to treatment is influenced by implant surface-specific features. Roccuzzo *et al*. (2017), in a study including 24 patients with peri-implantitis around implants with either a rough TPS or moderately rough surface (sandblasted large-grit acid-etched [SLA]), reported that reduction of PD and BoP was more pronounced at implants with the SLA surface than those with the TPS surface. Implants with TPS surfaces also demonstrated significantly higher frequencies of disease recurrence during the 7-year follow-up period after

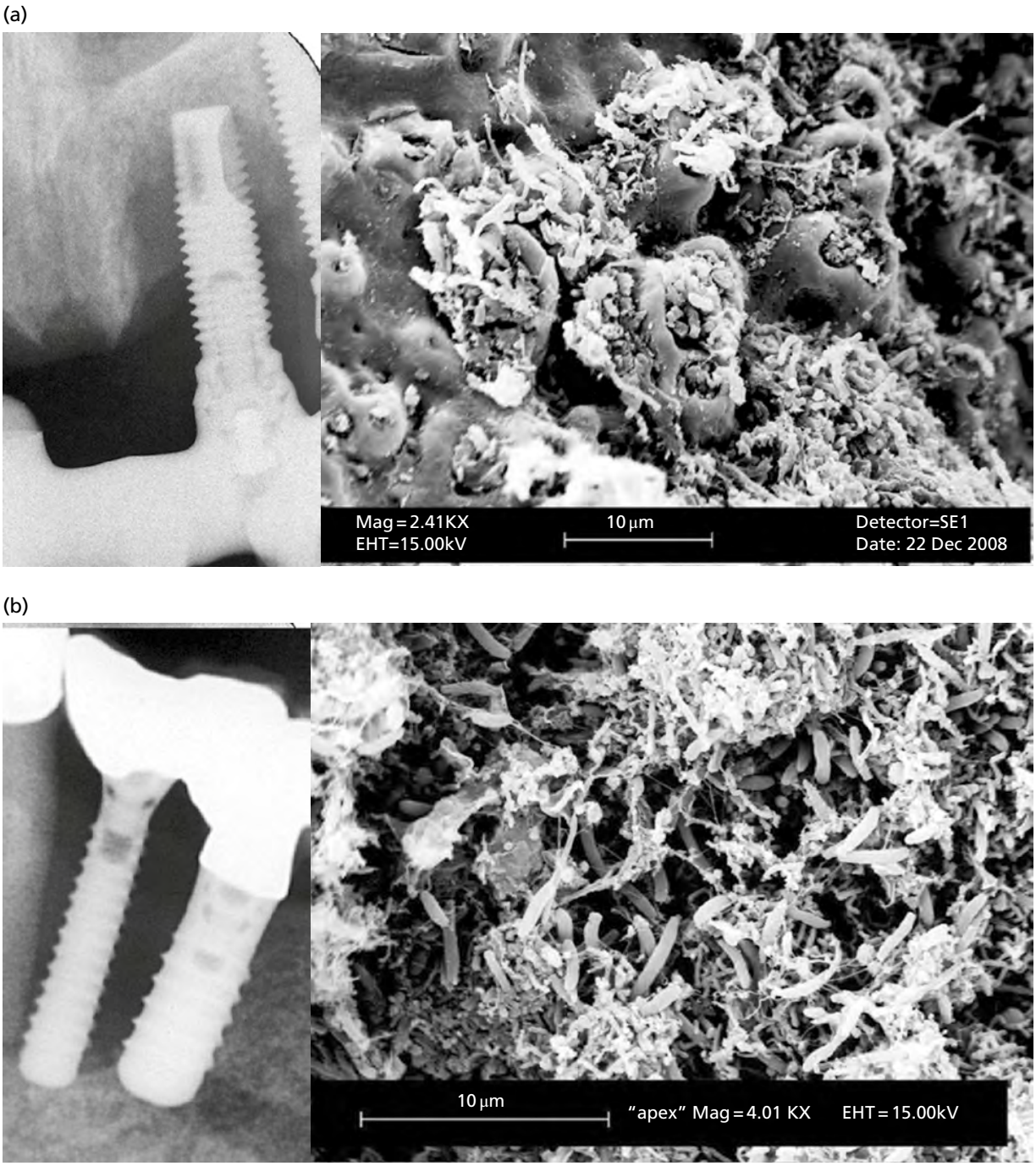

Fig. 35-5 The two implants affected by advanced peri-implantitis (a, b) were surgically removed. The high magnification of the scanning electron micrographs of the explanted implants reveals microorganisms of various morphotypes occupying compartments of the modified implant surfaces.

surgical treatment. Carcuac *et al*. (2017) evaluated 83 patients 3 years after surgical therapy of advanced peri-implantitis. Absence of additional bone loss following treatment was observed in 82% of implants with turned surfaces and in 49% of the implants with modified surface characteristics.

Taken together, there is ample evidence that resolution of peri-implantitis following anti-infective therapy is feasible and that implant surface characteristics have a profound impact on short- and long-term outcomes of surgical treatment of peri-implantitis.

Pocket elimination/reduction procedures

In addition to the decontamination procedures in conjunction with surgical treatment of peri-implantitis, the configuration of the bony defect that surrounds the implant has to be addressed. Similar to the planning of treatment of angular bone defects at periodontally involved sites, the surgical protocol for the treatment of peri-implantitis comprises pocket elimination/reduction or reconstructive procedures.

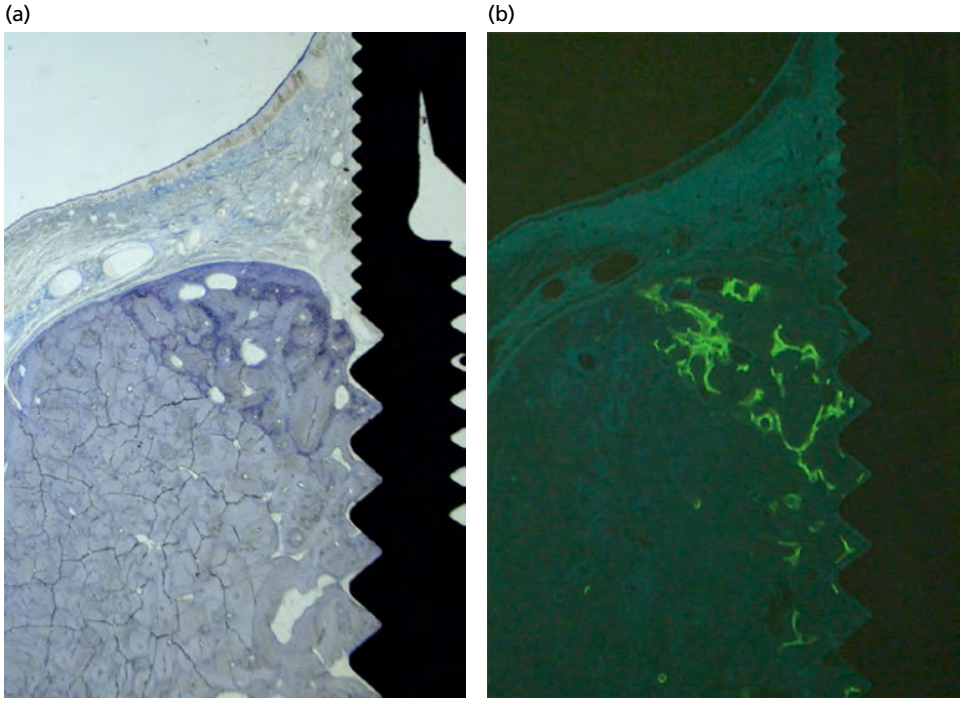

Fig. 35-6 (a) Histological ground section prepared from an implant site following 6 months of healing after treatment of peri-implantitis. Note the newly formed bone and high degree of re-osseointegration to the previously contaminated implant surface. (b) Micrograph including a fluorochrome marker indicating the original bone defect and newly formed bone following treatment.

Preclinical data

Surgical treatment of peri-implantitis including pocket elimination/reduction procedures has been evaluated in numerous preclinical studies. Persson *et al*. (1999) induced experimental peri-implantitis in dogs according to the model described by Lindhe *et al*. (1992). The subsequent treatment included (1) systemic administration of antibiotics, (2) elevation of full thickness flaps at the experimental sites and curettage of the hard tissue defect, (3) mechanical debridement of the exposed portion of the implants, and (4) flap management and closure of the soft tissue wound. Radiographs and biopsies were obtained after 7 months of submerged healing. The analysis of the radiographs indicated a complete bone fill in the hard tissue defects (Fig. 35-7). Histologic analysis of the biopsy sections revealed that treatment had resulted in a complete resolution of the soft tissue inflammation and the formation of substantial amounts of new bone in the previous hard tissue defects (Fig. 35-8).

Applying the same experimental model as Persson *et al*. (1999) did earlier, subsequent studies demonstrated that resolution of peri-implantitis was also possible without the use of systemic antimicrobial therapy. Thus, Albouy *et al*. (2011) and Carcuac *et al*. (2015) reported that radiographic bone fill and resolution of the soft tissue inflammation occurred and that outcomes of treatment were influenced by implant surface characteristics. This observation is in line with findings presented by Almohandes *et al*. (2019), using the same experimental set-up as described above. While pronounced radiographic defect fill and re-osseointegration at previously contaminated surfaces were observed overall (Fig. 35-6), outcomes

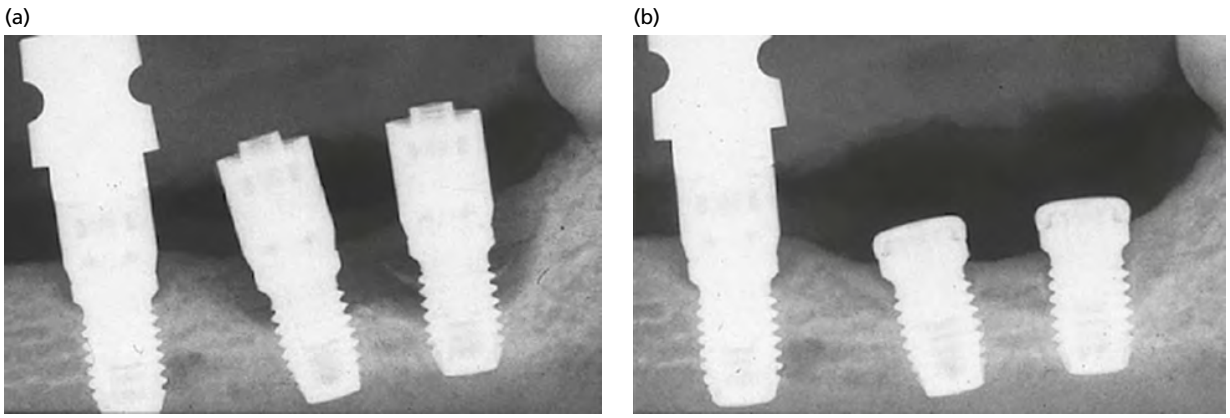

Fig. 35-7 Radiographs obtained from two sites exposed to experimental peri-implantitis. (a) Sites at 7 months of submerged healing after treatment of peri-implantitis. (b) Note the bone fill in the previous osseous defects.

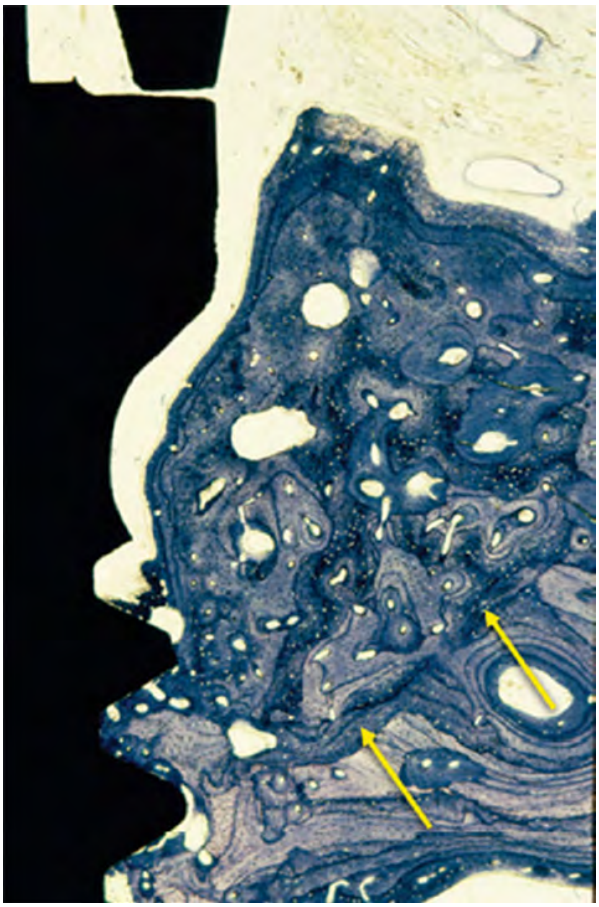

Fig. 35-8 Ground section following 7 months of submerged healing after treatment of peri-implantitis. Note the newly formed bone in the hard tissue defects (arrows).

were better at implants with smooth surfaces than implants with moderately rough surfaces.

Clinical data

Clinical studies evaluating surgical therapy of peri-implantitis applying a pocket elimination/reduction technique are illustrated in Table 35-1. The studies reported a pronounced reduction of PD and clinical signs of inflammation (BoP) and preservation of crestal bone levels at follow-up examinations ranging from 1 year to 5 years post-treatment.

In a retrospective analysis of 50 subjects treated for advanced peri-implantitis, Berglundh *et al*. (2018) observed a mean reduction of PD of 2.6 mm after an observation period of 2–11 years. A mean additional bone loss of 0.1 mm was noted. In line with preclinical data discussed earlier, outcomes were strongly influenced by implant surface characteristics. Thus, at implants with turned surfaces, mean reduction of PD amounted to 2.9 mm and a mean bone gain of 0.1 mm was recorded. These findings are in agreement with data presented in a prospective 5-year study by Heitz-Mayfield *et al*. (2018). It was reported that the reduction of PD and BoP was on average 2.8 mm and 42%, respectively. An additional and clinically relevant observation in the study by Heitz-Mayfield *et al*. (2018) was the substantial soft tissue recession of 1.8 mm that had occurred at the buccal aspect of the treated implants. A case illustrating soft tissue recession after surgical treatment of peri-implantitis is presented in Fig. 35-9.

Table 35-1 Clinical studies evaluating surgical therapy of peri-implantitis: pocket elimination/reduction procedures.

Study	Sample and follow-up	Inclusion criteria	Surgical procedures	Outcomes	Comments
Serino & Turri (2011) Sweden, case series	29 patients, 2 years	BoP + PD ≥6 mm Marginal bone loss ≥2 mm	Pocket elimination	Implant loss: 7 out of 86 implants Implants *in situ*: PD ≥6 mm & BoP+: 14 out of 79 implants	Systemic antibiotics prescribed. REC and PROMs not reported
De Waal *et al*. (2015), Netherlands, RCT	44 patients, 1 year	BoP + PD ≥5 mm Marginal bone loss ≥2 mm	Pocket elimination Decontamination with 0.12% chlorhexidine solution (+ 0.05% cetylpyridinium chloride)	MBL: 0.0 mm PD: -2.1 mm BoP: -28%	No systemic antibiotics prescribed. REC and PROMs not reported.
			Pocket elimination Decontamination with 2% chlorhexidine solution	MBL: 0.3 mm PD: -1.7 mm BoP: -21%	
Carcuac et al. (2017), Sweden, RCT.	83 patients, 3 years	BoP + PD ≥6 mm Marginal bone loss >3 mm	Pocket elimination	Absence of additional bone loss >0.5 mm: 44% Implants *in situ*: MBL: 0.5 mm PD: -2.4 mm BoP: -47%	REC and PROMs not reported.
			Pocket elimination and systemic antibiotics	Absence of additional bone loss >0.5 mm: 68% Implants *in situ*: MBL: -0.3 mm PD: -3.0 mm BoP: -34%	

(*Continued*)

Table 35-1 (*Continued*)

Study	Sample and follow-up	Inclusion criteria	Surgical procedures	Outcomes	Comments
Berglundh et al. (2018), Sweden, Case series.	50 patients, 2–11 years	BoP + PD ≥6 mm Marginal bone loss ≥3 mm	Pocket elimination	MBL: -0.1 mm PD: -2.6 mm BoP: -37%	Systemic antibiotics prescribed for 36 out of 50 cases. REC and PROMs not reported.
Heitz-Mayfield et al. (2018), Multi-center, Case series.	20 patients, 5 years	BoP + PD ≥5 mm Marginal bone loss ≥2 mm	Pocket elimination	Implant loss: 4 out of 28 implants Implants *in situ*: PD: -2.8 mm BoP: -42% REC: 1.8 mm	Systemic antibiotics prescribed. MBL and PROMs not reported.

BoP, bleeding on probing; MBL, marginal bone level; PD, probing pocket depth; RCT, randomized controlled trial; REC, soft tissue recession; PROMs, patient-reported outcome measures.

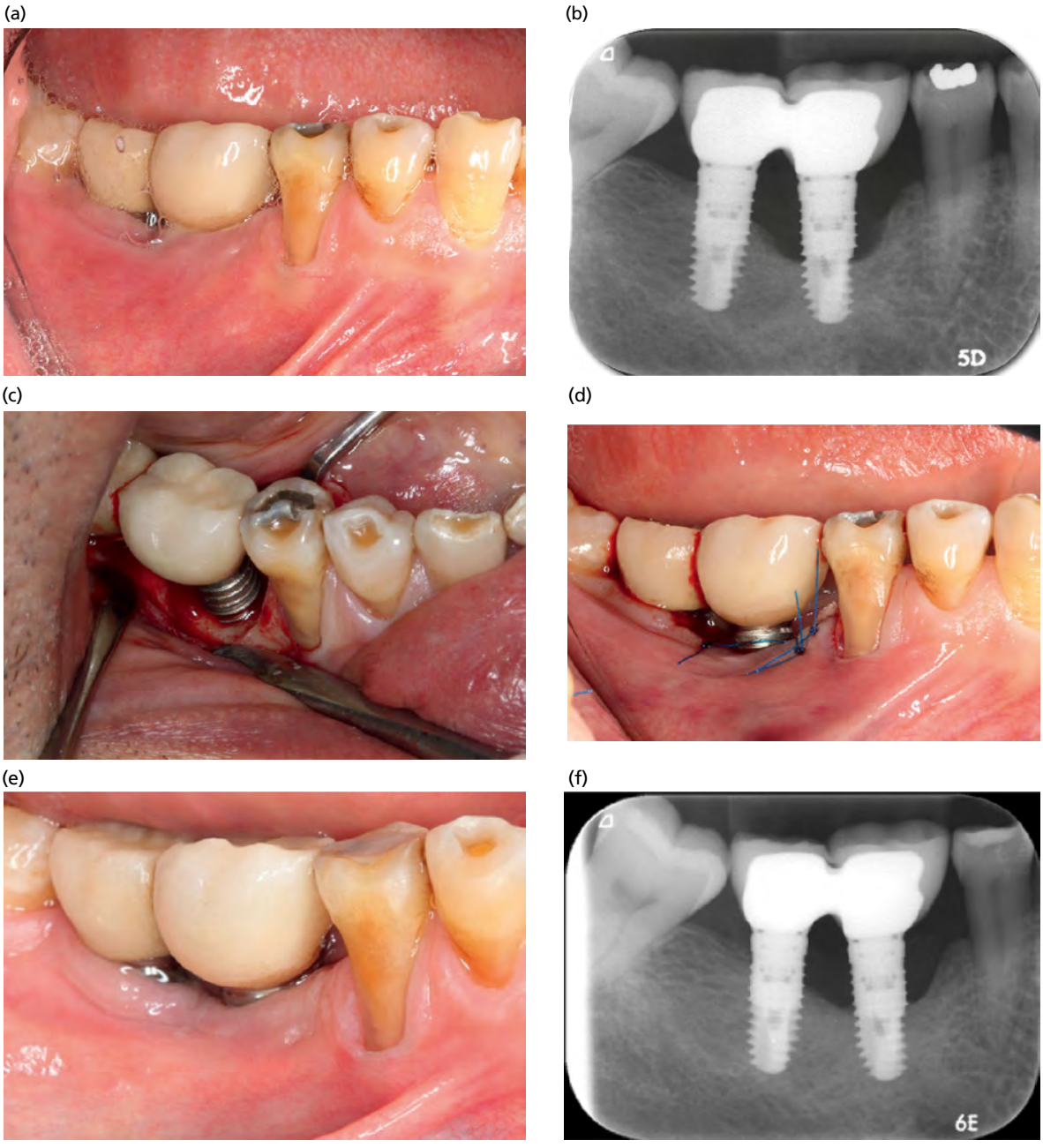

Fig. 35-9 (a, b) Implant demonstrating deep probing depth (9 mm), clinical signs of inflammation, and a reduced bone level. (c, d) Surgical access and decontamination of the implant surface followed by flap closure. (e) After 12 months of healing the peri-implant tissues display no signs of inflammation and shallow probing depth (3 mm). Note the soft tissue recession on the buccal aspect of the implant. (f) The 12-month radiograph indicates stable marginal bone levels relative to baseline.

The majority of studies in Table 35-1 described treatment protocols that included the administration of systemic antibiotics. Carcuac *et al*. (2017) reported 3-year outcomes of a randomized controlled trial evaluating the effect of a 10-day regimen of amoxicillin in conjunction with surgery. Out of the initially enrolled 100 subjects, 83 were available for the final assessment. Overall, the authors observed a reduction of PD and BoP as well as unchanged marginal bone levels following surgery. Outcomes were, however, significantly better at implants with turned surfaces than those with modified surfaces. In addition, a short-term benefit, which was limited to the first year of follow-up, of the adjunctive use of systemic antibiotics was observed for cases with modified surface implants, whereas no such benefit was seen in cases with turned surface implants. Thus, decisions on using systemic antibiotics as an adjunct to surgical therapy of peri-implantitis should be based on a careful analysis of the surface characteristics of the target implants and the fact that potential benefits are not sustained over time. The impact of implant surface characteristics on long-term outcomes following surgical treatment of peri-implantitis were further highlighted by the 5-year follow-up data presented by Carcuac *et al*. (2020). It was observed that, while the risk for recurrence of disease following the first year after treatment was 17% for implants with non-modified (turned) surfaces, the corresponding proportion for implants with modified surfaces was 52%.

Reconstructive procedures

The main goal of treatment of peri-implantitis is to resolve soft tissue inflammation and to prevent further crestal bone loss. An additional goal when using a reconstructive approach in surgical therapy is to restore the tissue damage that was caused by the disease. Whereas the management of peri-implant bone defects is considered a main component of reconstructive procedures, a clinical focus may also include the preservation of the soft tissue dimensions around the target implant following treatment. Thus, reconstructive procedures aiming at minimizing mucosal recession and promoting fill of the osseous defect may therefore be of particular relevance in sites located in the esthetic zone.

Another desirable outcome of reconstructive therapy of peri-implantitis is re-osseointegration. The finding in radiographs of bone fill of the osseous defect around the implant following surgical therapy, however, should not be taken to indicate that re-osseointegration has occurred. The term re-osseointegration can be defined as the establishment of *de novo* bone formation and *de novo* osseointegration to a portion of an implant that during the development of peri-implantitis suffered loss of bone–implant contact and became exposed to microbial colonization. Assessments of re-osseointegration require histological analysis (Fig. 35-6). In the clinical setting, a vast number of procedures have been proposed to promote bone fill of peri-implantitis-related bone defects. It is currently not known, however, if the use of bone grafts/substitutes or barrier membranes improves treatment outcomes following surgical therapy of peri-implantitis (Tomasi *et al*. 2019).

Preclinical data

Assessment of bone–implant contact requires histologic examination, which calls for the use of preclinical research models. As described in Chapter 20, experimental peri-implantitis can predictably be produced using well-established techniques (Lindhe *et al*. 1992) and different reconstructive treatment protocols can be applied accordingly. Re-osseointegration has been evaluated in a number of preclinical studies (e.g. Wetzel *et al*. 1999; Persson *et al*. 2001, 2004; Namgoong *et al*. 2015) and was found to be dependent on implant surface characteristics. Almohandes *et al*. (2019) in a study on treatment of experimentally induced peri-implantitis observed that radiographic bone fill occurred in the osseous defects surrounding the implants. In addition, histological evaluations performed 6 months after reconstructive surgery revealed evidence of re-osseointegration. The frequency of sites demonstrating re-osseointegration, however, varied depending on implant surface modification. Thus, 96% (23 out of 24) of the implants with a smooth surface exhibited re-osseointegration, while the corresponding figure for the implants with a moderately rough surface was 54% (13 out of 24) (Fig. 35-6). The results presented by Almohandes *et al*. (2019) indicate that the decontamination procedure was effective in removing the biofilm on implants with a smooth surface, but also that the surface became conducive for *de novo* bone formation.

Reconstructive techniques including the application of bone replacement grafts and/or membranes at peri-implantitis-related bone defects have also been compared in preclinical research. Almohandes *et al*. (2019) used bone replacement graft alone or in combination with membranes to reconstruct the experimentally induced peri-implant defects. While neither of the test groups demonstrated any benefit over empty controls at smooth-surface implants, the use of grafting material resulted in improved radiographic bone levels at implants with moderately rough surfaces. The additional use of a membrane did not result in improved outcomes. Overall differences between groups, however, were small and outweighed by the aforementioned differences observed between different types of surface characteristics.

Clinical data

Evidence on the use of different techniques for reconstruction of peri-implantitis-associated bone defects is limited. This is highlighted by the low number of studies using adequate controls. In a systematic review presented by Tomasi *et al*. (2019), only three publications comparing the adjunctive use of either bone replacement grafts (Wohlfahrt *et al*. 2012;

Table 35-2 Clinical studies evaluating surgical therapy of peri-implantitis: reconstructive procedures.

Study	Sample and follow-up	Inclusion criteria	Surgical procedures	Outcomes	Comments
Roos-Jansåker *et al*. (2007), Sweden, case series	36 patients, 1 year	BoP + Bone loss ≥1.8 mm	Hydroxyapatite and membrane	MBL: –1.5 mm REC: 1.3 mm PD: –2.9 mm BoP: –60%	Systemic antibiotics prescribed. PROMs not reported.
			Hydroxyapatite	MBL: –1.4 mm REC: 1.6 mm PD: –3.4 mm BoP: -68%	
Schwarz *et al*. (2012), Germany, RCT	24 patients, 2 years	PD >6 mm Depth of angular bone defect >3 mm Presence of keratinized peri-implant mucosa	Bovine bone mineral and membrane Decontamination with plastic curettes, cotton pellets and sterile saline	REC: 0.5 mm PD: –2.0 mm BOP: –60%	No systemic antibiotics prescribed. MBL and PROMs not reported.
			Bovine bone mineral and membrane Decontamination with Er:YAG laser	REC: 0.4 mm PD: –1.7 mm BOP: –55%	
Wohlfahrt *et al*. (2012), Norway, RCT	32 patients, 1 year	BoP + PD ≥5 mm Angular bone defect ≥4 mm	Open-flap debridement	MBL: –0.1 mm Defect fill: –15% PD: –2.0 mm	Systemic antibiotics prescribed. REC and PROMs not reported.
			Porous titanium granules	MBL: –2.0 mm Defect fill: 57% PD: –1.7 mm	
Isehed *et al*. (2016), Sweden, RCT	25 patients, 1 year	BoP + PD ≥5 mm Angular bone loss ≥3 mm	Open-flap debridement	MBL: –0.2 mm PD: –4.0 mm BoP: –20%	No systemic antibiotics prescribed. REC and PROMs not reported.
			Enamel matrix derivative	MBL: –0.7 mm PD: –2.5 mm BoP: –20%	
Jepsen *et al*. (2016), multi-center, RCT	59 patients, 1 year	BoP + PD ≥5 mm Angular bone defect ≥3 mm 3- or 4-wall defect	Open-flap debridement	MBL: –0.9 mm Defect fill: 23% PD: –2.6 mm BoP: –31%	Systemic antibiotics prescribed. REC and PROMs not reported.
			Porous titanium granules	MBL: –3.6 mm Defect fill: 77% PD: –2.8 mm BoP: –30%	
Roccuzzo *et al*. (2016), Italy, case series	71 patients, 1 year	PD ≥6 mm Crater-like lesion	Bovine bone mineral	PD: –2.9 mm BoP: –53% REC: varied from 0.5 to 0.9 mm	Systemic antibiotics prescribed. MBL and PROMs not reported.
Renvert *et al*. (2018), Sweden, RCT	41 patients, 1 year	BoP + PD ≥5 mm Angular bone defect ≥3 mm	Open-flap debridement	MBL: –0.2 mm PD: –2.5 mm BoP: –35%	Systemic antibiotics prescribed. REC and PROMs not reported.
			Bovine bone mineral	MBL: –0.7 mm PD: –3.6 mm BoP: –48%	
Tapia *et al*. (2019), Spain, RCT	27 patients, 1 year	BoP + PD ≥6 mm Angular bone defect ≥3 mm ≥2-wall defect Presence of keratinized peri-implant mucosa	Hydroyapatite/tricalcium phosphate and membrane decontamination with plastic ultrasonic scalers	REC: 0.2 mm MBL: –1.1 mm Defect fill: 52% PD: –2.9 mm BoP: –54%	Systemic antibiotics prescribed. PROMs not reported.
			Hydroxyapatite/tricalcium phosphate and membrane Decontamination with plastic ultrasonic scalers and titanium brush	REC: 0.6 mm MBL: –2.8 mm Defect fill: 81% PD: –4.9 mm BoP: –80%	

BoP, bleeding on probing; MBL, marginal bone level; PD, probing pocket depth; RCT, randomized controlled trial; REC, soft tissue recession; PROMs, patient-reported outcome measures.

Jepsen *et al*. 2016) or enamel matrix proteins (Isehed *et al*. 2016) to access flap alone were included. No controlled study evaluating the use of membranes was identified. Clinical studies on reconstructive procedures at peri-implantitis-affected sites are depicted in Table 35-2.

Results of the controlled studies, in particular studies evaluating bone replacement grafts (Wohlfahrt *et al*. 2012; Jepsen *et al*. 2016), indicated better radiographic outcomes in the test groups. Using a meta-analysis, Tomasi *et al*. (2019) observed an additional defect fill of 57% and a difference in crestal bone gain of 1.7 mm for the reconstructive procedures. Figure 35-10 illustrates a reconstructive procedure at an anteriorly positioned implant affected by advanced peri-implantitis. Radiographic bone fill and improved crestal bone levels are identified on the 12-month radiograph.

In contrast to the reported findings on radiographs, benefits in terms of clinical measures such as PD and BoP following reconstructive procedures have yet to be demonstrated (Tomasi *et al*. 2019). In addition, the effect of different techniques on esthetic outcomes (e.g. soft tissue recession) or on patient satisfaction has not been evaluated.

Long-term observations on outcomes following reconstructive surgical therapy of peri-implantitis demonstrated that the procedure is safe and effective in reducing peri-implant inflammation. Roccuzzo *et al*. (2017) used a bone replacement graft to reconstruct peri-implant bone defects and followed 26 patients for 7 years. The mean reduction of PD at the final examination was >3 mm. These data are in line with assessments of overall improvements presented in the systematic review by Tomasi *et al*. (2019). At 12 months, a PD reduction of 2.8 mm and a soft tissue

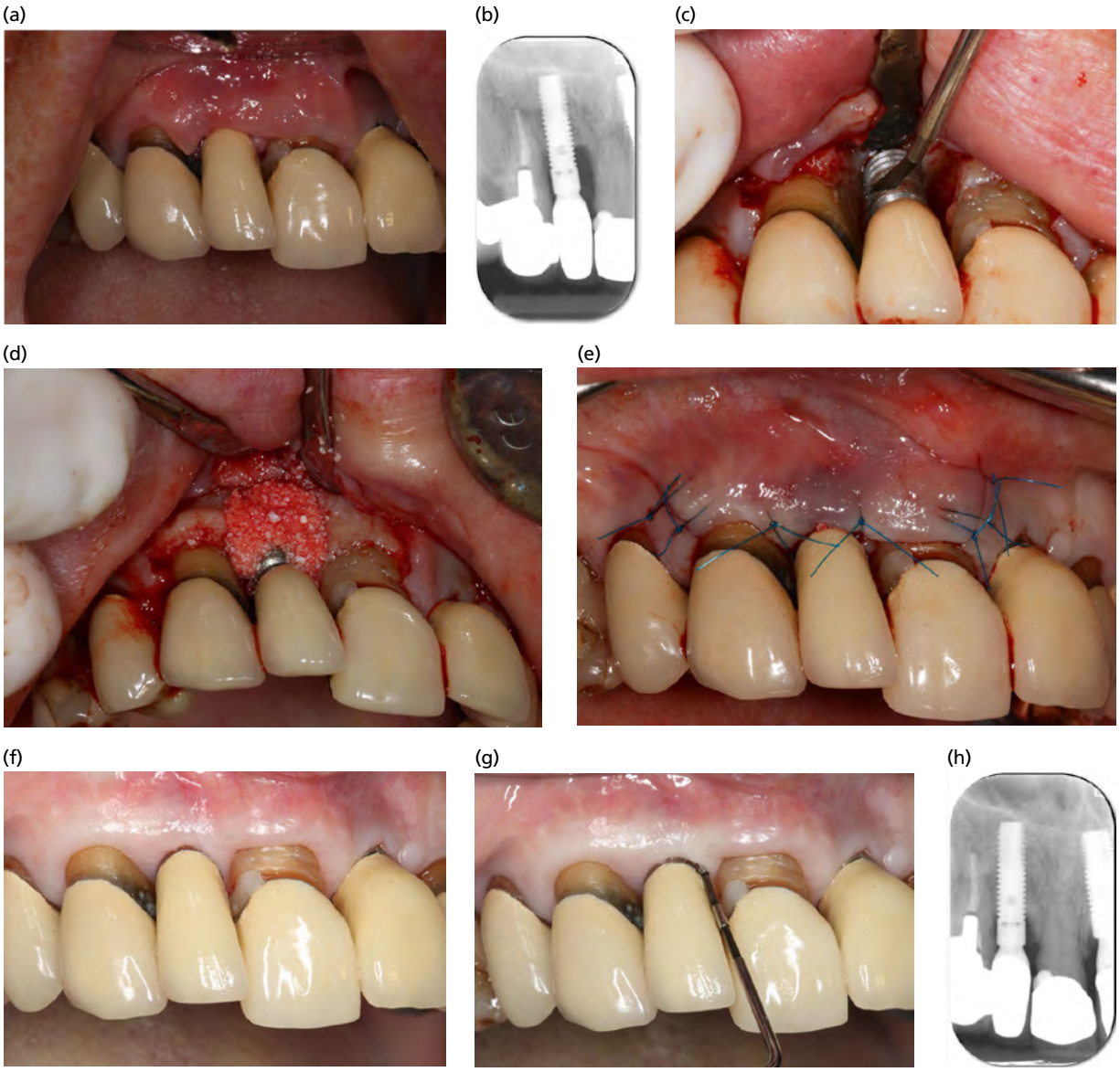

Fig. 35-10 (a, b) Implant demonstrating deep probing depth (9 mm), clinical signs of inflammation, and a reduced bone level. (c–e) Surgical access and decontamination of the implant surface followed by application of a bone replacement graft and suturing. (f, g) After 12 months of healing the peri-implant tissues display no signs of inflammation and shallow probing depth (3 mm). (h) The 12-month radiograph illustrates defect fill.

recession of 0.7 mm were estimated on the basis of the available evidence. Potential factors that influence outcomes following reconstructive therapy are (1) the type/quality of surface decontamination (Tapia *et al*. 2019), (2) the configuration of the bone defect (Schwarz *et al*. 2012), and (3) implant surface characteristics (Roccuzzo *et al*. 2017).

Conclusion

Pocket elimination/reduction procedures are effective in managing peri-implantitis. While the benefit of the adjunctive use of local antiseptic/antimicrobial agents for decontamination purposes remains to be demonstrated, the use of systemic antibiotics was shown to result in short-term improved outcomes after surgery. This benefit, however, was found to be limited to implants with modified implant surfaces and to the first year after treatment, only. Data from preclinical research suggest that re-osseointegration at previously contaminated implant surfaces is possible but depends on implant surface characteristics and the level of decontamination. While radiographic outcomes may be improved following the use of reconstructive techniques, clinical and patient-perceived benefits of the use of bone replacement grafts and/or membranes remain to be demonstrated. In general, treatment outcomes following surgical therapy of peri-implantitis appear to be highly dependent on implant surface characteristics, favoring smooth surface implants.

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Chapter 36

Systemic Antibiotics in Periodontal Therapy

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Introduction

Antibiotics are substances produced by a plethora of microorganisms such as bacteria (e.g., *Streptomyces* species) and fungi (e.g., *Penicillium* species) that selectively suppress the growth of other microorganisms and eventually may kill them (Fleming 2001; Watve *et al*. 2001; Mohr 2016). However, the term "antibiotics" is now extended to include synthetic or semisynthetic antimicrobial agents, such as sulfonamides and imidazoles, which are not produced by microbes (Mohr 2016). The modern era of antimicrobial therapy began with the production of penicillin in 1941, when this compound, discovered by Fleming in 1928, was finally mass produced and made available for clinical use (Chambers & Sande 1996). The outstanding success of penicillin in treating various infections quickly encouraged pharmaceutical laboratories to search for new antibiotics, produced from microorganisms isolated from soil samples; further successes came quickly (Chain 1972). Since then, hundreds of natural, semisynthetic, and synthetic antibiotics have been identified (Mohr 2016), and many of these drugs are essential in the treatment of numerous infections.

The widespread use of antibiotics over the past 80 years has led to the emergence of microorganisms tolerant to certain drugs, which is a primary reason for their failure to treat some infectious diseases, including life-threatening conditions (WHO 2014, 2015). A microorganism that survives exposure to an antimicrobial agent may become resistant to that agent, either by selecting for a mutation in its genome or by activating the expression of previously existing antibiotic-resistant genes. These resistant genes may be transferred within or between species, giving rise

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

to a new bacterial population tolerant to that agent (Davies & Davies 2010; Soares *et al*. 2012; Sekyere & Asante 2018). The emergence of side-effects is another disadvantage in the use of systemic antibiotics and must also be considered in the context of the risk–benefit evaluation of such therapies.

Considering the infectious nature of periodontitis, systemic antibiotics have been extensively studied as adjuncts in periodontal treatment (Herrera *et al*. 2002; Haffajee *et al*. 2003b; Sgolastra *et al*. 2012a, b, 2014; Zandbergen *et al*. 2013, 2016; Feres *et al*. 2015; Keestra *et al*. 2015a, b; Rabelo *et al*. 2015; Santos *et al*. 2015; Grellmann *et al*. 2016; Assem *et al*. 2017; Souto *et al*. 2018; Teughels *et al*. 2020). The recommendation for the use of antibiotics to treat periodontal infections should follow the same principles used for the treatment of any other infection in the body, that is: the risks need to be clearly offset by benefits to the patient – benefits that could not be otherwise achieved or which would be achieved with much greater difficulty or risk by other means. The aim of this chapter is to discuss the use of systemic antibiotics in the treatment of periodontitis, in an endeavor to provide clinicians with guidance on the use of these agents in daily clinical practice.

Microbiological basis for periodontal treatment

The idea of using antimicrobial agents in the management of periodontal diseases is based on the premise that these are infections triggered and magnified by microorganisms that colonize the oral cavity, above or below the gingival margin. Understanding the composition of the periodontal microbiota in health and in disease is essential for establishing effective periodontal treatments.

The long search for periodontal pathogens and the concept of beneficial species

Researchers first suggested a specific bacterial etiology for periodontal diseases during the golden era of medical bacteriology (1880–1920), when the etiologic agents of important bacterial infections, such as cholera and anthrax, were isolated (Socransky & Haffajee 1994). Regrettably, technical difficulties in evaluating the complex periodontal microbiota colonized by several strict anaerobes and fastidious pathogens have delayed a more accurate description of the subgingival microbial composition (Socransky *et al*. 1987). Despite these difficulties, the collective efforts of pioneer microbiologists using mainly open-ended culture techniques led to the isolation and identification of several important periodontal pathogens (Newman *et al*. 1976; Slots, 1976; Loesche *et al*. 1982, 1985; Keyes & Rams 1983; Moore *et al*. 1985; Socransky *et al*. 1988a, b; Haffajee & Socransky 1994; Marsh 1994; Zambon 1996; Riviere *et al*. 1996, 1997). This knowledge was significantly expanded after the introduction of target molecular diagnostic techniques in the 1980s and 1990s, such as monoclonal antibodies, enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and DNA probes (Dzink *et al*. 1983; Bonta *et al*. 1985; Zappa *et al*. 1990; Socransky *et al*. 1991; Watanabe & Frommel 1993; Gmur & Guggenheim 1994; Socransky *et al*. 1994; Ellwood *et al*. 1997; Socransky *et al*. 1998; Mombelli *et al*. 1999). One of these techniques, checkerboard DNA–DNA hybridization (Socransky *et al*. 1994), allowed for the quantification of many bacterial species in hundreds of thousands of plaque samples and introduced the concept of microbial complexes in 1998 (Socransky *et al*., 1998, 1999; Ximénez-Fyvie *et al*. 2000a, b, 2006; Colombo *et al*. 2002; Socransky & Haffajee 2002, 2005; Haffajee *et al*. 2004, 2005, 2006, 2008a, b; López *et al*. 2004; Teles *et al*. 2006; Faveri *et al*. 2009; da Silva-Boghossian *et al*. 2011; Uzel *et al*. 2011; Feres *et al*. 2015; Feres *et al*. 2016; Maciel *et al*. 2016). More recently, open-ended DNA sequencing technologies, including next-generation sequencing (NGS), opened up the possibilities of identifying all microorganisms in a given sample, including those that have never been cultivated before, revealing an even broader diversity within the periodontal microbiome (Paster *et al*. 2001; Griffen *et al*. 2012; Liu *et al*. 2012; Abusleme *et al*. 2013; Wang *et al*. 2013; Duran-Pinedo *et al*. 2014; Galimanas *et al*. 2014; Li *et al*. 2014; Camelo-Castillo *et al*. 2015; Chen *et al*. 2015; Kirst *et al*. 2015; Park *et al*. 2015; Pozhitkov *et al*. 2015; Dabdoub *et al*. 2016; Ganesan *et al*. 2017; Chen *et al*. 2018a; Shi *et al*. 2018; Pérez-Chaparro *et al*. 2018; Tsai *et al*. 2018; Schulz *et al*. 2019; Wei *et al*. 2019; Feres *et al*. 2020b; Ikeda *et al*. 2020). The labor-intensive work of the abovementioned microbiologists revealed that only a limited number of organisms are associated with the etiopathogenesis of periodontitis and that several other species colonizing the oral cavity were host-compatible or beneficial. The species considered "true" pathogens were those found in higher levels and proportions in patients with periodontitis than in healthy individuals (association studies), and were reduced in sites and patients who responded well to periodontal treatment (elimination/suppression studies), namely: *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia* (red complex pathogens), *Eubacterium nodatum*, and several *Fusobacteria*, *Prevotella*, and *Campylobacter* species (orange complex species), as well as *Eikenella corrodens*, *Selenomonas sputigena*, *Aggregatibacter actinomycetemcomitans*, and *Treponema socranskii*. The data provided by the studies using NGS confirmed previous knowledge of the role of these classic pathogenic species in the pathobiology of periodontal diseases and identified other taxa, such as *Filifactor alocis*, *Eubacterium saphenum*, *Dialister invisus*, and several other species from the genera *Treponema* and *Desulfobulbus*, as possible new pathogens (Pérez-Chaparro *et al*. 2014; Feres *et al*. 2020c) (Fig. 36-1). A recently introduced concept suggests that certain periodontal pathogens, named "keystone pathogens", are able to evade host

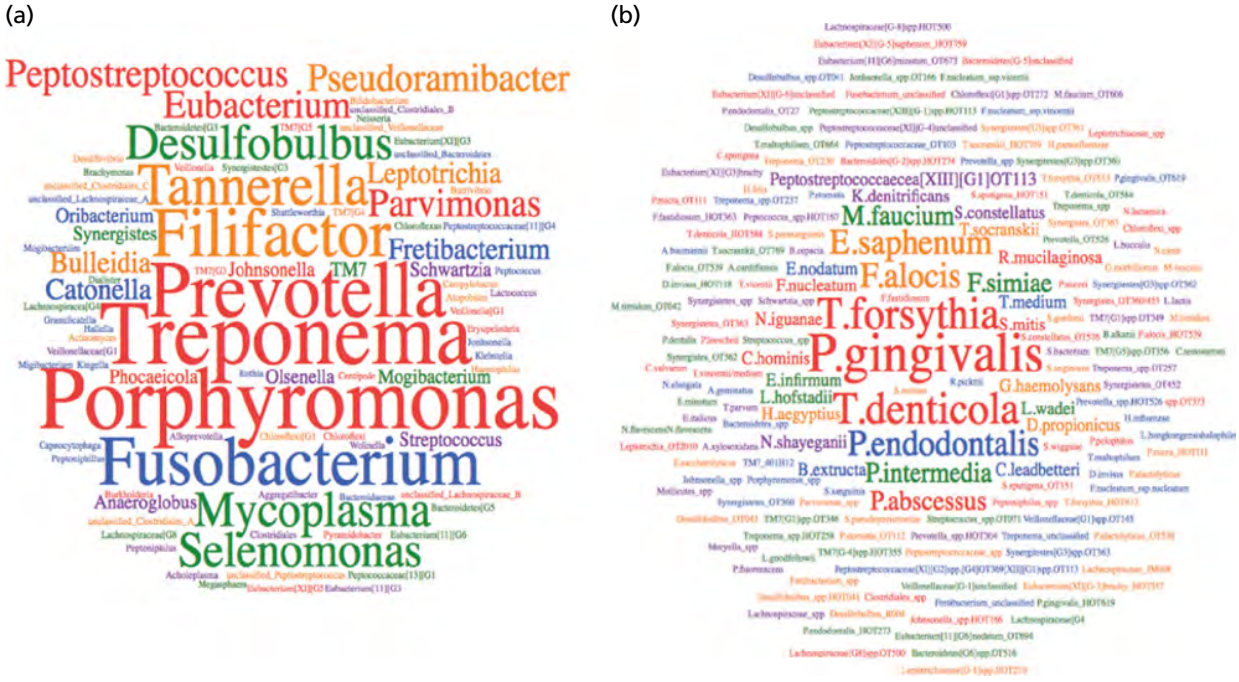

Fig. 36-1 Word clouds of the *genera* (a) and *species* (b) increased in periodontitis, according to the data from the association studies using next-generation sequencing (16S and metagenomic techniques). (Source: Adapted from Feres *et al*. 2020c. Reproduced with permission from John Wiley & Sons.)

response and mediate the conversion of the whole microbial community into dysbiosis. The broad disturbance of this community would cause and/or sustain the process of periodontal breakdown. *P. gingivalis* has been identified as a main keystone pathogen (Hajishengallis 2011; Hajishengallis & Lamont 2012; Hajishengallis *et al*. 2011).

Conversely, other microorganisms were considered host compatible as they were found elevated in periodontal health and increased in proportions after therapy. These included *Veillonella parvula* and *Actinomyces odontolyticus* (purple complex) and several species from the genera *Actinomyces*, *Streptococcus* (yellow complex), and *Capnocytophaga* (green complex) (Socransky *et al*. 1988a, b, 1998; Haffajee *et al*. 2006; Faveri *et al*. 2009; Teles *et al*. 2006, 2013). Species from the genera *Rothia*, *Neisseria*, *Leptotrichia*, *Corynebacterium*, and *Kingella* have also been recently associated with periodontal health (Feres *et al*. 2020c) (Fig. 36-2).

The accumulated knowledge about the composition of the subgingival microbiota in periodontal health and in periodontitis suggest that successful treatment would require a profound ecological change in the entire oral cavity. This may not be easy to achieve, especially considering that these microorganisms do not live in isolation but are part of complex microbial communities named biofilms.

Understanding the target: bacterial biofilms

Besides the great advance in our knowledge about the composition of the periodontal microbiota in the past 50 years, the notion that periodontitis is caused by bacteria growing in biofilms led to a big breakthrough in our understanding of treatment success and failure. Bill Costerton, the father of biofilm science, defined biofilm as "matrix-enclosed bacterial populations adherent to each other and to a solid (non-shedding) surface" (Costerton 1999). This definition has been refined to also include shedding surfaces (Hall-Stoodley *et al*. 2004). Thus, the term biofilm has come to encompass not only the bacterial communities attached to the tooth or other artificial surfaces in the mouth, but also those on the tongue and other oral soft tissues.

Biofilms are complex structures that may function as a physiological integrated community and provide several advantages to colonizing species, such as protection from undesirable environmental conditions (e.g. oxygen levels), antibiotics, and host defenses (Costerton *et al*. 1999; Marsh & Devine 2011). Most of the cells in biofilms are alive and may be spatially organized in patterns that facilitate metabolic cooperation. The presence of strict anaerobe pathogens in highly oxygenated niches of the oral cavity is a good example of biofilm protection. While in the subgingival environment these species are located in the outer layer of the biofilm, lining the epithelium (Kolenbrander *et al*. 2006; Zijnge *et al*. 2010), in the niches exposed to oxygen, the strict anaerobes are protected from oxygen within the deep layers of the biofilm (Marsh 1994). This explains how shallow pockets, tongue, saliva, oral mucosa, and the supragingival biofilm of subjects with periodontitis are highly colonized with several strict anaerobe periodontal pathogens, such as those from the red and orange complexes (Riviere *et al*. 1996, 1997;

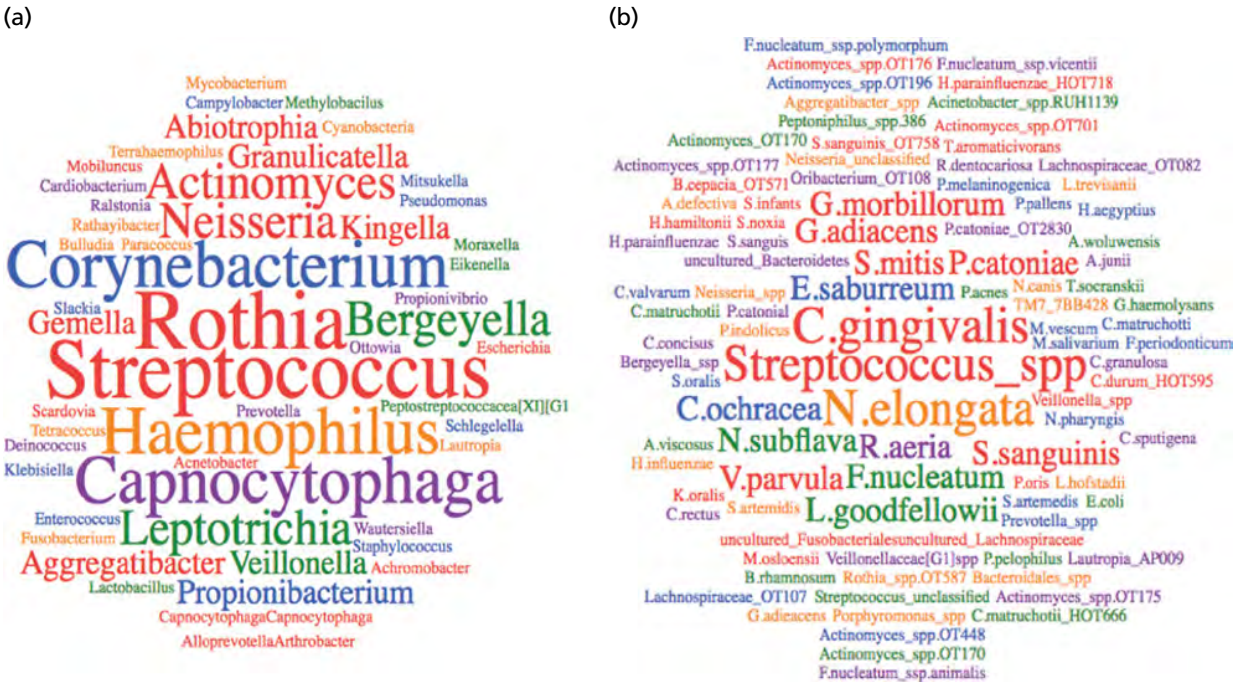

Fig. 36-2 Word clouds of the *genera* (a) and *species* (b) increased in periodontal health, according to the data from the association studies using next-generation sequencing (16S and metagenomic techniques). (Source: Adapted from Feres *et al*. 2020c. Reproduced with permission from John Wiley & Sons.)

Ximénez-Fyvie *et al*. 2000a, b; Mager *et al*. 2003; Beikler *et al*. 2004; Socransky & Haffajee 2005; Faveri *et al*. 2006a; Haffajee *et al*. 2008b). These findings impact treatment decisions, because they suggest that not only deep pockets, but also shallow pockets, and all other oral surfaces of patients with periodontitis demand biofilm-control treatment. If not eliminated or reduced, pathogens residing in the profound layers of different oxygenated niches in the oral cavity may be a source of recolonization of recently treated pockets.

The development of mixed biofilms is normally guided by the environmental conditions, nutrient availability, and the coaggregation (i.e. specific bindings) patterns of colonizing microorganisms. Determining the biogeography of microorganisms within biofilms is not simple, but the sequence of subgingival colonization has been suggested by a few authors (Socransky *et al*. 1998; Socransky & Haffajee 2005; Kolenbrander *et al*. 2006; Zijnge *et al*. 2010; Teles *et al*. 2012). The overall results of these studies suggested that the early colonizers are mostly host-compatible species such as *V. parvula* and species from the genera *Streptococcus*, *Capnocytophaga*, and *Actinomyces* (mostly members of the yellow, green, and purple complexes). Orange complex microorganisms from the genera *Fusobacterium*, *Prevotella*, and *Campylobacter* function as a bridge between the early colonizers and the late colonizers from the red complex (*P. gingivalis*, *T. forsythia*, and *T. denticola*). Other newly identified pathogens from the genera *Porphyromonas* and *Treponema* would probably colonize the biofilm later, but the pattern of colonization of other putative pathogens such as those from the genera *Filifactor*, *Dialister*, and *Desulfobulbus*, is still unknown.

The final stage of equilibrium between microorganisms and the environment within a biofilm is called the climax community (Socransky & Haffajee 2005). It is extremely difficult to change the composition of a climax community due to a biofilm property named resilience – the ability for survival, recovery, and adaptation. In periodontal health, resilience is a beneficial mechanism because it prevents small challenges to the healthy biofilm that may result in dysbiosis and, consequently, disease (Rosier *et al*. 2018). Regrettably, the climax community associated with disease is also extremely stable, especially in the nutrient-rich environment of severe periodontitis. In this case, resilience has a negative impact on treatment outcome as it helps the climax community return to its original dysbiotic composition, especially if the biofilm is only mildly disturbed by therapy. This may lead to disease recurrence.

Microorganisms living in biofilms may be 10 to 1000 times more resistant to the effects of antimicrobials than their planktonic (i.e. non-attached) counterparts (Costerton *et al*. 1999). The main mechanisms of resistance include: (1) limited drug diffusion into the inner layers of the biofilm through the extracellular matrix; (2) low level of bacterial metabolic activity inside the biofilm, which may reduce the efficacy of antibiotics that target processes that occur in actively growing bacteria; (3) post-treatment presence of dormant cells called "persistants", which are not induced by antibiotic administration but may resist antibiotic

inactivation and help to re-establish the original composition of the climax community; (4) inactivation of antibiotic molecules in the biofilm matrix by entrapped degrading enzymes; and (5) overexpression of resistant genes by sessile (i.e. attached) cells. It is not clear how many of these mechanisms happen concomitantly in the subgingival environment, but the compelling body of evidence showing that biofilms offer substantial protection against antimicrobials and host response has led to an overall consensus that systemic antibiotics should always be combined with the mechanical disruption of the biofilm (Herrera *et al*. 2008; Sanz *et al*. 2008)

Rationale for the use of adjunctive systemic antibiotics in periodontal treatment

The main clinical goals of periodontal treatment include reductions in probing depth (PD), bleeding on probing (BoP) and suppuration, and gains in clinical attachment level (CAL). In addition, and most importantly, treatment should prevent further disease progression. Numerous interventional studies, conducted over the past decades, have demonstrated that these results are attained when treatment is able to produce a rapid and marked reduction in levels and proportions of the abovementioned periodontal pathogens and an oral recolonization by a new climax community with higher proportions of host-compatible microorganisms (Cugini *et al*. 2000; De Soete *et al*. 2001; Socransky & Haffajee 2002; Colombo *et al*. 2005; Haffajee *et al*. 2006; Teles *et al*. 2006; Matarazzo *et al*. 2008; Mestnik *et al*. 2010; da Silva-Boghossian *et al*. 2011; Silva *et al*. 2011; Uzel *et al*. 2011; Faveri *et al*. 2014; Soares *et al*. 2014; Feres *et al*. 2015, 2016; Tamashiro *et al*. 2016) (Fig. 36-3). This is not an easy undertaking, especially considering the protective effect of the biofilm and its high potential of recovery (resilience). Hypothetically, systemic antibiotics may be useful tools in achieving these ecological changes.

Mechanical periodontal therapy and its limitations

Subgingival instrumentation, usually delivered as scaling and root planing (SRP) is the gold standard treatment for periodontitis and it improves all periodontal clinical parameters (Badersten *et al*. 1981; Pihlstrom *et al*. 1983; Ramfjord *et al*. 1987; Cobb 2002; Heitz-Mayfield *et al*. 2002; Hung & Douglass 2002). These clinical benefits are associated with a decrease in total counts of bacteria and also with a reduction in specific pathogens and a concomitant increase in host-compatible species (Hinrichs *et al*. 1985; Sbordone *et al*. 1990; Pedrazzoli *et al*. 1991; Ali *et al*. 1992; Haffajee *et al*. 1997, 2008a; Shiloah *et al*. 1997; Cugini *et al*. 2000; Fujise *et al*. 2002; Carvalho *et al*. 2005; Colombo *et al*. 2005; Haffajee *et al*. 2006; Ioannou *et al*. 2009; Knöfler *et al*. 2011; Rosalem *et al*. 2011; Silva *et al*. 2011; Feres *et al*. 2015, 2016; Mombelli 2018). Interestingly, although SRP does not target specific microorganisms, it leads to the recolonization of recently scaled sites with a microbiota more compatible with health. This is probably due to the typical post-treatment sequence of recolonization. The host-compatible species are the first to recolonize the recently instrumented tooth surfaces, while the main pathogens are late colonizers. These species, especially those from the red complex, are fastidious in nature and require several types of nutrients to grow, many of them produced by the inflammatory process associated with periodontitis. It has been proposed that periodontal treatment has a direct effect on biofilm and calculus and an indirect effect in the local host tissue. If an effective SRP is followed by adequate

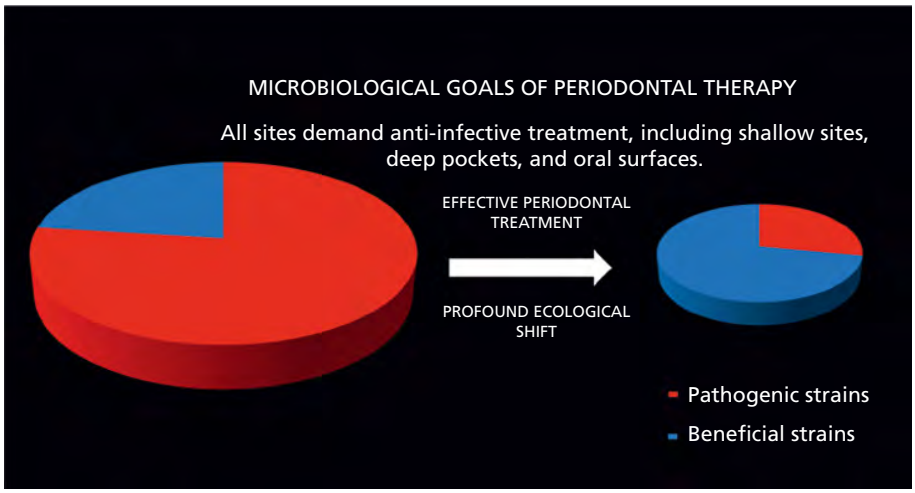

Fig. 36-3 Microbiological goals of periodontal therapy. It is important to highlight that treatment success depends on a profound change in the composition of the subgingival biofilm throughout the oral cavity, from a disease-related (dysbiosis) to a health-related (homeostasis) ecology. In order to obtain periodontal clinical stability, treatment must be able to lead to a reduction in the levels and proportions of pathogens and the concomitant increase in proportions of bacteria associated with periodontal health.

plaque control, the reduction in tissue inflammation is reached, together with low levels of gingival crevicular fluid, which represents an important source of nutrients for many fastidious pathogens (Socransky & Haffajee 2002; Socransky *et al*. 2004; Uzel *et al*. 2011; Teles *et al*. 2013). This new healthy environment prevents biofilm colonization by high proportions of pathogens due to restriction of nutrition and other bacterial growth requirements. Unfortunately, the clinical and microbiological improvements obtained after SRP are not always sustained over time, particularly in severe cases with the presence of many deep pockets and a severely dysbiotic biofilm. Thus, other forms of periodontal therapies, including local and systemic antimicrobials, have been proposed in conjunction with SRP with the objective of improving the clinical and microbiological outcomes of this treatment.

Local versus systemic antimicrobials

Antimicrobials for the treatment of periodontitis may be delivered locally or administered systemically. The concept of controlled local antimicrobial delivery in the treatment of periodontitis was introduced in 1979 by Max Goodson and co-workers (Goodson *et al*. 1979). The idea was rather appealing as the agents are directly applied at the infection site in very high concentrations, while systemic antimicrobials must navigate through multiple membranes surfaces within the body (e.g. gastrointestinal tract, endothelial, and epithelial surfaces) before reaching the gingival crevicular fluid and saliva. Locally delivered antimicrobials also cause fewer side effects than drugs prescribed systemically and have a reduced chance of developing bacterial resistance to the medications. Thus, different antibiotics and antiseptics (tetracycline, minocycline, doxycycline, metronidazole, piperacillin, tazobactam, chlorhexidine, etc.), delivered through different systems (non-resorbable polymer fibers, gels, chip of hydrolyzed gelatin) have been tested in the treatment of periodontitis (Herrera *et al*. 2020). The overall results suggest a beneficial effect of the adjunctive use of these products at a local level, but the outcomes, in general, were not as good as expected (for review, see Chapter 37). This may be partially explained by limitations of the release kinetics of the carrier systems and the complexity of the infection being treated. In order to effectively change the climax community associated with periodontitis, the antimicrobial agent must be released subgingivally over a long period of time (at least 7–10 days) in a controlled concentration. Regrettably, very few systems present with such kinetics. In addition, as discussed earlier in this chapter, the dysbiosis associated with periodontitis affects the whole oral cavity, including shallow sites, saliva, tongue, and cheeks. Thus, it is somehow expected that the use of locally delivered antimicrobials restricted to a subset of deep subgingival sites would be particularly limited. Therefore, local antimicrobial therapy has been recommended during the maintenance phase for treating remaining and isolated active pockets (Heasman *et al*. 2001; Hussein *et al*. 2007; Herrera *et al*. 2020).

The systemic administration of antibiotics mitigates some of the limitations of local delivery. The agents reach all the oral surfaces and fluids for a prolonged period of time and may reach periodontal pathogens that eventually invade the host's tissues (Rudney *et al*. 2005; Kim *et al*. 2010). The disadvantages of systemic administration over local delivery include adverse drug reactions (Slots & Rams 1990), uncertain patient compliance (Loesche *et al*. 1993; Guerrero *et al*. 2007), lower concentration of the drug at subgingival sites (Goodson 1994) and the increased risk of developing bacterial resistance (WHO 2015; Tacconelli *et al*. 2018). Several systemic antibiotics have been used as adjuncts to mechanical periodontal treatment with different degrees of success. The literature is reviewed in the following sections.

Systemic antibiotics in periodontal therapy

Should systemic antimicrobial therapy be aimed at specific pathogens?

The idea of using systemic antibiotics to target/eliminate specific pathogens from the subgingival biofilm is based on the historical attempt to parallel the pathobiology of periodontitis with that of classic infections and on evidences showing that a well-recognized pathogen, *A. actinomycetemcomitans*, is effectively reduced by a specific combination of antibiotics. These principles are summarized below.

The notion that periodontitis is associated with specific pathogens may have led to misinterpretations concerning its pathobiology and mode of treatment. Classic infections, such as syphilis and tuberculosis, are normally caused by an exogenous microorganism, but periodontitis is a complex disease associated with mainly endogenous pathogens that may trigger and/or promote tissue destruction in susceptible hosts (Haffajee & Socransky 1994; Teles *et al*. 2013). Several periodontal pathogens are involved in disease onset and progression concomitantly, and pathogens may be found in healthy individuals, albeit in low levels and proportions (Socransky & Haffajee 2005). The presence of pathogens in healthy individuals is not unique to periodontal diseases; they occur in virtually any infection, including the most classic ones. In classic infections, once disease is established, the accurate diagnosis of the causative agent and their sensitivities to different antibiotics are essential in order to ensure the effective elimination of the agent and, consequently, cure. In periodontitis, environmental factors may lead to the selection or overgrowth of different pathogens, including opportunistic (or accessory species) (Socransky & Haffajee, 2005; Darveau 2010;

Hajishengallis 2011; Hajishengallis & Lamont 2012) and possibly some yet unidentified/unnamed organisms (Pérez-Chaparro *et al*. 2014; Feres *et al*. 2020c). A microbial diagnosis would have limited value for treatment in this case, since the detection of one pathogen would not rule out the presence of others. In addition, a negative test does not mean the pathogen is absent, but simply means it was not detected in the sites sampled. And, finally, we should bear in mind that, as suggested previously in this chapter, effective periodontal treatment demands a striking change in the biofilm climax community, from a microbial profile associated with disease to a microbial profile compatible with health, rather than on the elimination of one or a few pathogens.

An argument that supported the notion that antibiotic therapy in periodontics should be driven by the presence of specific pathogens came from a series of elegantly designed studies carried out by van Winkelhoff and co-workers in the 1980s and 1990s. These authors convincingly demonstrated that the combination of metronidazole (MTZ) and amoxicillin (AMX) could reduce or eliminate *A. actinomycetemcomitans* from periodontal and oral sites in patients with periodontitis, and these reductions were associated with important clinical improvements (Christersson *et al*. 1985; van Winkelhoff *et al*. 1989, 1992; Goené *et al*. 1990; Renvert *et al*. 1990; Berglundh *et al*. 1998; Flemmig *et al*. 1998; Winkel *et al*. 1998). These findings reinforced the idea that specific antibiotics should only be prescribed in cases of periodontitis associated with specific pathogens. However, data from later clinical studies has challenged this notion by showing that patients not initially colonized by *A. actinomycetemcomitans* also benefited from the combination of MTZ plus AMX (MTZ+AMX) (Dannewitz *et al*. 2007; Mombelli *et al*. 2013), most probably due to the effect of these agents in inhibiting other important pathogens and in changing the microbiological profile towards health (Haffajee *et al*. 2006; Mestnik *et al*. 2010; Soares *et al*. 2014; Faveri *et al*. 2014; Feres *et al*. 2015; Tamashiro *et al*. 2016; Duarte *et al*. 2018). Indeed, a recent systematic review concluded that there is no compelling evidence in the literature that baseline detection of *A. actinomycetemcomitans* should be used as a criterion for prescribing adjunctive antibiotics, although the authors acknowledge the limitations of their review, because of the limited information available (Nibali *et al*. 2019). Conversely, some studies and/or secondary analysis indicated that patients with specific microbial profiles benefit more from adjunctive systemic antibiotics (Guerrero *et al*. 2014) and that targeting specific species or clonotypes (e.g. *A. actinomycetemcomitans* JP2) would be relevant in certain patients/conditions (van Winkelhoff *et al*. 1989, 1992; Haubek *et al*. 2008). In addition, the keystone pathogen hypothesis associating *P. gingivalis* with disease onset (Hajishengallis & Lamont 2014) rekindled the idea of a possible important role of targeting specific pathogens.

In summary, there is still controversy on the need for identifying a specific periodontal pathogen to achieve treatment success, and consequently, baseline microbiological tests are not routinely used in daily clinical practice and most randomized clinical trials (RCTs) in periodontology have not chosen patients and/or antibiotics according to specific microbial profiles.

Which antimicrobial(s) would provide the most predictable results? A historical perspective

The first clinical studies on the effect of systemic antimicrobials in periodontal treatment were conducted in the 1970s and 1980s. Most of those studies used tetracycline for treating young subjects with periodontal destruction localized in first molars and incisors, who did not respond to mechanical treatment: a condition at that time named localized juvenile periodontitis (later known as localized aggressive periodontitis, and currently molar/incisor pattern periodontitis). These studies showed that a regimen of 1 g/day of tetracycline HCl for 2–4 weeks enhanced the resolution of gingival inflammation and led to gains in CAL and alveolar bone (Lindhe & Liljenberg 1984; Novak *et al*. 1988, 1991). The two lipid soluble analogs, doxycycline and minocycline, which seemed to achieve higher gingival fluid levels with a lower dose regimen of 100–200 mg/day for 7–21 days (Ciancio *et al*. 1980, 1982; Pascale *et al*. 1986), also led to important clinical improvements in young subjects (Mandell & Socransky 1988; Müller *et al*. 1993). However, tetracycline and its analogs did not show similar benefits in adults (Listgarten & Helldén 1978; Helldén *et al*. 1979; Scopp *et al*. 1980; Ng & Bissada 1998).

Many results obtained with the tetracyclines, especially in young patients, seemed promising, and hence, during the 1980s and 1990s, several antibiotics were tested for their use in the treatment of periodontitis, culminating with the publication of the two first systematic reviews with meta-analyses on this topic at the beginning of the 2000s (Herrera *et al*. 2002; Haffajee *et al*. 2003b), which were presented at the European and World Workshops in Periodontology, respectively. Over 10 different antimicrobials or combination of drugs were included in the meta-analyses, and both studies suggested that the adjunctive use of systemic antibiotics to SRP provided some additional benefit over SRP alone in terms of CAL gain and PD reduction, especially in younger patients and in patients with severe/aggressive/"active" disease and/or specific microbiological profiles. Although neither study could assign superiority to any particular antibiotic due to insufficient numbers of studies for each agent tested, differences in study protocols, and small sample sizes, the body of evidence suggested that some antibiotics were more effective than others, and this information impacted the next round of studies in this area. It should be noted that

the majority of studies provided data up to 6 months post-treatment, and that the most recent literature encompassing studies with 1 year or more of follow-up converged on the use of three particular drugs/combinations: MTZ, MTZ+AMX and azithromycin (AZI) (Feres *et al*. 2015; Teughels *et al*. 2020).

Metronidazole

MTZ is a nitroimidazole compound discovered in the late 1950s, when researchers at Rhone-Poulenc Research Laboratories in France were trying to create a synthetic product from a *Streptomyces* spp. that would have activity against *Trichomonas vaginalis* (Freeman *et al*. 1997). Thus, MTZ was found initially to be effective against certain protozoan pathogens. Its antibacterial activity was discovered by accident in 1962, when a patient with *T. vaginalis* and acute ulcerative gingivitis had a "double cure" after a week of treatment with MTZ (Shinn, 1962). This clinical observation led to studies that established MTZ as an important bactericidal antimicrobial for anaerobic infections in the body (Falagas & Gorbach 1995; Stupnicki *et al*. 1996; Freeman *et al*. 1997), including the oral cavity (Proctor & Baker 1971; Loesche *et al*. 1982). MTZ can be considered a prodrug in the sense that it requires metabolic activation by anaerobic organisms; hence, all aerobic organisms are intrinsically resistant to this agent. The selective efficacy of MTZ against obligate anaerobes makes it particularly appealing for the treatment of periodontitis, considering that most periodontal pathogens are strict anaerobes, such as the three red complex species (*P. gingivalis, T. forsythia*, and *T. denticola)*.

Lindhe and co-workers (Lindhe *et al*. 1983a) were the first to observe that systemic MTZ (200 mg) taken four times a day for 14 days, in combination with mechanical therapy, was more effective in improving clinical parameters and reducing *spirochetes* than controls who received SRP alone. But it was Walter Loesche and co-workers who carried out the seminal clinical studies showing the benefits of MTZ for patient with periodontitis, especially in reducing the need for periodontal surgery (Loesche *et al*. 1987, 1991, 1992, 1996). Later, other RCTs demonstrated the effect of these agents in improving several periodontal clinical parameters and the composition of the subgingival microbiota (Feres *et al*. 2001, 2012; Sigusch *et al*. 2001; Carvalho *et al*. 2004, 2005; Xajigeorgiou *et al*. 2006; Matarazzo *et al*. 2008; Rooney *et al*. 2002; Silva *et al*. 2011; Preus *et al*. 2013; Soares *et al*. 2014).

Amoxicillin

AMX is a semisynthetic penicillin. The discovery of penicillin in 1928 and the beginning of its clinical use in 1941 represented a real turning point in human history. For the first time, patients desperately ill with staphylococcal and streptococcal infections could be cured. Cephalosporins and penicillins are the main classes of ß-lactam antibiotics. They are bactericidal agents and kill susceptible bacteria by inhibiting the synthesis of the bacterial peptidoglycan cell wall (Spratt 1978; Yocum *et al*. 1980). Because penicillin has a narrow spectrum of antimicrobial activity, research for alternative drugs with a broader range of antimicrobial activity led to the discovery of AMX by scientists at Beecham Research Laboratories, in 1972 (Gordon *et al*. 1972). The most important mechanism of resistance is β-lactamase-mediated hydrolysis of the β-lactam ring, resulting in inactivation of the antibiotic. A small proportion of the subgingival microbiota seems to be resistant to AMX (Sutter *et al*. 1983; Walker *et al*. 1983; Feres *et al*. 2002; Ardila *et al*. 2010; Rams *et al*. 2014), but an important number of patients will harbor, at least, one β-lactamase producing bacterial species (Herrera *et al*. 2000b).

Penicillin has not shown encouraging clinical results in the treatment of periodontitis, probably due to its antimicrobial effect being limited to aerobic microorganisms (Kinder *et al*. 1986; Drawz & Bonomo 2010), and only a few studies have described the clinical and microbiological outcomes of AMX, as an adjunct, in periodontal treatment (Feres *et al*. 2001; Matisko & Bissada 1993; Abu Fanas *et al*. 1991; Winkel *et al*. 1999). Feres *et al*. (2001) showed beneficial changes in clinical parameters and in the subgingival microbial composition in nine adults with periodontitis, treated by means of SRP and systemic AMX for 14 days. These changes were very striking during antibiotic administration and up to 14 days after the antibiotic was withdrawn, and most of the benefits were maintained for up to 1 year. However, of concern was the fact that the proportions of the *Actinomyces* species were reduced right after treatment and remained low up to 1-year post-therapy. This was considered an unwanted outcome of treatment, since these are host-compatible organisms that one expects to increase in proportion after treatment.

Metronidazole plus amoxicillin

Although AMX was not established as a drug of choice in the treatment of periodontitis, the important studies led by A.J. van Winkelhoff suggested that the combined use of AMX and MTZ could be a potent tool in the treatment of periodontitis, especially in patients harboring *A. actinomycetemcomitans* (van Winkelhoff *et al*. 1989, 1992; Pavicic *et al*. 1992, 1994). Many years later, the first placebo-controlled RCT demonstrating the benefits of the combination of AMX and MTZ in treating young adults with aggressive periodontitis was published (Guerrero *et al*. 2005), and this information was confirmed by other studies (Xajigeorgiou *et al*. 2006; Mestnik *et al*. 2010, 2012; Yek *et al*. 2010; Aimetti *et al*. 2012; Casarin *et al*. 2012). Similar benefits were also shown in adults with severe periodontitis (Moeintaghavi *et al*. 2007; Cionca *et al*. 2009, 2010;

Silva *et al*. 2011; Feres *et al*. 2012; Goodson *et al*. 2012; Feres *et al*. 2015; Harks *et al*. 2015; Usin *et al*. 2016; Saleh *et al*. 2016; Cosgarea *et al*. 2016, 2017; Borges *et al*. 2017; Mombelli *et al*. 2017; Rebeis *et al*. 2019) and in very young patients with localized disease (Beliveau *et al*. 2012; Merchant *et al*. 2014; Burgess *et al*. 2017; Rebeis *et al*. 2019), colonized or not by *A. actinomycetemcomitans*. These agents also showed added benefits in smokers (Matarazzo *et al*. 2008; Theodoro *et al*. 2018) and in patients with diabetes (Miranda *et al*. 2014; Tamashiro *et al*. 2016). Microbiological studies, evaluating 40 bacterial species, showed that the improvements in clinical parameters were associated, not only with a reduction in *A. actinomycetemcomitans*, but with a broader beneficial change in the subgingival microbial composition, as will be described later in this chapter (Haffajee *et al*. 2006; Matarazzo *et al*. 2008; Mestnik *et al*. 2010; Casarin *et al*. 2012; Soares *et al*. 2014; Feres *et al*. 2015; Miranda *et al*. 2014; Tamashiro *et al*. 2016).

Azithromycin

AZI is a relatively new macrolide that, due to excellent pharmacological properties, emerged as a promising drug in medicine in the early 1990s (Schönwald *et al*. 1990; Balmes *et al*. 1991; Hoepelman & Schneider 1995) and, more recently, in dentistry (Herrera *et al*. 2000a; Mascarenhas *et al*. 2005; Haffajee *et al*. 2006; Dastoor *et al*. 2007; Gomi *et al*. 2007; Haas *et al*. 2008, 2012; Yashima *et al*. 2009; Oteo *et al*. 2010; Botero *et al*. 2013; Martande *et al*. 2016). AZI is a semisynthetic, bacteriostatic, wide-spectrum antibiotic, rapidly absorbed by cells, such as leucocytes and fibroblasts, which helps to quickly bring the drug to the site of inflammation and to maintain its concentration 10–100 times higher in tissues than in serum (Hoepelman & Schneider 1995). In addition, AZI is slowly released to the tissues, which increases its half-life (Gladue *et al*. 1989; Gladue & Snider 1990). This favorable pharmacokinetic property allows AZI to be administered only once a day (500 mg) for short periods of time (from 3 to 6 days) (Henry *et al*. 2003). This simple dosage protocol and the low incidence of side-effects reported with the use of this antibiotic facilitate patient adherence to treatment, which represents a major advantage of AZI over MTZ, alone or in combination with AMX. Nonetheless, despite the good pharmacological properties and its easy dosage regimen, the results of RCTs assessing the clinical and microbiological effects of AZI in periodontal treatment diverged considerably. Whereas some authors demonstrated that AZI could enhance the outcomes of subgingival instrumentation of patients with periodontitis (Dastoor *et al*. 2007; Gomi *et al*. 2007; Haas *et al*. 2008; Haas *et al*. 2012; Botero *et al*. 2013; Martande *et al*. 2016), smokers (Mascarenhas *et al*. 2005), or in cases of mild/moderate periodontitis (Haffajee *et al*. 2007; Oteo *et al*. 2010; Smith *et al*. 2002), others could not show important benefits (Sampaio *et al*. 2011; Emingil *et al*. 2012; Han *et al*. 2012; Morales *et al*. 2018).

Which antimicrobial(s) would provide the most predictable results? Weighting the evidence: clinical outcomes in randomized clinical trials and systematic reviews

RCTs and systematic reviews with meta-analysis represent the highest level of evidence to assess the clinical effectiveness of a new intervention (Bero & Rennie 1995; Cook *et al*. 1995; Liberati *et al*. 2009; Spieth *et al*. 2016). These studies are the main pillars of what has been named "evidence-based clinical practice" (Bero & Rennie 1995; Cook *et al*. 1995; Bahtsevani *et al*. 2004). Thus, this section will present the results of such studies, in an attempt to determine the weight of evidence for the use of different systemic antimicrobials in the treatment of periodontitis.

RCTs testing adjunctive systemic antimicrobials in periodontal treatment have evaluated a variety of different agents or combinations. The majority of these studies have presented data for up to 6 months of follow-up and fewer provided longer term (≥1 year) data (Herrera *et al*. 2002; Haffajee *et al*. 2003b; Feres *et al*. 2015; Teughels *et al*. 2020). In general, clinical guidelines suggest that the best evidence for the use of a new treatment comes from studies with at least 1 year of follow-up and more than 100 patients (Hadorn *et al*. 1996). Nonetheless, such data are not always available in the literature, due to difficulties in selecting patients with less prevalent conditions and in retaining patients in studies for long periods of time. Thus, in periodontology, RCTs with at least 6 months of follow-up are normally accepted as good evidence to support the use of new treatment protocols (Herrera *et al*. 2002). Twenty-eight placebo-controlled (Al-Joburi *et al*. 1989; Bain *et al*. 1994; Berglundh *et al*. 1998; Rooney *et al*. 2002; Guerrero *et al*. 2005; Haas *et al*. 2008; Cionca *et al*. 2009; Mestnik *et al*. 2010; Oteo *et al*. 2010; Basegmez *et al*. 2011; Sampaio *et al*. 2011; Heller *et al*. 2011; Pradeep and Kathariya, 2011; Aimetti *et al*. 2012; Casarin *et al*. 2012; Emingil *et al*. 2012; Feres *et al*. 2012; Han *et al*. 2012; Pradeep *et al*. 2012; Preus *et al*. 2013; Ardila *et al*. 2015; Harks *et al*. 2015; Martande *et al*. 2016; Taiete *et al*. 2016; Andere *et al*. 2017; Borges *et al*. 2017; Cosgarea *et al*. 2017; Morales *et al*. 2018) and 19 non-placebo controlled RCTs (Lindhe *et al*. 1983b; Saxén & Asikainen 1993; Flemmig *et al*. 1998; Palmer *et al*. 1999; Ramberg *et al*. 2001; Blandino *et al*. 2004; Vergani *et al*. 2004; Ehmke *et al*. 2005; Mascarenhas *et al*. 2005; Xajigeorgiou *et al*. 2006; Gomi *et al*. 2007; Haffajee *et al*. 2007; Kaner *et al*. 2007; Guentsch *et al*. 2008; Yashima *et al*. 2009; Yek *et al*. 2010; Beliveau *et al*. 2012; Goodson *et al*. 2012; Jentsch *et al*. 2016), with at least 6 months of follow-up, have described the clinical outcomes of systemic antibiotics as adjuncts to SRP or subgingival mechanical instrumentation in periodontal treatment in systemically healthy individuals.

A recent systematic review, presented at the XVI European Workshop in Periodontology (2019), has evaluated the results of the 28 placebo-controlled studies available, which were reported in 34 publications (Teughels *et al*. 2020). The following agents were tested: MTZ+AMX ($n=17$), AZI ($n=7$), MTZ ($n=4$), spiramycin ($n=2$), clarithromycin (CLAR, $n=2$), moxifloxacin (MOX, $n=1$), AMX ($n=1$), minocycline (MINO, $n=1$), tetracycline ($n=1$), and ornidazole ($n=1$). Overall, the results of the meta-analysis, including 24 studies, suggested that antibiotics, adjunctive to SRP, led to a statistically significant additional full-mouth PD reduction and CAL gain, in agreement with observations from previous systematic reviews (Herrera *et al*. 2002, 2008; Haffajee *et al*. 2003b; Sgolastra *et al*. 2012a, b, 2014; Zandbergen *et al*. 2013, 2016; Keestra *et al*. 2015a, b; Rabelo *et al*. 2015). The level of evidence varied substantially among the different antibiotics studied. MTZ+AMX was the only adjunct supported by a high level of evidence, based on the results of 11 placebo-controlled RCTs, seven of them providing data for up to 1 or 2 years year of follow-up (Berglundh *et al*. 1998; Mestnik *et al*. 2010; Feres *et al*. 2012; Preus *et al*. 2013; Harks *et al*. 2015; Cosgarea *et al*. 2016; Borges *et al*. 2017). This treatment protocol led to statistically significant benefits over those obtained with SRP-only in all clinical outcomes evaluated, including PD reduction (primary outcome variable) and CAL gain in full-mouth and in initially moderately deep and deep pockets, percentage of pocket closure (sites changing from PD ≥4 to PD ≤3 mm) and frequency of pockets ≥4, 5, 6, and 7 mm, as well as of sites showing BoP. The level of evidence for the benefits brought about by the adjunctive use of MTZ and AZI was assessed as moderate, but the results for MTZ were more consistent. Although only two studies evaluated MTZ (Feres *et al*. 2012; Preus *et al*. 2013), the results were quite consistent in showing benefits of this agent, while the findings of the seven studies that assessed AZI were somewhat controversial. While three studies showed a significant benefit in CAL gain (Oteo *et al*. 2010; Emingil *et al*. 2012; Martande *et al*. 2016), another four studies described none or minor benefits for this parameter with the adjunctive use of AZI (Haas *et al*. 2008; Sampaio *et al*. 2011; Han *et al*. 2012; Morales *et al*. 2018). The level of evidence for CLAR, MINO, and MOX was considered low.

A rather relevant clinical benefit, that has been consistently demonstrated in patients treated with adjunctive MTZ+AMX, and to a lesser extent with MTZ, is the efficacy of these agents in reducing residual pockets, above the reduction obtained with mechanical treatment only (Guerrero *et al*. 2005; Cionca *et al*. 2009; Feres *et al*. 2012; Mestnik *et al*. 2012; Mombelli *et al*. 2013; Miranda *et al*. 2014; Borges *et al*. 2017; Cosgarea *et al*. 2017). These results have direct clinical implications, since a robust long-term risk assessment study showed that the presence of nine or more sites with PD ≥5 mm or of at least one site with PD ≥6 mm after treatment were associated with future disease progression in a population of 172 subjects treated for periodontitis, and in periodontal maintenance for an average period of 11.3 years (Matuliene *et al*. 2008). Other authors have also discussed the association between the presence of residual pockets, with and/or without BoP, and the lack of periodontal stability (Claffey & Egelberg 1995; Renvert & Persson 2002; Lang & Tonetti, 2003; Cionca *et al*. 2009; Feres *et al*. 2012; Borges *et al*. 2017; Graetz *et al*. 2017; Tonetti *et al*. 2018). Figure 36-4 provides a clear representation of the prominent effect of MTZ+AMX, and to a lesser extent MTZ, in reducing the number of sites with PD ≥5 mm at 6- and 12-months post-therapy (Teughels *et al*. 2020).

Additional interesting findings regarding the effect of antibiotics in reducing deep sites have been recently published. The presence of, at most, four sites with PD ≥5 mm, which has been proposed as a clinical endpoint for active periodontal treatment in clinical trials (Feres *et al*. 2012, 2020a), were reported by the six RCTs with 1–2 years of follow-up that tested MTZ+AMX (Feres *et al*. 2012; Mestnik *et al*. 2012; Harks *et al*. 2015; Tamashiro *et al*. 2016; Cosgarea *et al*. 2017; Borges *et al*. 2017). Taken together, these studies showed that 53–72% of the patients taking MTZ+AMX were able to achieve this clinical outcome, as opposed to 6.6–36.5% of the patients receiving mechanical treatment only. One study (Feres *et al*. 2012), comparing MTZ+AMX and MTZ, reported similar benefits for these two agents: 61.6% of the patients treated by SRP and MTZ achieved the clinical endpoint for treatment, 67.7% of those treated by means of SRP and MTZ+AMX, and 22.5% with SRP alone.

In summary, the available evidence has demonstrated an added clinical benefit of MTZ+AMX, and to a lesser extent of MTZ alone, in reducing the number of residual sites, which may impact the long-term clinical stability of treated periodontitis patients, together with the advantage of reducing the need for periodontal surgeries. Indeed, the reduced need for periodontal surgeries with the use of adjunctive MTZ was suggested by Walter Loesche almost 30 years ago (Loesche *et al*. 1987, 1991) and this same effect has recently been confirmed, for MTZ+AMX, in an elegantly designed RCT (Mombelli *et al*. 2015).

Which antimicrobial(s) would provide the most predictable results? Microbiological impact

The clinical benefits achieved with the adjunctive use of MTZ alone, or MTZ+AMX to SRP, are closely associated with the striking effect of these treatment protocols in reducing specific periodontal pathogens and in changing the subgingival microbial profile associated with disease to a profile compatible with periodontal health (Haffajee *et al*. 2006; Cionca *et al*. 2009; Mestnik *et al*. 2010; Heller *et al*. 2011; Silva

et al. 2011; Casarin *et al*. 2012; Miranda *et al*. 2014; Soares *et al*. 2014; Feres *et al*. 2015; Tamashiro *et al*. 2016; Usin *et al*. 2016; Mombelli *et al*. 2017). Figure 36-5 describes the mean proportions of microbial complexes at 1-year post-treatment in subgingival biofilm samples taken from subjects with severe periodontitis treated with: (1) SRP alone ($n = 55$); (2) SRP combined with 400 mg of MTZ, three times daily for 14 days ($n = 45$); or (3) SRP with 400 mg of MTZ + 500 mg of AMX, three times daily for 14 days ($n = 54$) (Feres *et al*. 2015). Nine subgingival biofilm samples were taken from each subject at each time point (baseline and at 3 and 6 months and 1-year post-treatment) and individually analyzed to determine their content of 40 bacterial species by checkerboard DNA–DNA hybridization. The overall proportions of the complexes harboring the pathogens (red and orange) decreased, while those harboring beneficial species increased over the course of the study, in all treatment groups. At 1-year post-treatment, subjects taking antibiotics exhibited a microbial profile more compatible with periodontal health than the control group, treated by SRP alone. Antibiotic treated subjects presented lower proportions of red and orange complexes, in comparison with those receiving SRP only, whereas subjects taking MTZ+AMX had an additional benefit, which was higher proportions of the host compatible *Actinomyces* spp., in comparison with the other two treatments (Fig. 36-5).

As mentioned in the first section of this chapter, the introduction of NGS technologies to study the oral microbiota has allowed a systematic evaluation of the periodontal microbiome, including the effects of treatments in the whole bacterial community. Thirteen interventional studies to date have assessed post-treatment changes occurring in the subgingival microbiome using sequencing techniques (Sakamoto *et al*. 2004; Valenza *et al*. 2009; Jünemann *et al*. 2012; Laksmana *et al*. 2012; Shi *et al*. 2015; Bizzarro *et al*. 2016; Martelli *et al*. 2016; Belstrøm *et al*. 2017; Han *et al*. 2017; Hagenfeld *et al*. 2018; Liu *et al*. 2018; Chen *et al*. 2018b; Feres *et al*. 2020b), including two RCTs (Bizzarro *et al*. 2016; Hagenfeld *et al*. 2018). SRP was the standard treatment in all studies, and systemic MTZ+AMX was used as adjunct in five investigations (Valenza *et al*. 2009; Jünemann *et al*. 2012; Laksmana *et al*. 2012; Bizzarro *et al*. 2016; Hagenfeld *et al*. 2018). Because the studies using these techniques were too diverse in terms of patients included, treatments used, and follow-up time periods, it is still difficult to draw definitive conclusions in terms of the effects of specific treatment protocols in changing abundance of these species. The results of the two RCTs and one clinical study that directly compared mechanical treatment alone or with adjunctive MTZ+AMX, revealed a more beneficial change in the microbiome when the antibiotics were used (Jünemann *et al*. 2012; Bizzarro *et al*. 2016; Hagenfeld *et al*. 2018). All three studies showed that antibiotics were more effective than SRP alone in reducing the proportions of species from the genera *Porphyromonas* and *Treponema* and in fostering host-compatible species from the genera *Veillonella* and *Haemophillus*. Other genera more affected by systemic antibiotics than by mechanical treatment alone were *Synergistetes*, *Filifactor*, and *Tannerella*, all three of them comprising pathogens. The study of Bizzarro *et al*. (2016) was the only one to provide microbiological data up to 1-year post-treatment for 37 patients. Although some rebound was observed, most of the beneficial effects of the antibiotics on the microbiome were maintained over time. Hagenfeld *et al*. (2018) included the larger sample size and provided data for 96 subjects up to 2 months post-treatment. These authors showed a clear compositional separation for samples taken before and after treatment in the antibiotic group, but not in subjects receiving subgingival instrumentation alone. These differences before and after antibiotic treatment in hierarchical clustering seemed to be associated with the striking and significant reductions in genera harboring periodontal pathogens and a concomitant increase in those harboring health-associated species. This trend was not observed with subgingival instrumentation alone. Although the results of these studies have provided an initial view of the effects of treatment in modulating the dysbiotic microbiome observed in periodontitis, it is essential to conduct further clinical trials evaluating many patients and individual samples to extend the current knowledge in this field.

The overall changes in biofilms achieved with MTZ+AMX intake may be due to a series of ecological benefits: (1) the effect of these antimicrobials in reducing the numbers of major periodontal pathogens, such as the impact of MTZ on *P. gingivalis* and other strict anaerobes, and of MTZ+AMX on *A. actinomycetemcomitans* (van Winkelhoff *et al*. 1989; Goené *et al*. 1990; van Winkelhoff *et al*. 1992; Berglundh *et al*. 1998; Flemmig *et al*. 1998; Winkel *et al*. 1998); (2) these antimicrobials could potentially control periodontal pathogens present on the other oral surfaces, tissues, fluids, epithelial cells, and connective tissue; and (3) the broad-spectrum activity of AMX might potentiate the effect of SRP, leading to a more rapid and profound reduction of the bacterial load in the subgingival space.

Another possible role of the antibiotics administrated at the initial phase (step 2) of periodontal therapy is to suppress the overgrowth of species, such as some proteolytic pathogens, that could benefit from tissue damage during subgingival scaling (Feres *et al*. 2015). This would diminish inflammation in the local tissues during healing, which, in turn, would hinder an increase in the proportions of these same pathogens, a common event in microbial ecology, where colonizing species affect the habitat, and the habitat affects the colonizing organisms (Socransky & Haffajee 2002). The combination of all these effects would allow a recolonization of the recently scaled pockets by the host-compatible initial colonizers, preventing the species of the red complex (and possibly

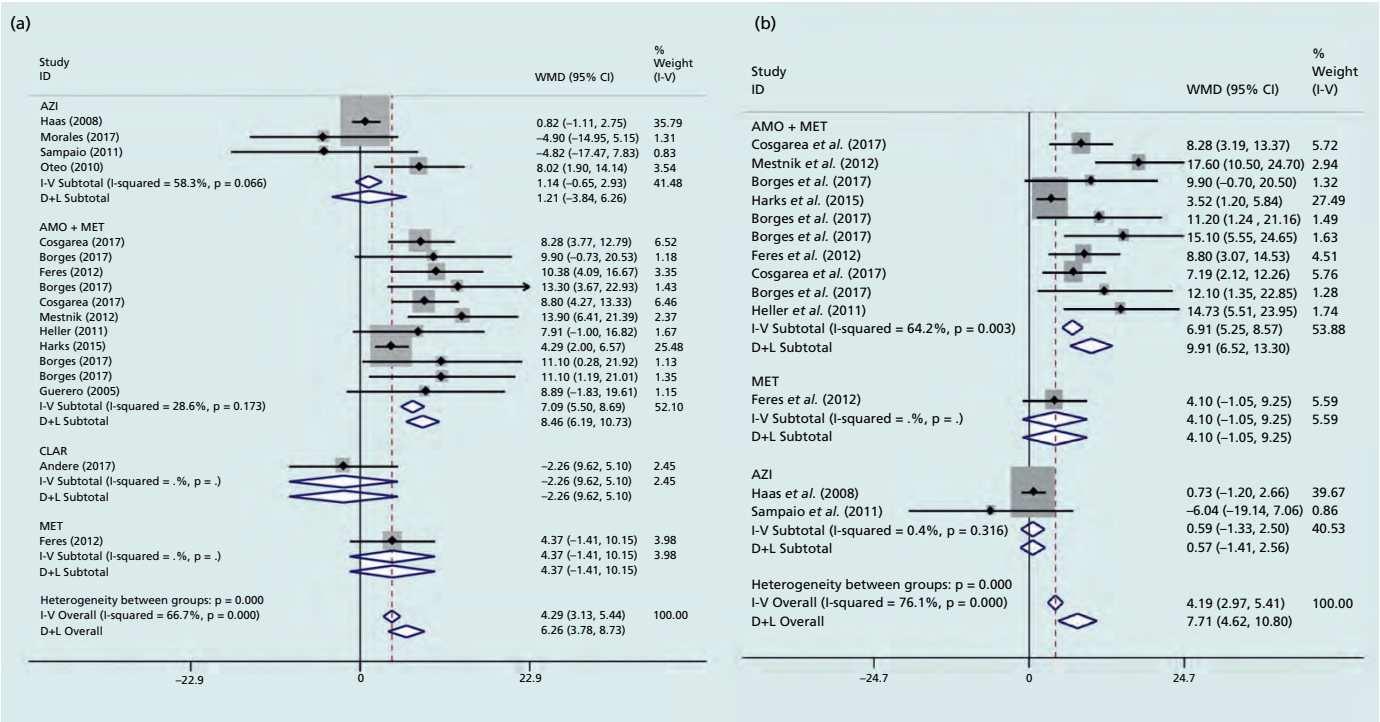

Fig. 36-4 Forest plot: meta-analysis for change in frequency of pockets ≥5 mm, 6 months (a) and 12 months (b), all types of periodontitis. (Source: Adapted from Teughels *et al*. 2020. Reproduced with permission from John Wiley & Sons.) WMD, weighted mean difference; ID, identification; CI, confidence interval; I-V, Inverse-Variance; D+L, DerSimonian and Laird. AZI, azithromycin; AMO, amoxicillin; MET, metronidazole; CLAR, clarithromycin.

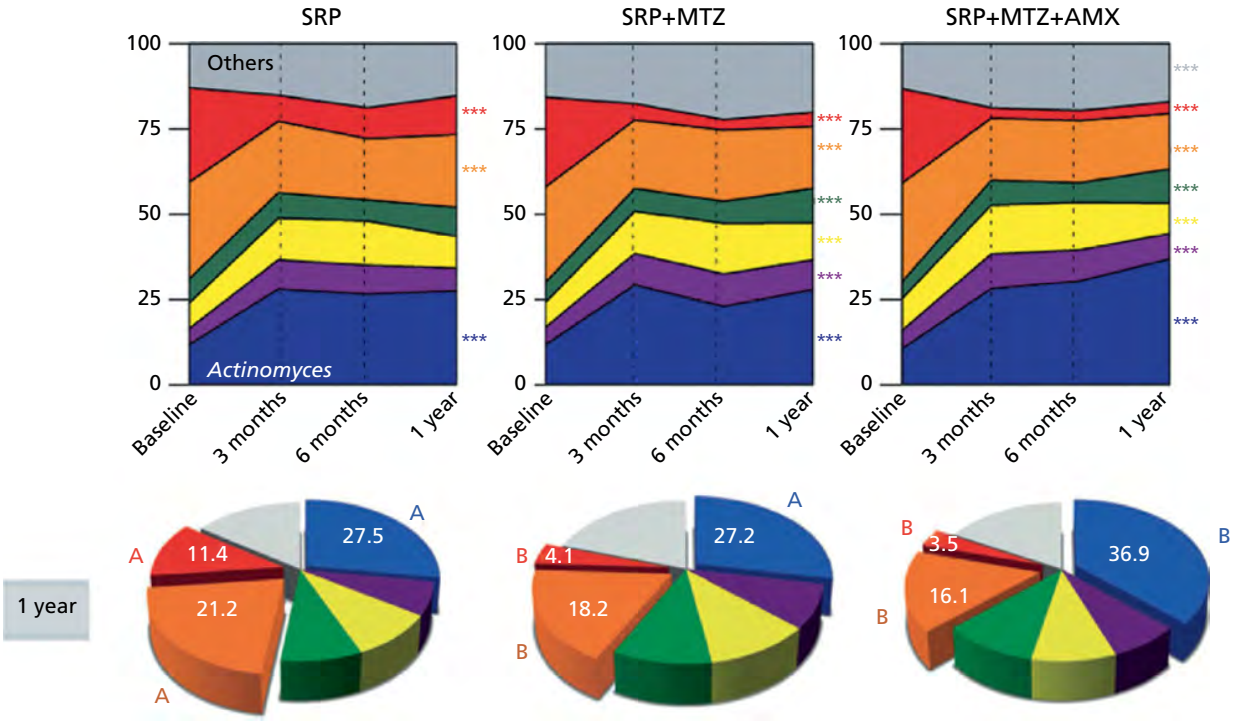

Fig. 36-5 Cumulative mean proportions of microbial complexes, as well as pie charts describing the mean proportions of microbial complexes at 1-year post-treatment, in subgingival biofilm samples taken from subjects with severe periodontitis treated with scaling and root planing (SRP) alone or with adjunctive systemic metronidazole (MTZ) or MTZ plus amoxicillin (AMX). The colors represent the different complexes described by Socransky *et al*. (1998). The grey color ('Others') represents species that did not fall into any complex, and *Actinomyces* spp. are represented in blue. The significance of differences among time points was determined using repeated-measures analysis of variance (***P <0.001). The significance of differences among groups at 1-year post-treatment was determined using one-way analysis of variance and Tukey's multiple comparison tests (different letters indicate significant differences between pairs of groups, P <0.05). (Source: Adapted from Feres *et al*. 2015. Reproduced with permission from John Wiley & Sons.)

other pathogens) from recolonizing in high numbers and proportions (Feres *et al*. 2015; Soares *et al*. 2014; Tamashiro *et al*. 2016; Hagenfeld *et al*. 2018; Feres *et al*. 2020b).

Which subjects would benefit most from systemic antimicrobial therapy?

As indicated in the previous section, there is consistent evidence from the literature showing that the adjunctive use of systemic antimicrobials improves the outcomes of SRP. It is also clear from the results of the available studies that not all patients with periodontitis equally benefit from these agents. Hence, in order to properly use systemic antimicrobials in the treatment of periodontitis, it is crucial to define which patients would consistently benefit from this adjunctive treatment.

Pioneer studies using tetracycline (Lindhe & Liljenberg 1984; Novak *et al*. 1988, 1991) and doxycycline (Pascale *et al*. 1986; Mandell & Socransky 1988) and later, MTZ+AMX (Beliveau *et al*. 2012; Merchant *et al*. 2014; Miller *et al*. 2017; Burgess *et al*. 2017), in the treatment of young subjects with localized (juvenile or aggressive) periodontitis, clearly indicated the benefits of systemic antimicrobials in the treatment of these patients. Most of them would be classified today as periodontitis with a molar-incisor pattern. Apparently, this therapeutic benefit is largely associated with the reduction of *A. actinomycetemcomitans*, which is difficult to control by mechanical treatment only (Christersson *et al*. 1985; Renvert *et al*. 1990; Winkel *et al*. 1998). At least two studies suggested that young subjects with periodontitis are highly colonized by *A. actinomycetemcomitans*, and the levels and proportions of this pathogen may decrease with increasing age (Rodenburg *et al*. 1990; Faveri *et al*. 2009). Thus, very young subjects with periodontal destruction should be treated with adjunctive antimicrobials, with the best evidence for MTZ+AMX.

The use of adjunctive antibiotics in the treatment of young adults and adults has been a subject of continuous debate. Some clinical studies have suggested that only adults colonized by *A. actinomycetemcomitans* should be treated with MTZ+AMX (van Winkelhoff *et al*. 1989; Pavicic *et al*. 1992, 1994; van Winkelhoff *et al*. 1992; Flemmig *et al*. 1998), while MTZ demonstrated a good effect in patients colonized by *P. gingivalis* or those refractory to treatment (Winkel *et al*. 1997; Soder *et al*. 1999). However, at least four RCTs showed that adults not colonized by *A. actinomycetemcomitans* also benefited from adjunctive MTZ+AMX (Winkel *et al*. 2001; Rooney *et al*. 2002; Cionca *et al*. 2010; Mombelli *et al*. 2013), although patients colonized by this species at baseline benefited the most from this treatment protocol (Flemmig

et al. 1998; Winkel *et al*. 2001). A recent systematic review indicated that SRP with MTZ+AMX was more effective than SRP alone in reducing pockets (PD ≥5 mm), irrespective of *A. actinomycetemcomitans* detection at baseline (Nibali *et al*. 2019). As alluded in the previous section, MTZ+AMX, and also MTZ, promote a broad rebiosis in the subgingival microbial biofilm that seems to go beyond their effects in controlling *A. actinomycetemcomitans*. The benefits in the biofilm composition include a striking reduction in several periodontal pathogens from the red and orange complexes and some newly identified taxa, and an increase in the proportions of host-compatibles species (Haffajee *et al*. 2006; Mestnik *et al*. 2010; Silva *et al*. 2011; Soares *et al*. 2014; Tamashiro *et al*. 2016; Hagenfeld *et al*. 2018; Feres *et al*. 2020b) (Fig. 36-5). Altogether, these data indicate a lack of evidence that the decision-making regarding antibiotic prescription should be based on the colonization of specific microorganisms. Determining clinical parameters/profiles that may guide this therapeutic decision may be an alternative practical approach.

In 1999, two main clinical categories of periodontitis (phenotypes) were described: aggressive and chronic (Armitage 1999). Since then, innumerous studies have explored specific differences in the subgingival microbial composition between chronic and aggressive periodontitis. The abovementioned pioneer investigations showing high prevalence and levels of *A. actinomycetemcomitans* in young patients with aggressive periodontitis contributed to the formation of the long-lasting notion in the periodontal field that only young patients with aggressive periodontitis would benefit from adjunctive antibiotics. Nonetheless, over the years, clear differences in the pathobiology of these two clinical conditions were not confirmed. A recent systematic review evaluated 56 studies that compared microbiological data of chronic and aggressive patients and concluded that, to date, no species or groups of microorganisms were unique to or could differentiate between these two disease categories (Montenegro *et al*. 2020). Other studies also failed to show distinct immune-inflammatory responses of subjects with chronic and aggressive periodontitis (Duarte *et al*. 2015; Amaral *et al*. 2019). Indeed, the most recent systematic review and meta-analysis on the effects of antibiotics in periodontal treatment described significant benefits with the use of these agents, specifically for MTZ+AMX, but these benefits did not differ between aggressive and chronic periodontitis (Teughels *et al*. 2020). These findings supported the current classification scheme for periodontal diseases and conditions that grouped aggressive and chronic periodontitis in one single condition named periodontitis (Papapanou *et al*. 2018; Tonetti *et al*. 2018). This classification scheme applies a staging and grading system that allows the assessment of several dimensions of the disease, including severity/past destruction, complexity of treatment, and risk for future disease progression, based on grade modifiers (e.g. smoking and diabetes). It represents a central paradigm-shifting in the periodontal field and an important step towards personalized care (for review, see Chapter 16). Thus, researchers and clinicians should now make an effort to extrapolate the results of the available studies, entirely based on chronic and aggressive periodontitis, to treat patients that will, from now on, be classified according to stages and grades. A detailed evaluation of the inclusion criteria and baseline data of the RCTs testing systemic antibiotics for periodontal treatment suggest that most studies included patients with generalized stage III and stage IV periodontitis. Very few studies have assessed patients with mild or moderate disease (Dastoor *et al*. 2007; Haffajee *et al*. 2007; Oteo *et al*. 2010; Preus *et al*. 2017), and the additional benefits of antibiotics in those cases were not so evident. Additionally, patients with less severe disease and shallower pockets respond well to mechanical treatment alone (Jepsen & Jepsen 2016). Thus, the current literature indicates that systemic antibiotics in adult patients should be restricted for those with generalized stage III and stage IV periodontitis.

Another aspect to be considered when defining the adjunctive use of antibiotics in the treatment plan is the presence of a risk factor/grade modifier, e.g. smoking and diabetes. Smokers are a group of individuals who might particularly benefit from systemic antibiotics because they respond less favorably to mechanical periodontal treatment (Haffajee & Socransky 2001; Labriola *et al*. 2005; Heasman *et al*. 2006; Johnson & Guthmiller 2007). Apparently, it is more difficult to reduce periodontal pathogens and to foster the growth of host-compatible species in smokers than in non-smokers (Darby *et al*. 2005; Mascarenhas *et al*. 2005; Grossi *et al*. 2007; Matarazzo *et al*. 2008; Meulman *et al*. 2012), most probably because of their impaired immune system and inflammatory response (Kinane & Chestnutt 2000; Palmer *et al*. 2005; Ryder 2007; Mouzakiti *et al*. 2012). Some clinical studies have suggested that AZI (Mascarenhas *et al*. 2005), MTZ (Soder *et al*. 1999) or MTZ+AMX (Pahkla *et al*. 2006; Matarazzo *et al*. 2008) may improve the outcomes of mechanical treatment of smokers, with MTZ+AMX showing the most encouraging results (Matarazzo *et al*. 2008). However, smokers do not seem to respond as well as non-smokers to these agents as they exhibit more residual pockets and less mean reduction in PD and CAL than non-smokers after being treated with SRP plus MTZ+AMX (Faveri *et al*. 2014). This impaired clinical response of smokers to different periodontal treatments seem to be associated with a lack of reduction in the levels and proportions of the putative pathogens from the orange complex, in particular *Fusobacterium* spp. (Matarazzo *et al*. 2008).

Systemic antibiotics have also been proposed in the treatment of patients with diabetes mellitus, a major risk factor for periodontitis. Patients with diabetes present increased prevalence and severity of

periodontal destruction, compared with systemically healthy individuals (Llambes *et al*. 2015), although they do not seem to have a poorer clinical response to treatment when compared with non-diabetic patients (Duarte *et al*. 2018). SRP provides significant clinical benefits in the treatment of diabetic patients, but many of these patients still present a high number of residual pockets as well as high proportions of periodontal pathogens after mechanical treatment alone (Santos *et al*. 2013; Tamashiro *et al*. 2016). Thus, there has been an increasing interest in studying adjunctive therapies that could improve the clinical and microbiological outcomes of SRP in these patients, including systemic antibiotics (Grellmann *et al*. 2016; Souto *et al*. 2018). Nonetheless, only a few RCTs to date have assessed the effects of adjunctive antibiotics in the treatment of diabetic patients, and the most widely studied agent is doxycycline. There was a general belief that doxycycline could provide benefits for diabetic patients due to its ability to inhibit matrix metalloproteinase activity, but the results from RCTs using this agent were not very encouraging (Singh *et al*. 2008; Al-Zahrani *et al*. 2009; Gaikwad *et al*. 2013; Al-Zahrani *et al*. 2014; Tsalikis *et al*. 2014). A systematic review, with a meta-analysis of five studies, has suggested only a modest benefit from the use of adjunctive antibiotics in PD reduction and in mean percentage of sites with BoP in diabetic patients (Grellmann *et al*. 2016). Three of these studies tested doxycycline, including one that used low-dose doxycycline, which does not present antimicrobial effects. In 2014, the first RCT on the effects of MTZ+AMX in the treatment of patients with type 2 diabetes was published (Miranda *et al*. 2014). The results of that study and of a subsequent paper reporting the 2-year follow-up of these patients (Tamashiro *et al*. 2016) showed important additional clinical and microbiological benefits in the test group. For up to 2 years post-treatment, the antibiotic-treated subjects presented an average of 10 less residual sites with PD ≥5 mm, than those who received SRP alone, and 76% of the subjects in the antibiotic-treated group reached the clinical endpoint for treatment "≤4 sites with PD ≥5 mm" (Feres *et al*. 2020a), as opposed to only 22% of the subjects treated by means of SRP-only. Furthermore, MTZ+AMX intake was the only significant predictor for subjects achieving this clinical endpoint at 2 years with an odds ratio (OR) of 20.9 (P <0.001). The important reduction in the number of residual pockets with the use of MTZ+AMX and, consequently, in the need for surgical interventions, may represent a major benefit for patients with diabetes. Besides the stress and financial costs associated with surgical procedures, diabetic subjects have a lower healing capacity, which may hamper or complicate their recovery from surgeries (Tsourdi *et al*. 2013; Miranda *et al*. 2014).

In summary, the current literature suggests that some patient groups may benefit the most from systemic antibiotics: (1) young subjects, especially those with periodontitis with a molar-incisor pattern; (2) adult patients with generalized stage III and stage IV periodontitis; and (3) those cases associated with grade modifiers (e.g. diabetes). A future challenge will be to define which individuals, among those presenting stages III and IV periodontitis, would benefit even further from treatment. A recent analysis in 345 patients treated or not with adjunctive MTZ+AMX and followed for 2 years suggested that patients <55 years of age, or with ≥35% sites with PD ≥5 mm, or with a mean CAL level >5 mm at baseline, would benefit the most from this treatment protocol. Patients presenting at least one of these clinical features, who took MTZ+AMX, showed a greater reduction in median CAL after 2 years, when compared with those not taking antibiotics (Eickholz *et al*. 2019). Further analysis of this type should be conducted in order to better understand the proper and most efficient use of antibiotics in periodontal treatment.

Protocols of use of systemic antimicrobials in periodontics

Defining clear protocols of administration of systemic antibiotics in periodontal treatment is crucial to optimize the effects of these agents and to develop personalized treatments. The main questions to be addressed are: (1) what is the ideal dose and duration of the antibiotic(s); (2) in which step of the periodontal treatment should the antibiotic(s) be prescribed; and (3) if antibiotics should be combined with other treatment protocols to improve efficacy. These questions are addressed in the following sections.

What is the ideal dose and duration of the antimicrobial(s)?

The optimal dose and duration of systemic antibiotics for the treatment of periodontitis have not yet been fully established. These are very important parameters because they may directly impact the desirable (e.g. infection control) and undesirable (e.g. side effects and emergence of bacterial resistance) impacts of the agents. For example, an antibiotic taken above the optimal dose may lead to an increase in the side effects of the drug, whereas an under-dose use may not eliminate the target species but yield bacterial tolerance to the drug.

The dose and duration of adjunctive antibiotics in periodontal treatment have varied significantly since the pioneer studies conducted in the 1970s. In those initial studies, tetracyclines were normally prescribed at a dose of 1 g/day for 2–4 weeks (Slots & Rosling 1983; Lindhe & Liljenberg 1984; Kornman & Robertson 1985; Mandell *et al*. 1986; Novak *et al*. 1988; Novak *et al*. 1991) and doxycycline or MINO were prescribed at a dose of 100 or 200 mg/day for 7–21 days (Ciancio *et al*. 1980, 1982; Mandell & Socransky 1988; Müller *et al*. 1993; Xajigeorgiou *et al*. 2006). The recently introduced AZI is usually prescribed at a dose of 500 mg/day for 3–5 days (Smith *et al*. 2002; Mascarenhas *et al*. 2005; Dastoor *et al*. 2007; Yashima

et al. 2009; Oteo *et al*. 2010; Sampaio *et al*. 2011; Haas *et al*. 2012; Han *et al*. 2012; Feres *et al*. 2015; Teughels *et al*. 2020), while MTZ and AMX, or MTZ alone, have been administered for 3, 7, 10, or 14 days (Feres *et al*. 2015; Teughels *et al*. 2020). The dose of MTZ varies substantially (e.g. 200, 250, 400, and 500 mg/three times daily), while AMX seems to be an exception as it has normally been prescribed at a dose of 500 mg three times daily, although the pioneer studies by van Winkelhoff and colleagues used a dose of 375 mg (Pavicic *et al*. 1994).

Only a few studies to date have directly compared different durations of antibiotic intake in periodontal treatment, and they have all assessed MTZ+AMX. Two RCTs tested MTZ+AMX for 3 or 7 days (Cosgarea *et al*. 2016; Boia *et al*. 2019). While Cosgarea *et al*. (2016, 2017) showed similar benefits with both protocols, Boia *et al*. (2019) observed that 7 days of antibiotic intake was more effective than 3 days in improving clinical parameters and reducing several periodontal pathogens. Borges *et al*. (2017) compared 7 and 14 days of MTZ+AMX administration and two different dosages of MTZ (250 and 400 mg) in the treatment of adults with severe periodontitis and provided data for up to 1 year of follow-up. The duration of antibiotic intake had a greater impact on treatment outcomes than the dose of MTZ, and no differences in side effects were observed with the different protocols tested. The authors concluded that adjunctive use of 400 or 250 mg of MTZ plus 500 mg of AMX three times daily for 14 days offered statistically significant and clinically relevant benefits over those achieved with SRP alone. The added benefits of the 7-day regimen in this population were less evident. However, it should be highlighted that studies using 7 days of MTZ+AMX administration have also provided clinical important advantages over SRP alone (Guerrero *et al*. 2005; Xajigeorgiou *et al*. 2006; Cionca *et al*. 2009; Yek *et al*. 2010; Aimetti *et al*. 2012; Harks *et al*. 2015). Differences in severity of disease may partially explain the efficacy of MTZ+AMX administered during different periods of time. For example, Harks *et al*. (2015) showed that 7 days of adjunctive MTZ (400 mg) + AMX (500 mg), three times a day, provided results similar to those observed in the 14-days group of Borges *et al*. (2017): approximately 60% of the subjects in both studies achieved the clinical endpoint of "≤4 sites with PD ≥5 mm" (Feres *et al*. 2020a) post-treatment. Nonetheless, the population treated by Harks *et al*. (2015) had less severe disease than that treated by Borges *et al*. (2017).

In which phase of the mechanical treatment should the antimicrobial be prescribed?

Two different questions, related to the ideal timing for systemic antimicrobial prescription in periodontal treatment, should be addressed: (1) should it be administered during the active phase of therapy or after re-evaluation (i.e. 3 or 6 months after active treatment), and (2) should it be administered on the first or last day of the SRP procedure?

To date, no RCT has directly compared the effects of systemic antibiotics administered during the active phase of therapy or after re-evaluation. Two previous investigations, one retrospective study (Kaner *et al*. 2007), and a RCT (Griffiths *et al*. 2011), have indirectly addressed this topic, and the results of both studies suggested greater clinical benefits when MTZ+AMX was prescribed at the initial phase of therapy, than after the re-evaluation. Similarly, two clinical studies described the effects of MTZ+AMX either during or after the initial phase of treatment, in young patients with periodontitis with molar/incisor pattern (Beliveau *et al*. 2012), or in adults with generalized stage III and stage IV periodontitis (Mombelli *et al*. 2015). Both studies indicated that MTZ+AMX given at the active phase of treatment allowed for better clinical improvements early in the course of treatment and was thus associated with a reduction in the need for additional interventions.

When assessing if the drugs should be administered at the first or after the last session of SRP, no RCT has directly addressed this question, but there is a strong biological reason for administering the antibiotics immediately after the subgingival mechanical disruption of biofilm (Herrera *et al*. 2008), and the consensus of the European Workshop clearly suggested that biofilm disruption should precede antibiotic prescription, that disruption should be accomplished in a short period of time (limited time between appointments), and the prescription should start immediately after the last session of debridement (Sanz *et al*. 2008). The main advantage of such protocol is to reduce the protective effect of the biofilm before the drug is delivered to the site of infection. Indeed, most RCTs have used this strategy, either by starting antibiotic intake 1 or 2 days after full-mouth SRP (Guerrero *et al*. 2005; Harks *et al*. 2015) or after the first session of full-mouth debridement followed by quadrant-wise scaling (Carvalho *et al*. 2004; Matarazzo *et al*. 2008; Silva *et al*. 2011; Feres *et al*. 2012; Goodson *et al*. 2012; Mestnik *et al*. 2012; Borges *et al*. 2017).

The abovementioned observations, suggesting that antibiotics should be administered during the active phase of treatment and right after disruption of the subgingival biofilm, are in line with the notion, already strengthened in this chapter, that a rapid and striking reduction in the subgingival microbiota would be necessary in order to obtain the most beneficial recolonization possible of the recently scaled pockets. Milder and sequential perturbations to the mature biofilm might not be enough to change its highly stable and resilient climax community (Socransky & Haffajee 2002). More assertive treatments applied at once, such as the association of SRP and systemic antibiotics during the initial therapy (step 2), may have greater potential to create an entirely new and stable climax community, similar to that observed in health.

Should antimicrobials be combined with other treatment protocols to improve its efficacy?

Some studies have shown important clinical and/or microbiological benefits when the administration of systemic antibiotics, more specifically MTZ or MTZ+AMX, are combined with a weekly professional removal of the supragingival biofilm for 3 months or with chemical control of biofilm by means of chlorhexidine rinsing for 2 months (Haffajee *et al*. 2003a; Carvalho *et al*. 2004, 2005; Feres *et al*. 2012; Soares *et al*. 2014). These data are in line with previous publications suggesting that strict mechanical (Nyman *et al*. 1975; Rosling *et al*. 1976; Lindhe *et al*. 1982a, b; Westfelt *et al*. 1983; Ximenez-Fyvie *et al*. 2000) or chemical (Faveri *et al*. 2006b; Feres *et al*. 2009) control of supragingival plaque, during and after mechanical treatment, positively impact clinical parameters and the composition of the subgingival biofilm. These favorable results may be attributed to preventing periodontal pathogen migration to recently scaled pockets, as it has been recognized that several of these species may colonize the supragingival environment (Ximenez-Fyvie *et al*. 2000). An indirect effect may be related to the reduction of inflammation on the adjacent periodontal tissues, and the consequent reduction on the availability of nutrients necessary for the multiplication of proteolytic pathogens (Socransky & Haffajee 2002). In addition, the beneficial effects of chlorhexidine rinsing in changing the subgingival microbial composition, when used in combination with SRP (Feres *et al*. 2009) or with MTZ+AMX (Soares *et al*. 2014) may be correlated to the effect of this antiseptic in reducing periodontal pathogen reservoirs, that are not reached by the mechanical removal of supragingival biofilm, such as the tongue (Faveri *et al*. 2006a), saliva and, oral mucosa (Mager *et al*. 2003).

Finally, it should be highlighted that all RCTs published to date, showing benefits for systemic antimicrobials in clinical and microbiological periodontal parameters, have enrolled patients in a regular maintenance program after initial treatment. Thus, keeping patients under periodontal maintenance with low levels of biofilm is mandatory to assure long-term periodontal stability.

Use of systemic antimicrobials: associated risks

Adverse events/reactions

The use of systemic antibiotics is frequently associated with unwanted/side effects for the individual patient. The systematic review by Teughels *et al*. (2020) included RCTs with 6 months or more of follow-up. Twenty-five of the included studies reported information on adverse events and/or patient reported outcome measures (PROMs), and 22 of them described some of the following events: "nausea/stomach upset/vomiting", "diarrhea/gastrointestinal disturbance", "metallic taste", "oral ulceration", "dizziness", "fever", "headache", "periodontal abscess", "general unwellness (e.g. irritability)" and "allergic reactions". It was concluded that, in general, these side effects were more frequently reported in the antimicrobial (ranging from 0% to 36.36%) than in the placebo (ranging from 0% to 20%) groups and that the highest frequency of each listed side effects was always reported for MTZ+AMX.

Relevant differences in the frequency, type, and severity of adverse effects are evident when comparing different drugs (for review, see Hersh & Moore 2008). Overall, penicillins present low frequency and severity of unwanted effects, being considered among the safest drugs; however, they may induce hypersensitivity reactions, which can be mild (just a skin rash), but may also induce anaphylactic reactions in sensitized patients, which can be life-threatening. Tetracyclines are also considered as very safe, and associated side effects normally affect the digestive tract (pain, vomiting, or diarrhea), although deposition in calcified areas may induce tooth discoloration. AZI, as most macrolides, presents low frequency of adverse events and, when happening, they are usually mild and affecting the digestive tract. Clindamycin and MTZ have been associated with antibiotic-associated colitis and other, less relevant, gastrointestinal problems. In addition, MTZ has been associated with nausea, headache, anorexia and vomiting, especially if combined with alcohol intake (known as Antabuse-like effect) (Mergenhagen *et al*. 2020), peripheral neuropathies, and some carcinogenic risks have been suggested (Adil *et al*. 2018).

Emergence of resistant strains/global increase in antibiotic resistance

Antibacterial drugs have been available for human use since the beginning of the twentieth century, and rapidly became a much used, successful treatment. However, since they started to be used, there were warnings that bacteria could become resistant to antibiotics, as stated by Alexander Fleming during his Nobel Prize speech in 1945. Development of resistance is a normal evolutionary process, but it is clearly and dramatically accelerated by selective pressure derived from widespread and inappropriate use. The increase in bacterial resistance, together with the lack of development of new antimicrobial drugs, is now becoming a major global public health problem, that may challenge global health at completely unseen level (WHO 2014).

Recently, a report requested by the European Centre for Disease Prevention and Control estimated the magnitude of the problem in the European Union and in the European Economic Area (Cassini *et al*. 2019): in 2015, 671 689 infections with antibiotic-resistant bacteria were estimated, with 33 110 attributable deaths and 874 541

disability-adjusted life-years (DALYs). The burden was highest in infants and older people, and had increased since 2007.

Excessive and incorrect use of systemic antimicrobials contributes to the emergence of specific-drug-resistant and multidrug-resistant bacterial species (WHO 2014; Elias *et al*. 2017). It should be noted that the antimicrobial resistance profiles of periodontal pathogens are higher in populations with higher frequencies of exposure to systemic antimicrobials (van Winkelhoff *et al*. 2005). This has led to a call for controls on the use of systemic antimicrobial drugs and, when prescriptions are necessary, that they are used judiciously. For this reason, the "Proposals for EU guidelines on the prudent use of antimicrobials in humans" (ECDC 2017) were developed and published in 2017. Among the general recommendations made for all health professionals, the following are listed: "ensure that appropriate microbiological samples are taken before starting antimicrobial treatment"; "avoid antimicrobial combinations unless there is a clear indication outlined in the guidelines"; "select an antimicrobial in accordance with relevant guidelines, at an appropriate dose, for the shortest effective duration and with appropriate route of administration (preferably oral if possible)"; "select an antimicrobial with a spectrum of activity as narrow as possible". Although, to date, there is no compelling evidence to support the need for microbiological testing to prescribe systemic adjunctive antibiotics in periodontal treatment, more research in this area should be conducted. Similarly, other systemic drugs should be investigated as alternatives to the combination of MTZ and the large spectrum AMX.

Concluding remarks and recommendations for clinical practice

The ecological concepts and clinical data discussed in this chapter support the notion that certain systemic antimicrobial protocols can enhance the effects of periodontal therapy and thus are important adjunctive tools in the treatment of periodontitis. However, there are risks associated with antibiotic intake, such as the worldwide increase in antibiotic resistance and the unwanted systemic effects of these agents. A recently published clinical practice guideline, derived from the consensus report by the European Federation of Periodontology (Sanz *et al*. 2020) has concluded the following, when answering the question "Does adjunctive systemically administered antibiotics improve the clinical outcome of non-surgical periodontal therapy?: (1) due to concerns about patient health and the impact of systemic antibiotic use on public health, its routine use as an adjunct to subgingival debridement in patients with periodontitis is not recommended; (2) the adjunctive use of specific systemic antibiotics may be considered for specific patient categories (e.g. generalized periodontitis stage III in young adults)". Thus, the decision to use an antibiotic to treat periodontitis should be based on an accurate risk–benefit evaluation, based on a thorough evaluation of the RCTs and systematic reviews available. According to the most recent literature discussed in different sections of this chapter, the patients who benefit the most from adjunctive systemic antibiotics are those with generalized stage III and stage IV periodontitis (systemically healthy or with diabetes mellitus), and patients presenting with periodontitis with a molar-incisor pattern.

At present, the most thoroughly documented antibiotic protocol in periodontal therapy is MTZ+AMX. Other agents, including AZI and especially, MTZ, may be considered (Teughels *et al*. 2020), but more studies are necessary in order to establish the real benefits of these agents in clinical practice. The duration and dosage of the MTZ+AMX treatment have been tested by a few RCTs and still needs further assessment (Cosgarea *et al*. 2016; Borges *et al*. 2017; Boia *et al*. 2019). The available literature also suggests that, when indicated, systemic antibiotic intake should start immediately after subgingival biofilm disruption and should not be postponed to the maintenance phase (Kaner *et al*. 2007; Griffiths *et al*. 2011; Beliveau *et al*. 2012).

Finally, the recommendations for prescribers, suggested by the European Centre for Disease Prevention and Control (ECDC 2017), are also relevant for clinicians when deciding whether or not to use systemic antibiotics as adjuncts in periodontal treatment, and for information on how to use them. Of special relevance are those specific recommendations for dentists: "Dentists should prescribe antimicrobials in accordance with guidelines. Antimicrobials should not be used by dentists or other healthcare professionals as a substitute for dental operative intervention". Thus, systemic antibiotics must never replace subgingival instrumentation (e.g. SRP) or be used to compensate for a poorly performed instrumentation.

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Chapter 37

Local Antimicrobial Delivery for the Treatment of Periodontitis and Peri-Implant Diseases

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General principles of local drug delivery

Rationale of local drug delivery

Treatment of periodontitis is routinely based on dental biofilm control, with oral hygiene and supra- and subgingival biofilm instrumentation as main elements (Graziani *et al*. 2017). Given the bacterial etiology and the inflammatory pathogenesis of periodontitis, the adjunctive use of locally applied or systemic administration of antimicrobials and/or host response-modulating medications has been proposed. Localized therapy has received significant attention because of the site-specific pattern of destruction of periodontal infections and the potential side effects of systemic antimicrobials and host-modulating agents. Another important rationale for the development of effective ways to locally apply medications into the periodontal pockets comes from the fact that systemic administration of many medications (and antibiotics in particular) results in marginally effective local concentrations of free, active drug in the periodontal pocket and surrounding tissues.

There are three basic routes to localized adjunctive pharmacologic periodontal therapy:

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

1. *Mouth rinses, toothpaste, or varnishes*. Rinses are useful for supragingival biofilm control, modulation of gingival inflammation, and potentially for recolonization of the subgingival environment following periodontal treatment. Their major limitation, in the context of pharmacologic therapy of periodontitis, is that they do not gain access to the subgingival environment and therefore do not reach the desired site of action (Pitcher *et al*. 1980) (see also Chapter 29).
2. *Subgingival irrigation*. Irrigation solutions placed directly into periodontal pockets initially reach effective concentrations in the area, but the flow of the gingival crevicular fluid (GCF), which is replaced about 40 times per hour, leads to rapid clearance of subgingivally placed drugs. Clearance of a medication locally placed in a periodontal pocket follows exponential kinetics and it has been calculated that the concentration of a highly concentrated irrigating solution of a non-substantive (non-binding) drug becomes ineffective about 15 minutes following application. This time can be prolonged by the application of substantive drugs, such as tetracyclines or chlorhexidine, that bind to the root surface and/or the soft tissue wall of the periodontal pocket and thus establish a drug reservoir that can be slowly released to counteract the clearance by the GCF flow. Limitations on reservoir volume, however, limit the duration of the possible pharmacologic effect. Thus, efficient delivery of pharmacologic agents into the periodontal microenvironment is difficult to achieve using rinses and irrigating solutions.
3. *Periodontal application of local, sustained-release delivery systems*. Goodson, a pharmacologist who in the early 1970s pioneered the field of local delivery to treat periodontitis (Goodson *et al*. 1979), pointed out that successful pharmacologic control of the periodontal microbiota would require:
   - The delivery of an intrinsically efficacious drug to the site of action (periodontal pocket and surrounding tissues).
   - A concentration of the drug higher than the minimum efficacious concentration.
   - The maintenance of this concentration long enough for the effect to occur.

These three principles (namely, site, concentration, and time) are the key parameters in the optimization of local pharmacologic treatment (Goodson 1989, 1996).

Subgingival pharmacokinetics

The action of an intrinsically efficacious drug in a body site is dependent upon the bioavailability of free active medication at the desired location: here, specifically, the periodontal pocket and the neighboring soft and hard tissues. From a pharmacologic standpoint, the periodontal pocket is a challenging microenvironment: it is characterized by the rapid flow of GCF, has a small resting volume, and has an uneven topography. Periodontal pockets are uneven in terms of depth, width, presence of furcation involvements, composition and amounts of subgingival biofilm, and calculus deposits. These characteristics translate into specific difficulties for the design of periodontal local delivery devices.

Clearance of a drug placed into a periodontal pocket follows the exponential function:

$$C_{(t)} = C_{(0)} e^{-t\frac{F}{V}}$$

where $C_{(t)}$ is the concentration of the drug as a function of time (t), $C_{(0)}$ is the initial concentration obtained in the GCF, F is the GCF flow rate, and V is the resting fluid volume of the pocket.

Using an estimated periodontal pocket volume of 0.5 µL (Binder *et al*. 1987) and a GCF flow rate of 20 µL/h (Goodson 1989), the half-time (the time that it takes to reach half of the initial concentration) for a non-substantive medication placed in the periodontal pocket will be 0.017 hours (or about 1 minute). From these calculations, Goodson (1989) concluded that the subgingival irrigation route is theoretically feasible only for very potent (i.e. antimicrobials that can act at very low concentrations) substantive drugs. In the case of a substantive compound, the exponential function can be rewritten by introducing a multiplicative constant K into the denominator of the exponential term to account for binding of the drug to the root surface (and/or periodontal pocket wall):

$$C_{(t)} = C_{(0)} e^{-t\frac{F}{KV}}$$

where K is the affinity constant, which is experimentally estimated from the determined clearance half-time. This equation can be conveniently rearranged to estimate the effect of the various parameters on the duration of the desired therapeutic effect:

$$t_{(MIC)} = \frac{KV}{F} \ln \frac{C_{(0)}}{C_{(MIC)}}$$

where $C_{(MIC)}$ is the minimum inhibitory concentration (MIC) and $t_{(MIC)}$ is the time taken to reach the MIC or the expected time of antibacterial action.

From this relation, it is apparent that the time over which a therapeutic effect is observed ($t_{(MIC)}$) will be longer when the:

- Volume of the pocket is large.
- GCF flow rate is low.
- Affinity constant for the drug is higher, that is a highly substantive drugs is used.
- Initial concentration is very high, that is the drug has good solubility in the applied vehicle.
- Minimum inhibitory concentration (MIC) is low, that is a very potent agent is used.

While the first two parameters relate to the specific disease state of each tooth and thus cannot be easily modified without intervention, the remaining three parameters relate to the choice of drug. Preclinical data related to the *in vitro* antimicrobial susceptibility profile and pharmacokinetic data are at the base of the rationale choice of the active agent.

Development of subgingival delivery devices

To overcome the challenges represented by the pharmacokinetic parameters of the local microenvironment, Goodson designed a first generation of local drug delivery devices for application into periodontal pockets. The concept was to constantly replenish the free drug in the periodontal pocket that is cleared by the GCF flow with the release of drug from a drug reservoir placed into the periodontal pocket (Goodson *et al*. 1979). These devices consisted of permeable hollow cellulose acetate fibers (with an internal thickness of 200 μm) filled with a 20% tetracycline–HCl solution. The fiber was tied around the crevice of the pocket, pressed into the subgingival environment, and removed after 24 hours. In spite of the short duration of application, an important effect on the composition of the subgingival microbiota was observed. A subsequent clinical study compared hollow fibers, left in place for 2 days, with scaling and root planing (SRP). Microbial and clinical parameters improved, but less than in the SRP group (Lindhe *et al*. 1979). These early attempts produced limited clinical outcomes and this was explained by the insufficient duration of drug delivery. Subsequent efforts focused on leaving the delivery device longer in the periodontal pocket, but it became apparent that these devices were exhausted relatively quickly (Addy *et al*. 1982; Coventry & Newman 1982).

Better release profiles were obtained with a second generation of devices characterized by a monolithic design (drug crystals interspersed within an inert matrix), such as acrylic strips or extruded ethylene vinyl acetate fibers (Addy *et al*. 1982; Goodson *et al*. 1983). In particular, following placement of 0.5-mm diameter 25% tetracycline fibers, GCF concentrations in the order of 500–1500 μg/mL were reported (Tonetti *et al*. 1990). Parallel efforts with bioresorbable matrices focused on chlorhexidine in cellulose acetate (Soskolne *et al*. 1983) and on release platforms made of hydroxypropylcellulose (Noguchi *et al*. 1984) or collagen matrices (Minabe *et al*. 1989a, b).

Studies have estimated that the resting fluid volume of a 5-mm pocket is about 0.5 μL (or 0.5 mm^3). While deeper pockets and pockets around dental implants (that also include a sizeable mucosal tunnel) may have a significantly larger volume, these data indicate that any subgingival delivery device needs to be able to expand the pocket volume, in order to establish a large enough drug reservoir that will be able to release free drug over time to counteract the GCF clearance. Early attempts using dimensionally stable acrylic strips or tetracycline fibers achieved pocket expansion.

Phase I and II studies with these devices reported improvements in the microbiota and clinical parameters (Addy & Langeroudi 1984; Goodson *et al*. 1985a, b). The pivotal trial required for regulatory clearance by the USA Food and Drug Administration (FDA) of 25% tetracycline–HCl ethylene vinyl acetate fibers was the first multicenter trial in the field of periodontology to be conducted under stringent quality control and was a stepping stone towards modern clinical trial design and execution in dentistry (Goodson *et al*. 1991a, b).

Over the following three decades, several local antimicrobial delivery devices have been developed and have undergone clinical testing for safety and effectiveness to satisfy clearance by the local regulatory agencies, in order to be available in the market. These products will be presented in the next sections.

Antimicrobial effects of subgingival delivery devices

Early studies, mandated by regulatory agencies to provide proof of efficacy of the locally delivered antimicrobial alone, showed consistent suppression of total bacterial loads and frequency of detection of target pathogens. Later studies, however, showed that better clinical and microbiologic outcomes were obtained by combining mechanical instrumentation with local delivery of the antimicrobial. This established the key role of mechanical instrumentation in successful clinical strategies for application of local delivery devices (Johnson *et al*. 2002).

Clinical studies evaluating microbiologic outcomes of local delivery devices, used in combination with mechanical instrumentation (e.g. SRP), have shown drastic reductions in both total bacterial load and periodontal pathogens counts and detection. With the most effective devices (those delivering high concentrations of intrinsically efficacious antimicrobials for >1 week), suppression of 99–99.9% of total microbial load was reported, leading to effective disinfection of the treated periodontal pocket. After exhaustion of the drug reservoir, however, rapid recolonization was observed. Three possible sources for this recolonization were hypothesized: (1) Regrowth from the residual microbiota from within the periodontal pocket; (2) recolonization from other intraoral areas of infection; (3) re-infection of the patient from other subjects.

Different studies addressed the source of recolonization. The pivotal study by the Goodson group in 1988 led to FDA approval of tetracycline fibers (Goodson *et al*. 1991a, b). They employed tetracycline fibers and SRP, with or without chlorhexidine mouth rinsing, to complete the treatment of the subjects. The hypothesis was that the intraoral antibacterial effect of chlorhexidine would modulate

bacterial recolonization of tetracycline fiber-treated pockets. Results showed that chlorhexidine mouth rinsing over a 28-day period led to significant reductions of the bacterial recolonization profiles for three target pathogens. The data were interpreted as an indication that the overall oral ecology of the patient was a critical determinant of success with this therapeutic modality. This concept was further assessed by a study conducted at the University of Berne. Subjects with generalized periodontitis, who were *Porphyromonas gingivalis* positive, were enrolled into a controlled randomized clinical trial (RCT) testing two extreme forms of therapy: localized treatment of two isolated pockets (with the rest of the dentition being monitored over the study period) and full-mouth disinfection of the whole dentition by tetracycline fiber application, SRP, and chlorhexidine mouth rinsing for 4 weeks. Clinical and radiographic outcomes showed greater improvement in the index teeth of the full-mouth disinfection group compared with the index teeth of the localized treatment group (Mombelli *et al*. 1996, 1997; Fourmousis *et al*. 1998). Most importantly, while similar levels of pocket disinfection were achieved for total bacterial counts, at the time of tetracycline fiber removal, the recolonization kinetics showed rapid return towards baseline bacterial levels in the localized treatment group (Fig. 37-1). Persistent, stable suppression of bacterial levels was observed in the full-mouth disinfection group. Interestingly, early recolonization kinetics predicted clinical (reduction of pocket depth and bleeding on probing) and radiographic (hard and soft tissue subtraction analysis) outcomes 3 and 6 months later. Several important conclusions were drawn from these studies and these represent important strategic elements for the rationale use of local delivery devices:

1. Effective subgingival delivery devices have the potential to dramatically change the microbial profile of treated periodontal pockets. Recolonization, however, is a critical phenomenon that may undermine clinical benefit.
2. Bacteria present in other areas of the mouth are the major source of recolonization and need to be addressed by improved oral hygiene measures, treatment of the whole dentition and, perhaps, antimicrobial mouth rinsing.
3. Subgingival delivery devices are not a promising treatment for subjects who are unable or unwilling to achieve improved (optimal) oral hygiene levels.

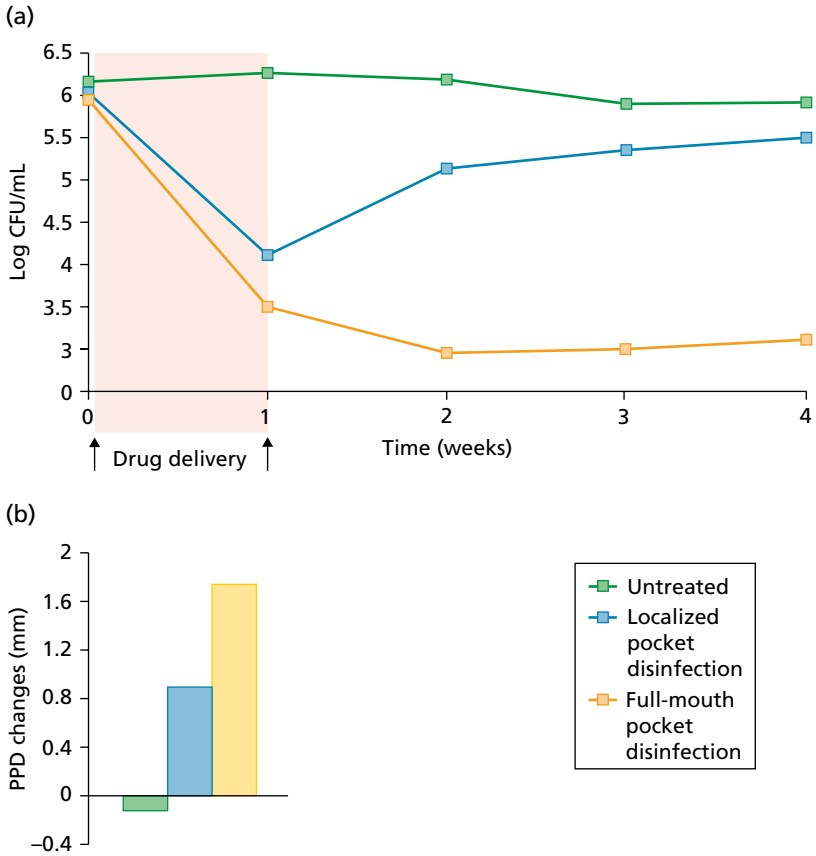

Fig. 37-1 (a) Kinetics of change following local drug delivery with tetracycline fibers in untreated sites; localized treated areas (only two teeth treated in subjects with widespread periodontitis and *P. gingivalis* infection); and full-mouth pocket disinfection (all pockets treated plus chlorhexidine mouth rinse in subjects with widespread periodontitis and *P. gingivalis* infection). Note the different patterns of recolonization. The vertical axis displays total colony forming units (CFU) (Log10)/mL. (b) Changes in probing depths at 6 months for the three groups displayed in (a). Note the greater pocket depth reductions (PPD) observed in the full-mouth pocket disinfection group.

Local antimicrobial delivery for the treatment of periodontitis

Efficacy of subgingival delivery devices

Several clinical studies have assessed the effects of locally delivered antimicrobials in fibers, gels, chips, or microspheres, mainly in untreated patients, but also in treated sites with poor response or with recurrent disease, and their results have been summarized in different systematic reviews (Hanes & Purvis 2003; Bonito *et al*. 2005; Matesanz-Pérez *et al*. 2013; Smiley *et al*. 2015). More recently, a systematic review (Herrera *et al*. 2020) was presented at the XVI European Workshop on Periodontology, for the development of a Clinical Practice Guideline (CPG) in periodontal therapy for periodontitis in stages I–III (Sanz *et al*. 2020). The present section will follow the results of the latter work, which is based on 6-month RCTs, in which the adjunctive use of locally delivered antimicrobials is compared with SRP, alone or plus a placebo, in split-mouth or parallel studies, and probing pocket depth (PPD) changes were considered the primary outcome.

Characteristics of the available studies

A total of 50 studies (described in 59 papers) were identified: 38 were single-blinded; 26 had a parallel design and 23 a split-mouth design, with one combining both (Jeffcoat *et al.* 1998); 33 were single-center studies, while 11 included two or more centers; most studies were performed at university clinics (41), while three took place exclusively at private clinics, and one combined both types of settings (Bogren *et al.* 2008). Studies were carried out in 16 different countries from four continents. The most typical study duration was 6 months (30), followed by 9 months (7) and 12 months (10); only three studies reported more than 12-month follow-up data (in addition, an extension of a 6-month study reported 60-month data in a subset of the original population; Wilson *et al.* 1997). In 22 studies, periodontitis was defined as chronic or adult; in 11 studies, the terminology used was recurrent/refractory/relapsing in already treated patients or patients in supportive periodontal care (SPC), while in five studies the only definition of disease was "periodontitis" and it was not reported in nine studies. In two studies, two groups were included: both aggressive and chronic periodontitis (Agan *et al*. 2006), and untreated and recurrent (Eickholz *et al*. 2002). In just one study, additional microbiological criteria were used (Jones *et al*. 1994). With regards to the extension of the disease, in two studies it was considered as localized and in four as generalized, while it was not reported in 45 studies. For severity, in 20 studies it was "moderate–severe" or "advanced", while in two it was "severe" or "advanced", and in another two "mild" or "initial to moderate". Twenty-six studies did not report on the severity of the disease (Table 37-1).

Seventeen studies used a full-mouth approach to assess clinical outcome variables, either by evaluating all sites, or a group of sites according to a part of the mouth (e.g. a quadrant) or according to a clinical criterion (e.g. PPD >4 mm); in contrast, 36 studies selected some specific sites/teeth for evaluation, based on clinical, radiological, or biomarker criteria, including furcation lesion sites (Tonetti *et al*. 1998; Tomasi *et al*. 2008; Dannewitz *et al*. 2009; Tomasi & Wennstrom 2011). In three studies, both full-mouth and partial-mouth evaluations were reported (Timmerman *et al*. 1996; Gonçalves *et al*. 2004).

In most cases, the studies described periodontal therapies which were rendered before the main intervention, and in common for all study groups, including oral hygiene instructions alone (n=15) or in combination with supragingival professional mechanical plaque removal (PMPR) (n=12) or with SRP (n=4); in some studies, the intervention was PMPR alone (n=3), and in 16 studies, no such an intervention was mentioned. The study intervention was local SRP in 19 studies, full-mouth SRP in 22 studies, while supragingival PMPR was the main mechanical therapy in two studies (Heasman *et al*. 2001; Gonzales *et al*. 2011). Forty-eight out of the 50 studies clearly explained that the local antimicrobial was placed/delivered immediately after instrumentation, with two exceptions: in one study, it was placed before instrumentation (Tonetti *et al*. 1998), and SRP was rendered at fiber removal; and in other study, it was placed 1 week after instrumentation (Flemmig *et al*. 1996). Forty-three studies had SRP alone as main control group, while eight had a vehicle control (placebo), with three of the studies presenting both control groups. Four studies presented an additional untreated control, while one study presented two SRP alone controls, one in adjacent sites and another in remote sites (Henderson *et al*. 2002).

Tested products/formulations

The test groups with commercialized local antimicrobials aimed to assess: Actisite (n=10), Arestin (8), Atridox (4), Aureomycin (1), Chlosite (2), Dentomycin (1) and Periocline (2) (same formulation with different brand names), Elyzol (7), Ligosan (3), PerioChip (11), Periofilm (1); among those not commercially available, were chitosan (1), chitosan with metronidazole (1), minocycline powder (1), tetracycline strips, just using one (1), or multiple (1). Brand names are used to avoid confusion but information on composition can be found in Table 37-2.

The number of applications varied among products and study protocols, just one application being the most frequent, in 34 study groups; two applications were performed in 10 study groups and more than two in five. In six study groups, one initial application was performed, while a second (three studies) or a third one (three studies) was decided based on the dislodging on the first application or on the presence of pockets. When more than one application was scheduled, the protocols were highly heterogeneous. In some cases (16 study groups), a cyanoacrylate or periodontal dressing was used after the local antimicrobial application that was kept in place for 3–13 days; dislodging of the antimicrobial or dressing was recorded in 12 study groups.

Table 37-1 Randomized clinical trials of at least 6-month duration, evaluating locally delivered antimicrobials: description of characteristic of periodontitis (type, extension, and severity) and the distribution, number, and criteria for the evaluated teeth/sites.

Study reference	Extension	Type	Severity	Assessment (FM/PM)
Agan *et al*. (2006)	NR	Aggressive/chronic	NR	PM – 2 sites
Ahamed *et al*. (2013)	NR	Chronic (adult)	NR	PM – 5 sites
Aimetti *et al*. (2004)	NR	Recurrent (refractory)	NR	PM – 2 teeth
Akncbay *et al*. (2007)	NR	Chronic (adult)	Sev	FM – PD 5–7 & BoP
Azmak *et al*. (2002)	NR	Chronic (adult)	Mod-sev	PM – 1 site
Bogren *et al*. (2008)	NR	Recurrent (refractory)	Mod-sev	FM – PD >4
Buduneli *et al*. (2001)	NR	Chronic (adult)	NR	PM – 2–3 sites
Carvalho *et al*. (2007)	NR	Chronic (adult)	Mild-mod	PM – 1 site
Cortelli *et al*. (2006)	NR	Chronic (adult)	Sev	PM – 2 sites
D'Aiuto *et al*. (2006)	Generalized	NR	Sev	FM
Dannewitz *et al*. (2009)	NR	Recurrent (refractory)	Mod-sev	PM – all furcation lesions
Eickholz *et al*. (2002), Ratka-Krüger *et al*. (2005)	NR	Untreated /recurrent	Mod-sev	PM – 1 site
Flemmig *et al*. (1996)	NR	Recurrent (refractory)	NR	PM – 1 tooth
Friesen *et al*. (2002)	NR	Periodontitis	NR	PM – 1 tooth
Gonçalves *et al*. (2004), Colombo *et al*. (2003), Rodrigues *et al*. (2004)	NR	Chronic (adult)	NR	FM/PM – 4 sites
Gonzales *et al*. (2011)	NR	Chronic (adult)	NR	PM – 12 teeth
Goodson *et al*. (2012), Socransky *et al*. (2013)	NR	NR	NR	FM
Goodson *et al*. (1985a)	NR	NR	NR	FM
Griffiths *et al*. (2000)	NR	Chronic (adult)	NR	FM – PD >4
Grisi *et al*. (2002)	NR	Chronic (adult)	NR	PM – 2–3 sites
Heasman *et al*. (2001)	NR	Recurrent (refractory)	Mod-sev	FM –PD >4 & BoP
Henderson *et al*. (2002)	NR	Chronic (adult)	Mod-sev	PM – 1 site
Jeffcoat *et al*. (1998), Jeffcoat *et al*. (2000)	NR	Chronic (adult)	Mild-mod	PM – 1 tooth
Jones *et al*. (1994)	NR	Chronic (adult) & presence of P.g, P.i., A.a	Mod-sev	FM – PD >4
Kasaj *et al*. (2007)	NR	Chronic (adult)	NR	PM – 2 sites
Killeen *et al*. (2016)	NR	Recurrent (refractory)	Mod-sev	PM – 1 site
Kinane & Radvar (1999)	NR	Recurrent (refractory)	NR	PM – 1 site
Lauenstein *et al*. (2013)	NR	Chronic (adult)	NR	PM – 4 sites
Leiknes *et al*. (2007)	NR	NR	NR	PM – 1 site
Lie *et al*. (1998)	NR	Chronic (adult)	Mod-sev	PM – 1 site
Matesanz *et al*. (2013)	Generalized	Recurrent (refractory)	NR	PM – 4–10 sites
Mizrak *et al*. (2006)	NR	Periodontitis	NR	PM – 1 site
Newman *et al*. (1994), Wilson *et al*. (1997)	NR	Recurrent (refractory)	NR	PM – 1 tooth
Palmer *et al*. (1998), Palmer *et al*. (1999)	NR	NR	NR	FM – PD >4
Paolantonio *et al*. (2008b)	NR	NR	Mod-sev	PM – 1 site
Paolantonio *et al*. (2008a)	NR	Periodontitis	Mod-sev	PM – 1 site
Paolantonio *et al*. (2009)	NR	Periodontitis	Mod-sev	PM – 1 site
Romano *et al*. (2005)	NR	NR	NR	PM – 2 sites
Sakellari *et al*. (2010)	Generalized	Chronic (adult)	NR	FM*
Soeroso *et al*. (2017)	Localized	Chronic (adult)	NR	FM
Stelzel & Florès-de-Jacoby (2000)	NR	Chronic (adult)	NR	FM – PD >4
Tabenski *et al*. (2017)	Generalized	Chronic (adult)	Mod-sev	PM – 4 teeth
Timmerman *et al*. (1996)	NR	Chronic (adult)	Mod-sev	FM/PM – 4–10 sites

Table 37-1 (*Continued*)

Study reference	Extension	Type	Severity	Assessment (FM/PM)
Tomasi *et al*. (2008), Tomasi & Wennstrom (2011)	NR	Chronic (adult)	Mod-sev	FM/PM – all furcation lesions
Tonetti *et al*. (2012)	NR	NR	Mod-sev	FM – PD >3
Tonetti *et al*. (1998)	NR	Recurrent (refractory)	NR	PM – 1 furcation lesion
Van Dyke *et al*. (2002)	NR	Periodontitis	Mod-sev	PM – 2 teeth
Williams *et al*. (2001)	NR	Chronic (adult)	Mod-sev	FM – PD >4
Wong *et al*. (1998), Wong *et al*. (1999)	Localized	Recurrent (refractory)	NR	PM – 1–2 sites
Zingale *et al*. (2012)	NR	NR	Mod-sev	PM – 1 site

A.a., *A. actinomycetemcomitans*; BoP, bleeding on probing; FM, full-mouth (all sites, specific criteria); Mod, moderate; NR, not reported; PD, probing depth; P.g., *P. gingivalis*; P.i., *P. intermedia*; PM, partial-mouth (selected sites); Sev, severe or advanced.
*Full mouth assessment, with only four selected sites treated with local antimicrobial.

Table 37-2 Brand names and product description of the tested products, in alphabetic order, and relevant information on availability (in 2019) in the European and other markets.

Descriptive name	Brand name(s)	Manufacturer	Composition	Information on availability*
Actisite	Actisite	ALZA Corporation, Palo Alto, CA, USA	500 µg/cm tetracycline hydrochloride loaded in 0.5 cm-diameter ethylene vinyl acetate co-polymer fiber (23 cm, 12.7 mg of tetracycline)	No availability
Arestin	Arestin	OraPharma, Warminster, PA, USA	1 mg minocycline microencapsulated in poly(glycolide-co-DL-lactide)	Israel, Poland, UK, USA
Atridox	Atridox	Block Drug, Jersey City, NJ, USA; Atrix Laboratories Inc., Fort Collins, CO, USA	8.8–10% doxycycline hyclate in a biodegradable liquid polymer gel	Canada, UK, USA
Aureomycin	Aureomycin	Lederle, UK	3% tetracycline ointment	Not specific for dentistry
Chlosite	Chlosite	Ghimas, Casalecchio di Reno, Bologna, Italy	0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride in a xanthan-based syringeable gel system	Austria, Georgia, Germany, Israel, Italy, The Netherlands, Poland, Russia, Spain
Dentomycin	Dentomycin	Atrix Laboratories, Germany	2% minocycline hydrochloride dihydrate	Poland, UK
	Periocline	Sunstar, Osaka, Japan	2% minocycline hydrochloride, 0.5 g in microcapsules gel	France, Ireland
Elyzol	Elyzol	Dumex, Copenhagen, Denmark	40% metronidazole benzoate corresponding to 25% metronidazole in a mixture of glycerol mono-oleate and sesame oil	Italy, UK
Ligosan	Ligosan, Adjusan	Kulzer (Germany)	15% doxycycline-hyclate in a polyethylene glycolactid/glycolid copolymer gel	Austria, Germany, Hungary, Italy, Poland, Spain (Ligosan), The Netherlands (Adjusan)
Minocycline powder	Not available	Not available	1 mg minocycline hydrochloride microencapsulated in a biodegradable polymer, poly(glycolide-co-DL-lactide)	Not commercially available.
Periochip	Periochip	Dexcel Pharma, Israel	2.5 mg of chlorhexidine gluconate in a bioabsorbable chip of hydrolysed gelatine	Austria, Germany, Greece, Ireland, Israel, Italy, The Netherlands, Poland, Singapore, Switzerland, Ukraine, UK, USA
Periofilm	Periofilm, Gelcide	MedTechDental, Switzerland	Powder (sodium piperacillin 100 mg and sodium tazobactam 12.5 mg) plus liquid (amino-alkyl-methacrylate copolymer, ammonium methacrylate co- polymer, ethanol 95 %, and purified water)	Croatia, France, Italy, Lithuania, Poland, Switzerland
Tetracycline strip	Not available	ALZA Corporation, Palo Alto, CA, USA	Tetracycline hydrochloride loaded in ethylene vinyl acetate co-polymer strips (0.65 mm thick, 1 mm wide, 5 cm length, 13.5 mg tetracycline)	Not commercially available

* Direct information from 22 European countries (Austria, *Azerbaijan, Belgium*, Croatia, *Denmark*, *Finland*, Germany, Lithuania, Hungary, Ireland, Israel, Italy, The Netherlands, Poland, *Portugal*, *Serbia*, *Slovenia*, Spain, Switzerland, *Turkey*, Ukraine, UK) and from some manufacturers. None of the listed products was available in 2019 in the countries shown in italics in the previous sentence.

Overall efficacy of locally delivered antimicrobials

The overall meta-analysis, combining all test groups, demonstrated statistically significant PPD reductions and clinical attachment level (CAL) gains, with weighted mean differences (WMD) in 6–9 month studies, of 0.365 mm and 0.263 mm, respectively, when compared with control groups. In addition, minor or no adverse effects were observed, with no differences between test and control groups. However, significant heterogeneity was observed in most of the analyses. These results were similar to those reported in the previously mentioned systematic reviews (Bonito *et al*. 2005; Hanes & Purvis, 2003; Matesanz-Pérez *et al*. 2013; Smiley *et al*. 2015), with additional PPD reductions ranging between 0.3 mm and 0.6 mm. Overall, systematic reviews demonstrate that locally delivered antimicrobials, as adjuncts to SRP, can improve the clinical outcomes of mechanical treatment alone or with a placebo.

It is important to highlight that, among the sources of heterogeneity, relevant aspects of the study design can have a significant impact on the results of the studies. In the systematic review by Herrera *et al*. (2020), and using meta-regression, the following factors were identified: with statistically significant impact, study design (with larger benefits for split-mouth studies, as compared with parallel studies) and the type of assessment (with larger benefits for partial-mouth assessments, as compared with full-mouth evaluation); studies on treated patients tended to achieve larger PPD reductions (as compared with studies in untreated patients), and studies with placebo tended to achieve smaller benefits, as compared with those in which the control group was SRP alone.

Efficacy of specific locally delivered antimicrobials (in alphabetic order)

Actisite (ALZA Corporation, Palo Alto, CA, USA). Tetracycline has been included in non-resorbable plastic co-polymers, and other vehicles, and clinically tested. The most extensively tested tetracycline-releasing device is the Actisite periodontal fiber. This currently unavailable product consists of a monolithic thread of a biologically inert, non-resorbable plastic co-polymer (ethylene and vinyl-acetate) containing 25% tetracycline–HCl powder. The fiber is packed into the periodontal pocket, secured with a thin layer of cyanoacrylate adhesive, and left in place for 7–12 days (Goodson *et al*. 1983, 1991b). The continuous delivery of tetracycline maintains a local concentration of the active drug in excess of 1000 mg/L throughout that period. In the reference systematic review (Herrera *et al*. 2020), seven studies (with 255 control and 257 test patients) with Actisite were included in the primary analysis (PPD changes after 6–9 months), demonstrating a statistically significant added benefit (WMD) of 0.729 mm (95% confidence interval [CI] 0.696; 0.761, P <0.001) with no heterogeneity.

Arestin (OraPharma, Warminster, PA, USA). It is composed of 1 mg minocycline microencapsulated in poly(glycolide-co-DL-lactide). In the reference systematic review (Herrera *et al*. 2020), six studies (with 567 control and 564 test patients) were included in the primary analysis (PPD changes after 6–9 months), demonstrating an additional reduction (WMD) of 0.279 mm (95% CI 0.203; 0.356, P <0.001) with no heterogeneity.

Atridox (Block Drug, Jersey City, NJ, USA; Atrix Laboratories Inc., Fort Collins, CO, USA). It is a 8.8–10% doxycycline hyclate in a biodegradable liquid polymer gel, with a two-syringe mixing system. One syringe contains the delivery vehicle, flowable bioabsorbable poly(DL-lactide) dissolved in N-methyl-2-pyrrolidone, and the other a doxycycline hyclate powder. In the reference systematic review (Herrera *et al*. 2020), two studies (with 19 control and 19 test patients) were included in the primary analysis (PPD changes after 6–9 months), demonstrating a statistically significant added benefit (WMD) of 0.800 mm (95% CI 0.084; 1.516, P = 0.026) with no heterogeneity.

Chlosite (Ghimas, Casalecchio di Reno, Bologna, Italy). It is composed of 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride, in a xanthan-based syringeable gel system. In the reference systematic review (Herrera *et al*. 2020), two studies (with 109 control and 108 test patients) were included in the primary analysis (PPD changes after 6–9 months), not showing statistically significant added benefits (WMD = 0.486 mm, 95% CI -0.238; 1.211, P = 0.188) with significant heterogeneity (P = 0.002) (Fig. 37-2).

Dentomycin (Dentomycin, Cyanamid, Lederle Division, Wayne, NJ, USA; Dentomycin, Atrix Laboratories, Germany; Periocline, Sunstar, Osaka, Japan). It is 2% minocycline hydrochloride dihydrate, presented in a 5 g microcapsule gel. In the reference systematic review (Herrera *et al*. 2020), two studies (with 65 control and 41 test patients) were included in the primary analysis (PPD changes after 6–9 months), not showing statistically significant added benefits (WMD = 0.377 mm, 95% CI -0.036; 0.790, P = 0.073) with no heterogeneity.

Elyzol (Dumex, Copenhagen, Denmark). It is a 40% metronidazole benzoate, corresponding to 25% metronidazole, in a mixture of glycerol mono-oleate and sesame oil. Dialysis tubing, acrylic strips, and poly-OH-butyric acid strips have been tested as solid devices for delivery of metronidazole. The most extensively used device for metronidazole application is Elyzol Dental Gel, which is applied with a syringe into the pocket, and its viscosity should increase after placement. In the reference systematic review (Herrera *et al*. 2020), five studies (with 136 control and 135 test patients) were included in the primary analysis (PPD changes after 6–9 months), not showing statistically significant added benefits (WMD = 0.140 mm, 95% CI -0.041; 0.322, P = 0.130) with no heterogeneity.

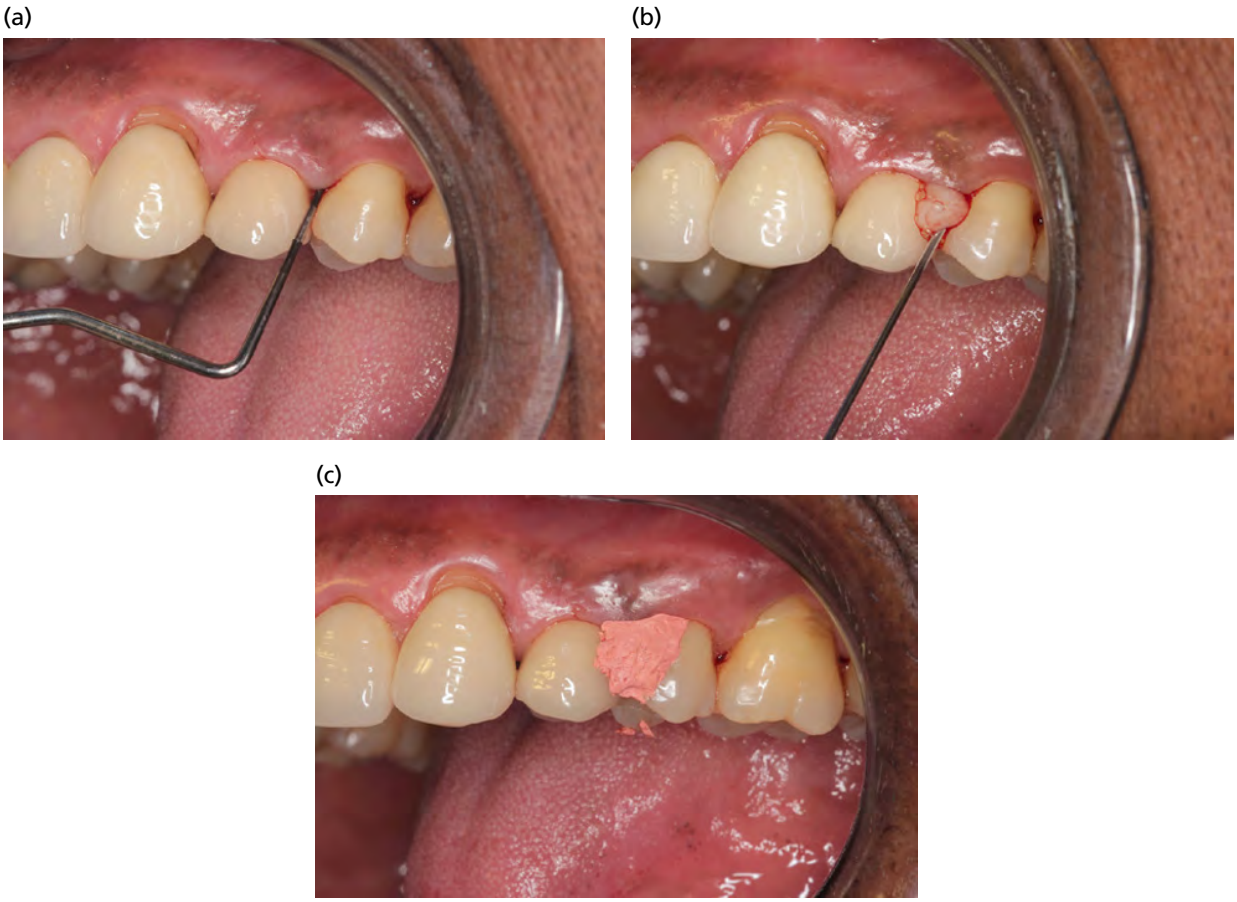

Fig. 37-2 Adjunctive use of chlorhexidine in a xanthan-based syringeable gel system, (a) Deep pocket in the mesiobuccal aspect of tooth number 25. (b) Insertion of the gel with a syringe. (c) Placement of a periodontal dressing to protect the treated area. (Source: Courtesy of Dr. Paula Matesanz.)

Ligosan (also Adjusan, Kulzer, Germany). It is a 15% doxycycline-hyclate in a polyethylene glycolactid/glycolid copolymer gel. In the reference systematic review (Herrera *et al*. 2020), three studies (with 236 control and 232 test patients) were included in the primary analysis (PPD changes after 6–9 months), demonstrating a statistically significant added benefit (WMD) of 0.525 mm (95% CI 0.283; 0.767, P <0.001), with no heterogeneity.

PerioChip (Dexcel Pharma, Israel). It is composed of 2.5 mg of chlorhexidine gluconate in a bioabsorbable chip of hydrolysed gelatine. In the reference systematic review (Herrera *et al*. 2020), nine studies (with 718 control and 719 test patients) were included in the primary analysis (PPD changes after 6–9 months), demonstrating a statistically significant added benefit (WMD) of 0.230 mm (95% CI 0.120; 0.341, P <0.001), with significant heterogeneity (P <0.001) (Fig. 37-3).

Periofilm (also marketed as Gelcide, MedTechDental, Switzerland). It is a mixture of a powder (sodium piperacillin 100 mg and sodium tazobactam 12.5 mg) and a liquid (amino-alkyl-methacrylate copolymer, ammonium methacrylate co-polymer, ethanol 95%, and purified water). In the reference systematic review (Herrera *et al*. 2020), only one study (with 14 control and 18 test patients) was included in the primary analysis (PPD changes after 6–9 months), with no added benefits (WMD) of -0.100 mm (95% CI -1.053; 0.853, P = 0.837).

Efficacy of other locally delivered antimicrobials

Aureomycin (Lederle, UK). It is a 3% tetracycline ointment, not specifically developed for dentistry. In the reference systematic review (Herrera *et al*. 2020), only one study (with 18 control and 18 test patients) was included in the primary analysis (PPD changes after 6–9 months), not showing statistically significant added benefits (WMD = 0.6 mm, 95% CI -0.339; 1.539, P = 0.219). There are reasonable doubts to include this product in the category of sustained-release local antimicrobials.

Tetracycline strip (ALZA Corporation, Palo Alto, CA, USA). It is tetracycline hydrochloride loaded in ethylene vinyl acetate co-polymer strips (0.65 mm thick, 1 mm wide, 5 cm length, 13.5 mg tetracycline), and it has never been marketed. In the reference systematic review (Herrera *et al*. 2020), only one study (with 24 control and 24 test patients) was included in the primary analysis (PPD changes after 6–9 months), demonstrating an additional reduction (WMD) of

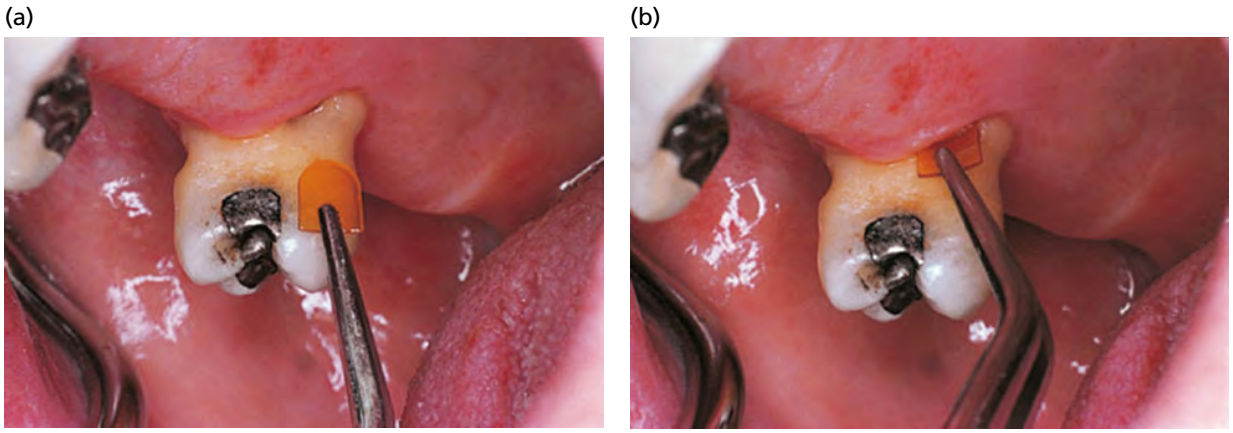

Fig. 37-3 (a) Chlorhexidine chip. (b) Insertion of a chlorhexidine chip into a residual pocket mesial of an upper molar with a furcation involvement.

0.44 mm (95% CI -0.025; 0.905, $P = 0.064$) for the application of one strip, and 0.48 mm (95% CI 0.087; 0.873, $P = 0.017$) for the application of multiple strips.

Azithromycin gel. At 0.5%, it has been tested in at least two studies from the same research group (Pradeep *et al*. 2008, 2013), but it was not included in the reference systematic review due to the limited follow up (Pradeep *et al*. 2008), or because the inclusion criteria restricted the selected sample to smokers (Pradeep *et al*. 2013). There are reasonable doubts to include this product within the category of sustained-release local antimicrobials.

Chlorhexidine varnish. It has been tested by a research group in different investigations (Cosyn *et al*. 2006, 2007). There are reasonable doubts to include this product and the protocol tested within the category of sustained-release local antimicrobials.

Selection of the most effective locally delivered antimicrobial

Based on the individual analysis of each product, it is difficult to provide a global assessment of the use of sustained-released local antimicrobials because each product has unique properties. In addition, the variable availability of these products in different countries makes it more difficult to provide consistent recommendations. Usability should also be considered; some products are very easy to apply, while others are less user-friendly. Some need repeated application, while others must be removed after 7–10 days and/or be protected by using a dressing or cyanoacrylate on the treated area. The use of antiseptics, such as chlorhexidine, which have fewer risks, rather than the use of antibiotics, is also a consideration. However, they are not as effective when compared with products based on doxycycline, minocycline, or tetracycline. The cost–benefit ratio of these technologies should also be considered. Henke *et al*. (2001) suggested that the increased cost of initial therapy is compensated by fewer surgical interventions; however, more consistent analyses are needed, similar to those already available for peri-implant diseases (Listl *et al*. 2015). A cost-effectiveness analysis concluded that systemic antimicrobials are more cost-effective than locally delivered antimicrobials (Heasman *et al*. 2011).

Ideally, to understand which products are most effective, a direct comparison is preferable. However, in the reference systematic review (Herrera *et al*. 2020), only two studies included more than one local antimicrobial test group, comparing Actisite, Dentomycin, and Elyzol Dental Gel (where better results were reported for Actisite) (Kinane & Radvar 1999) or Elyzol and Aureomycin (reporting similar results) (Lie *et al*. 1998). Few other direct comparisons are available. Salvi *et al*. (2002), assessed Atridox, Elyzol Dental Gel, and PerioChip, concluding that Atridox provided the best results.

Indications for locally delivered, sustained-release antimicrobials

Studies assessing the adjunctive benefits of local delivery devices to mechanical instrumentation have identified a range of clinical conditions where the addition of these devices may lead to improved outcomes (Tonetti *et al*. 1994; Tonetti, 1998; Greenstein & Tonetti 2000; Matesanz-Pérez *et al*. 2013) including special local conditions and special patient groups.

Clinical indications: deep, localized pockets

Because the majority of untreated shallow (4–5 mm) pockets are expected to heal with mechanical instrumentation alone, local antimicrobials are of potential benefit for deeper pockets (6–8 mm range). Furthermore, incorporation of local delivery devices into the treatment armamentarium requires reconciliation of the localized nature of the treatment target (the periodontal pocket) with the overall ecologic determinants of clinical outcomes in light of

available treatment alternatives. In general, adjunctive treatment with local antimicrobials is favored when there are relatively few residual pockets and systemic delivery of the antimicrobial may not be warranted.

Clinical indications: localized residual pockets

Deep localized pockets may be found after treatment, either non-responding sites or disease recurrence during SPC. In the reference systematic review (Herrera *et al*. 2020), 11 studies defined the disease condition as recurrent or "refractory" or relapsing, in already treated patients or in patients SPC. For the assessment of the same product (Chlosite), some authors selected non-responding or refractory sites (Matesanz *et al*. 2013), while others recruited untreated patients (Paolantonio *et al*. 2009), with poorer response in non-responding/refractory cases, which could be explained by a larger potential for healing in untreated sites (Harrel & Nunn 2001), or by specific microbiological profiles or immunological conditions in non-responding/refractory cases (Haffajee *et al*. 2004). However, in the overall evaluation, studies on treated patients tended to achieve larger PPD reductions (as compared with studies in untreated patients). Despite the fact that non-responding sites after therapy or recurrent disease during SPC may represent a reasonable indication for local antimicrobials (because only local sites/teeth may be affected), limited attention has been paid to differential outcomes in those cases, as compared with untreated patients, even when both types of patients were included in the same study (Eickholz *et al*. 2002).

Clinical indications: residual pockets in sites with furcation involvement

Few studies have addressed the management of furcation defects with local antimicrobials. Short-term adjunctive benefits in controlling gingival inflammation as well as improvements in probing depths and CALs have been reported (Tonetti *et al*. 1998; Tomasi *et al*. 2008; Dannewitz *et al*. 2009; Tomasi & Wennstrom, 2011). Interestingly, but perhaps not unexpectedly, the benefits did not persist medium to long term in these difficult anatomic areas.

Clinical indications: residual pockets in the aesthetic zone

Another potentially important application is when residual pockets are present in the so-called aesthetic zone, where a surgical intervention may compromise aesthetics and/or phonetics. Lastly, application of local delivery devices seems to be a rational choice at sites with deep pockets and persistent bleeding on probing that are associated with intrabony defects after completion of the cause-related phase of therapy. As these sites are likely to be treated with periodontal regeneration and the outcome of periodontal regeneration is negatively affected by the degree of bacterial contamination and spectrum of pathogens persisting into the lesion (Heitz-Mayfield *et al*. 2006), local drug delivery may be an important means of pocket disinfection before regenerative periodontal surgery.

Patient indications: special patient categories

From a clinical standpoint, important attenuations of the expected benefits of non-surgical and surgical treatment have been observed in high-risk groups. These include smokers and subjects with diabetes, significant co-morbidities, or erratic compliance with oral hygiene and/or long-term adherence to the necessary SPC program. The effect of adjunctive local drug delivery has been assessed in such subjects, and although very limited and initial evidence is available, it may open new possible indications for the use of local antimicrobials:

- Studies have reported that the adjunctive effect of local drug delivery may not be adversely affected by cigarette smoking (Ryder *et al*. 1999). In a planned secondary analysis of a multicenter trial, assessing the adjunctive benefits of minocycline microspheres, the enhanced response to local delivery device application was greatest among smokers (Paquette *et al*. 2003).
- Older patients as well as those with concomitant self-reported cardiovascular disease have also been reported to respond better to adjunctive local delivery than to mechanical instrumentation alone (Lessem & Hanlon 2004). Local drug delivery may contribute to better control of periodontitis in subjects with relative or absolute contraindications to surgical intervention.
- Lastly, in patients with diabetes and periodontitis, recent RCTs have shown benefits in the control of gingival inflammation and better clinical outcomes from the application of adjunctive local drug delivery with respect to subgingival instrumentation alone (Agarwal *et al*. 2017)

Locally or systemically delivered antimicrobials

Very limited information on a direct comparison of local or systemic antimicrobials is available. For patients with chronic periodontitis, one study reported better results for SRP supplemented with Elyzol than adjunctive systemic metronidazole (Noyan *et al*. 1997). For patients with aggressive periodontitis, SRP plus amoxicillin and metronidazole provided better clinical results after 6 months than PerioChip (Kaner *et al*. 2007).

Summary

Local drug delivery into the periodontal pocket is an effective treatment adjunct to mechanical instrumentation. Clinical application requires the use of a well-designed technology platform that is able to counteract GCF clearance of the locally applied antimicrobial and maintain effective concentrations for long enough for the desired pharmacologic effect to occur. Pocket disinfection is feasible, but recolonization is a critical phenomenon that needs to be prevented with a specific clinical strategy: optimal supragingival hygiene, full-mouth approach, and/or use of an antiseptic mouth rinse. Clinical applications range from the management of few residual pockets in otherwise healthy subjects to the management of residual lesions in groups at high risk because of age, smoking, frailty, or the presence of important co-morbidities.

The main limitation of these recommendations is the limited quality of the available RCTs. Although some methodological aspects, such as blinding and randomization, were acceptable in most cases, the global risk of bias was considered as high in most of the included publications in the reference systematic review (Herrera *et al*. 2020), and only three of them were classified as having a moderate risk of bias (Eickholz *et al*. 2002; Killeen *et al*. 2016; Tabenski *et al*. 2017). In addition, when combining data (meta-analyses), statistically significant heterogeneity was observed for most of the analyses, which limits the results of the systematic review. Furthermore, the risk of bias in selected studies may have been increased by the participation of the manufacturing companies in most studies, either through sponsorship or by inclusion of their personnel in the research teams.

The European Federation of Periodontology (EFP) S3 Level Clinical Practice Guideline on the Treatment of Stage I–III Periodontitis (Sanz *et al.* 2020) has assessed the role of local delivery of antiseptics (chlorhexidine) and antibiotics, based on the systematic review by Herrera *et al.* (2020). After due consideration, a consensus was reached on the following clinical recommendation: "specific locally administered sustained release chlorhexidine and antibiotics, as an adjunct to subgingival instrumentation, in patients with stage I–III periodontitis may be considered" (Sanz *et al.* 2020).

Local antimicrobial delivery for the treatment of peri-implant diseases

Clinical rationale

Prevention and control of biofilm-induced inflammation at the transmucosal portion of dental implants is particularly challenging due to the special limitations in effectiveness of professional mechanical plaque removal, in both peri-implant mucositis (Schwarz *et al*. 2015a) and peri-implantitis (Schwarz *et al*. 2015b). The adjunctive use of local antimicrobials has long been suggested as a potential approach to overcome some of the limitations. The use of local delivery devices has been tested in early proof of principle studies with some success. Potential uses for locally delivered antimicrobials furthermore include the treatment of peri-implant infections (Mombelli *et al*. 2001; Renvert *et al*. 2006). The sulcus around dental implants shares some of the pharmacokinetic characteristics of periodontal pockets: the presence of a high flow rate of peri-implant sulcus fluid, a relatively small resting volume, and difficulty of access of mouth rinses and dentifrices to the submucosal environment where the biofilm accumulates.

Efficacy of subgingival delivery devices in peri-implant diseases

Very limited information is available on the use of locally delivered antimicrobials (tetracycline fibers) in peri-implant mucositis (Schenk *et al*. 1997), and its relevance has been considered as small (Schwarz *et al*. 2015a, b).

In the non-surgical therapy of peri-implantitis, the early proof of principle studies showed some efficacy of adjunctive locally delivered antimicrobials (Mombelli *et al*. 2001; Salvi *et al*. 2007). More recently, different studies have been conducted assessing minocycline microspheres (Renvert *et al*. 2006, 2008), chlorhexidine chips (Machtei *et al*. 2012), or doxycycline gel (Buchter *et al*. 2004), and systematic reviews on effective interventions for peri-implantitis have globally assessed their impact (Esposito *et al*. 2012; Muthukuru *et al*. 2012; Schwarz *et al*. 2015b; de Almeida *et al*. 2017), identifying some initial evidence that local delivery, combined with subgingival instrumentation, may be of greater benefit than subgingival instrumentation alone. These studies, however, failed to identify decisive clinical benefits from the adjunctive application of local delivery devices to control peri-implant dysbiosis and further studies are necessary in this area. Network meta-analyses have also explored the relative potential of various adjuncts to peri-implant debridement/biofilm removal alone and again have not been able to recommend strategies to better control peri-implantitis (Faggion *et al*. 2014).

Indications for locally delivered, sustained-release antimicrobials in peri-implantitis

Given the limited evidence of efficacy, the adjunctive application of local delivery of antimicrobials is best limited to selected cases and in the context of better control of peri-implant mucosal tissue inflammation during the preparation phase of surgical (resective or regenerative) therapy. In some specific cases, the local adjunctive antimicrobial effect may provide significant short-term anti-inflammatory benefits (Fig. 37-4).

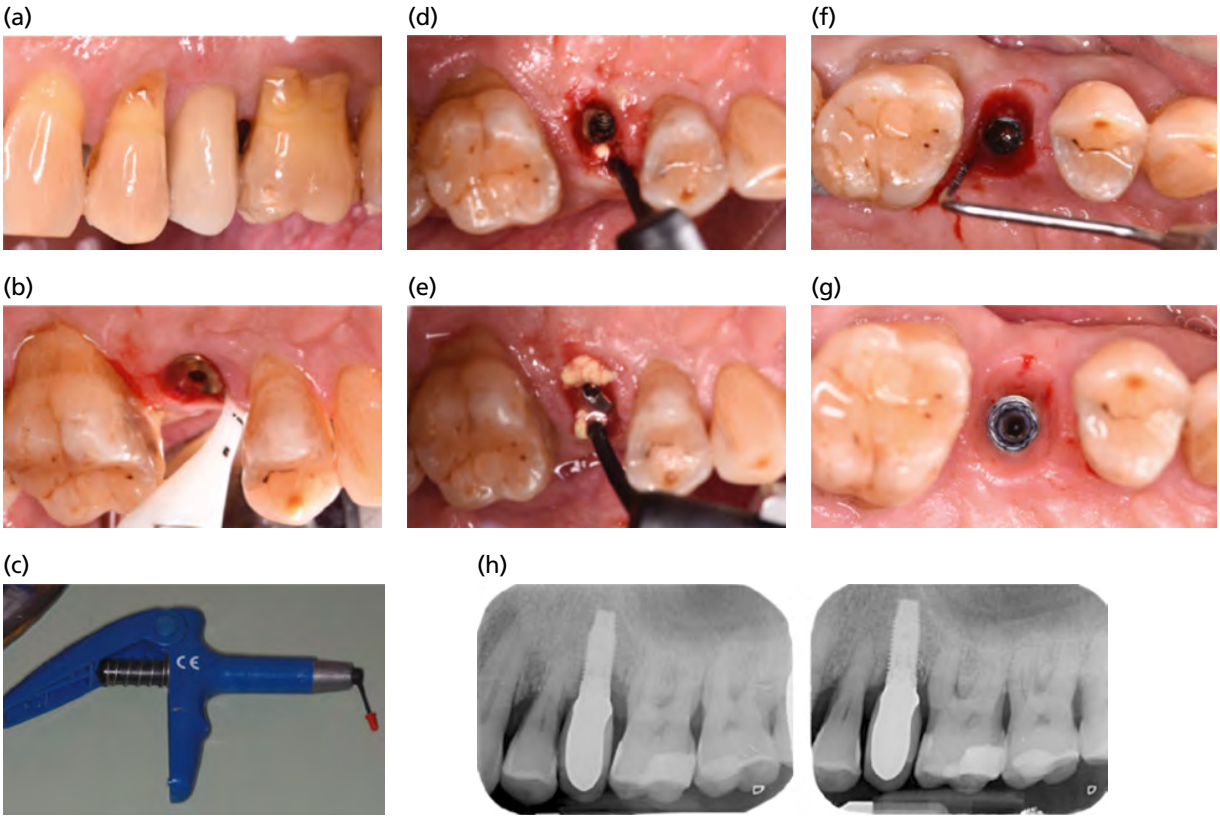

Fig. 37-4 Adjunctive use of doxycycline hyclate in peri-implantitis: (a) Baseline clinical condition in dental implant in position number 25. (b) Implant surface decontamination. (c) Syringe. (d) Initial placement of antimicrobial. (e) Final placement of antimicrobial. (f) Occlusal view at baseline. (g) Occlusal view after 1 month. (h) Radiographs at baseline (left) and after 1 year (right). (Source: Courtesy of Dr. Juan Bollain.)

Summary

Local drug delivery as an adjunct to mechanical debridement for the management of peri-implant diseases, and peri-implantitis in particular, is potentially interesting. For a specific application, the relatively low intrinsic efficacy of mechanical debridement alone may render this treatment modality an important adjunct. More research is necessary to fully understand the benefits and indications.

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Part 13: Reconstructive Therapy

Chapter 38

Regenerative Periodontal Therapy

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Introduction

The advances in the understanding of the biology of wound healing and periodontal regenerative technologies are applied to improve long-term clinical outcomes of teeth that are periodontally compromised by intrabony or interradicular defects. The treatment objective is to obtain shallow, maintainable pockets by reconstruction of the destroyed attachment apparatus and thereby also limit recession of the gingival margin. In general, periodontal regeneration is selected to obtain: (1) an increase in the periodontal attachment of a severely compromised tooth; (2) a decrease in deep pockets to a more maintainable range; and (3) a reduction of the vertical and horizontal component of furcation defects. Current approaches, however, remain technique sensitive and clinical success requires application of meticulous diagnostic and treatment strategies.

Classification and diagnosis of periodontal osseous defects

Site-specific periodontal breakdown compromises the long-term prognosis of teeth by producing three types of defects: suprabony (or horizontal) defects, infrabony (or vertical) defects, and interradicular (or furcation) defects.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

According to the classification by Goldman and Cohen (1958), suprabony defects are those where the base of the pocket is located coronal to the alveolar crest. This chapter does not deal with suprabony defects.

Infrabony defects, on the other hand, are defined by the apical location of the base of the pocket with respect to the residual alveolar crest. With regard to infrabony defects, two types can be recognized: intrabony defects and craters. Intrabony defects are bony defects whose infrabony component affects primarily one tooth, while in craters the defect affects two adjacent root surfaces to a similar extent. Intrabony defects (Fig. 38-1) have been classified according to their morphology in terms of residual bony walls, width of the defect (or radiographic angle), and topographic extension around the tooth. Three-wall, two-wall, and one-wall defects have been defined on the basis of the number of residual alveolar bone walls. This represents the primary classification system. Frequently, intrabony defects present a complex anatomy consisting of a three-wall component in the most apical portion of the defect, and two- and/or one-wall components in the more superficial portions. Hemiseptal defects, that is vertical defects in the presence of adjacent roots and where half of a septum remains on one tooth, represent a special case of one-wall defects. Several authors have also used descriptive terms to define special morphologic characteristics: funnel-shaped defects, moat-like defects, trenches, etc.

Of particular interest is a special morphology: the crater (Fig. 38-1). It is defined as a cup- or bowl-shaped defect in the interdental alveolar bone with bone loss nearly equal from the roots of two contiguous teeth and a more coronal position of the buccal and lingual alveolar crest; the facial and lingual/palatal walls may be of unequal height. This defect can be considered to be the result of the apical spread of periodontitis along two adjacent roots in a relatively narrow (mesiodistally) interproximal area. Notably, all the definitions above are not based on radiographic assessments, but on the actual morphology of the defects after flap elevation. Conditions entailing pathologic resorption of bone within the furcation of a multirooted tooth, defined as furcation invasions, are also classed as periodontal bony defects; the reader is referred to Chapter 33 for a discussion of the anatomy and classification of furcations.

The diagnosis of the presence and the morphology of periodontal osseous lesions represents a major clinical challenge. It is primarily performed by combining clinical information derived from the evaluation of the attachment level with information derived from diagnostic-quality parallel-technique intraoral radiographs. A precise knowledge of root anatomy and its variations is also important for the diagnosis of periodontal osseous defects, and interradicular defects in particular. Diagnostic-quality radiographs provide additional information on the morphology of the alveolar bone resorption. In this context, interpretation of the radiographic image of the interdental septum is complicated, since the radiograph provides a two-dimensional image of a three-dimensional anatomy consisting of superimposed structures, including alveolar bone, hard tooth substances, and soft tissue. This complexity of the visualized structures means that a certain amount of tissue destruction must occur before it can be radiographically detected, often rendering incipient bone lesions obscure. Furthermore, even advanced lesions may be masked by the presence of superimposed structures. It is therefore generally stated that radiographic diagnosis has a high positive predictability (i.e. the visualized lesions are indeed there) but a low negative predictability (i.e. the absence of radiographically detectable bone loss does not exclude the presence of an osseous lesion).

Clinical attachment level (CAL), on the other hand, is a highly sensitive diagnostic tool; its combination with radiographs, therefore, confers a higher degree of accuracy to the diagnostic approach (Tonetti *et al*. 1993b). In particular, the site-specific comparison of radiographic bone loss with clinical attachment loss allows the clinician to make a qualified guess of the true osseous architecture, whose exact morphology, however, can only be established after flap elevation. Detection of the defect, its location and extension, along with its major morphologic features, should be performed before flap elevation. A further aid to this end is the use of transgingival probing or bone sounding.

Clinical indications

Periodontal treatment, either surgical or non-surgical, results in recession of the gingival margin after healing (Isidor *et al*. 1984). In advanced cases of periodontitis, this may lead to poor esthetics in the front areas of the dentition, in particular when applying surgical procedures with osseous recountouring for the eradication of bone defects. In addition, osseous resection applied to sites with severe bone destruction and deep intrabony defects may result in unacceptable removal of residual supporting bone to the involved and neighboring teeth. Treatment of such cases without bone contouring, on the other hand, may result in residual pockets inaccessible to proper cleaning during post-treatment maintenance. These problems can be avoided or reduced by applying regenerative surgical procedures to restore the lost periodontal attachment in the bone defects. Thus, the indication for applying regenerative periodontal therapy is often based on the anatomy of bone destruction and on esthetic considerations, besides the fact that the function or long-term prognosis of the treated teeth may be improved. Case reports exist demonstrating that "hopeless" teeth with deep vertical defects, increased tooth mobility or through-and-through furcations can be successfully treated with regenerative periodontal

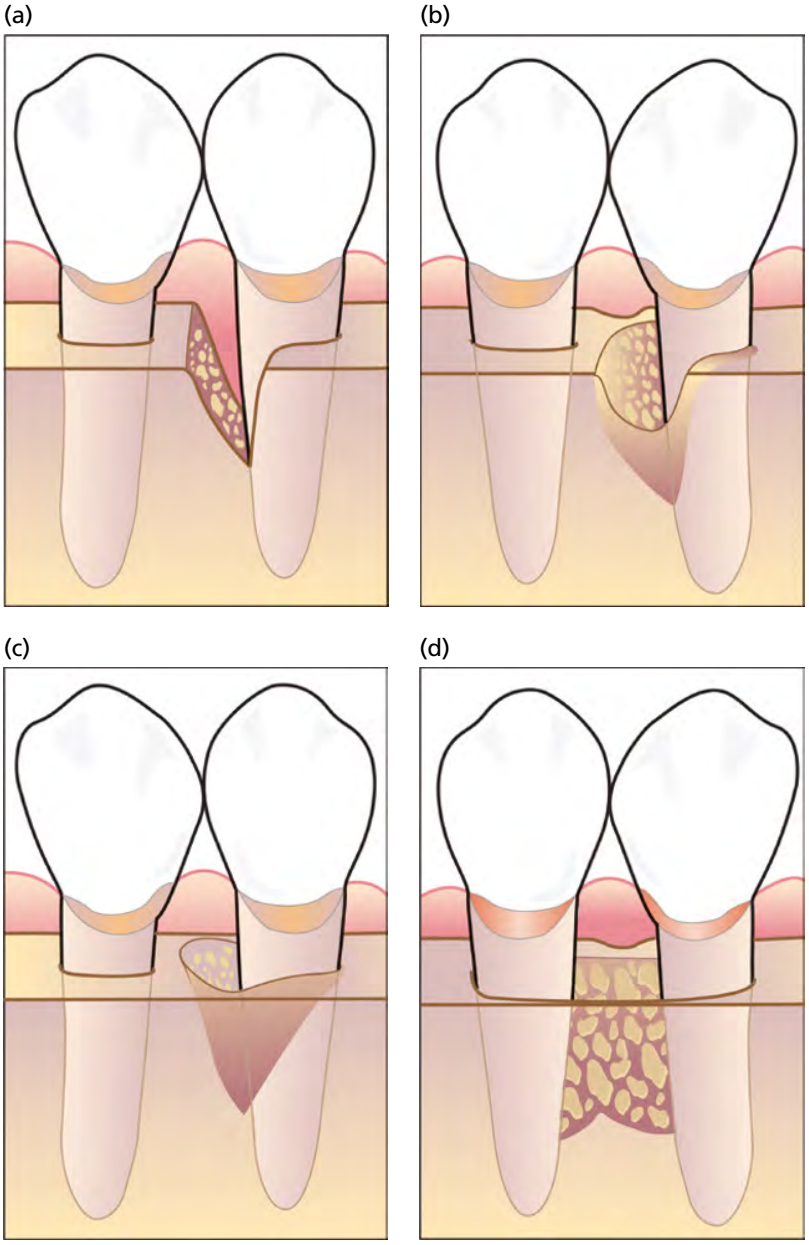


Fig. 38-1 Infrabony defects. (a) One-wall intrabony defect; (b) two-wall intrabony defect; (c) three-wall intrabony defect; (d) interproximal crater. (Source: Papapanou & Tonetti 2000. Reproduced with permission from John Wiley & Sons.)

therapy (Gottlow *et al*. 1986). Teeth with deep pockets associated with deep intrabony defects are considered a clinical challenge. Most authors have classified such teeth as having either a questionable or a hopeless prognosis. Key elements supporting these opinions are the complex interplay of reduced residual periodontal attachment, deep pocketing, functional demands, and frequently the resulting tooth hypermobility (Lang & Tonetti 1996; McGuire & Nunn 1996a, b; Kwok & Caton 2007). It is therefore clear that the possibility of changing the prognosis of a tooth from "questionable" or "hopeless" to "fair" or "favorable" would greatly help clinicians and patients in the difficult job of maintaining teeth over time, and the possibility of gaining periodontal support would help improve patient comfort and function. A randomized controlled clinical trial reported 92% survival at 5 years and 88% at 10 years of "hopeless" teeth treated with periodontal regeneration (Cortellini *et al*. 2011, 2020b). A recent meta-analysis concluded that application of regenerative materials in combination with papillary preservation flaps should be considered the treatment of choice for residual pockets with deep (≥3 mm) intrabony defects (Nibali *et al*. 2020). The XVI European Workshop in Periodontology in periodontology developed clinical guidelines using the format of a structured consensus development conference. From the conference came a strong recommendation "to treat teeth with residual deep pockets associated with intrabony defects 3 mm or deeper with periodontal regenerative surgery" (Sanz *et al*. 2020).

Other indications for regenerative periodontal therapy include furcation-involved teeth. The furcation area is often inaccessible to adequate instrumentation and frequently the roots present concavities and furrows that make proper cleaning of the area impossible after access or resective surgery. Considering the long-term results and complications

reported following treatment of furcation involvements by traditional surgical therapy (Hamp *et al*. 1975; Bühler 1988), the long-term prognosis of furcation-involved teeth can be improved considerably by successful regenerative periodontal therapy. The EFP 2019 workshop expressed a consensus on a recommendation "to treat mandibular molars with residual pockets associated with class II furcation involvement with periodontal regenerative surgery"; and a suggestion "to treat molars with residual pockets associated with maxillary buccal class II furcation involvement with periodontal regenerative surgery" (Sanz *et al*. 2020).

Long-term effects and benefits of regeneration

A pertinent question with respect to regenerative treatment is whether or not the achieved attachment level gains can be maintained over an extended period of time. In a long-term follow-up study, Gottlow *et al*. (1992) assessed the stability of new attachment gained through guided tissue regeneration (GTR) procedures. Eighty sites in 39 patients, which 6 months after surgery exhibited a gain of clinical attachment of ≥2 mm (2–7 mm), were monitored over an additional period of 1–5 years. Of the 80 sites, 65 were monitored for 2 years, 40 for 3 years, 17 for 4 years, and nine for 5 years. The results of this study and those of other trials indicate that attachment gain obtained following GTR treatment can be maintained on a long-term basis (Becker & Becker 1993; McClain & Schallhorn 1993).

An investigation of intrabony defects demonstrated that the stability of sites treated with GTR was dependent on patient participation in a recall program, and on the absence of bacterial plaque, bleeding on probing (BoP), and re-infection of the treated sites with periodontal pathogens (Cortellini *et al*. 1994). The susceptibility to disease recurrence at sites treated with non-bioresorbable barrier membranes was assessed in a study comparing long-term changes in attachment levels at regenerated and non-regenerated sites in the same patient (Cortellini *et al*. 1996a). Results indicated that there was a high degree of concordance in the clinical outcomes (stability versus recurrence of attachment loss) within the same patient, suggesting that patient factors, rather than site factors, including the specifics of the histologic type of expected wound healing, are associated with disease recurrence. Among patient factors, compliance with oral hygiene, smoking habits, and susceptibility to disease progression were the major determinants of stability of the treated sites, rather than the employed treatment modality.

Support for a limited impact of the histologic type of healing comes from an experimental study. In a study in monkeys (Kostopoulos & Karring 1994), periodontal breakdown was produced by the placement and retention of orthodontic elastics on experimental teeth until 50% bone loss was recorded. The experimental teeth were endodontically treated and subjected to a flap operation, and all granulation tissue was removed. The crowns of the teeth were resected at the level of the cementoenamel junction and a barrier membrane was placed to cover the roots before they were submerged. Following 4 weeks of healing, the membranes were removed. At the same time, the contralateral teeth that served as controls were endodontically treated and subjected to a sham operation during which the crowns were resected at the level of the cementoenamel junction. Artificial composite crowns were then placed on both the experimental and the control roots. The sites were allowed to heal for 3 months during which period careful plaque control was performed. At the end of this period, cotton-floss ligatures were placed on both experimental and control teeth to induce periodontal tissue breakdown. After another 6 months, the animals were sacrificed. With respect to attachment level, bone level, probing pocket depth (PPD), and gingival recession, similar results were recorded in the histologic specimens of experimental (Fig. 38-2) and control (Fig. 38-3) teeth.

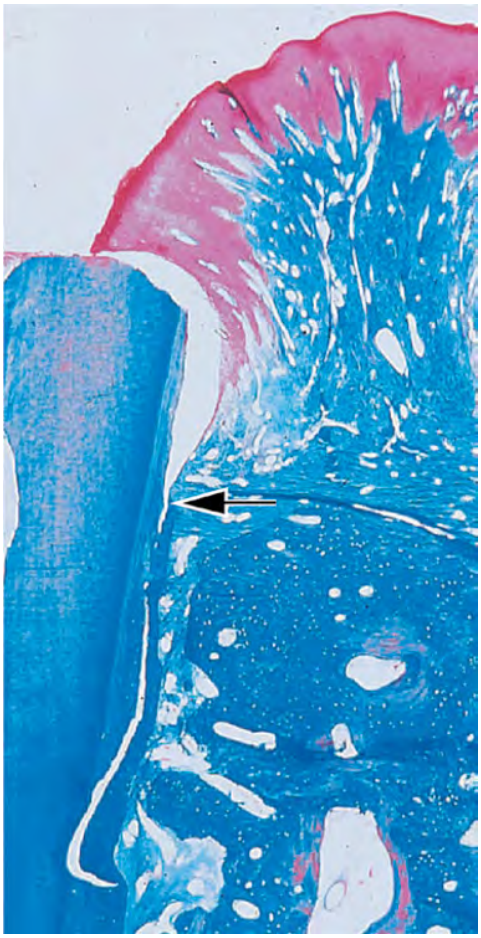


Fig. 38-2 Microphotograph of test specimen with a reformed connective tissue attachment. After 6 months of ligature-induced periodontitis, loss of attachment has occurred from the coronal cut root surface to the level indicated by the arrow.

This indicates that the new connective tissue attachment formed with GTR is no more susceptible to periodontitis than the naturally existing periodontium.

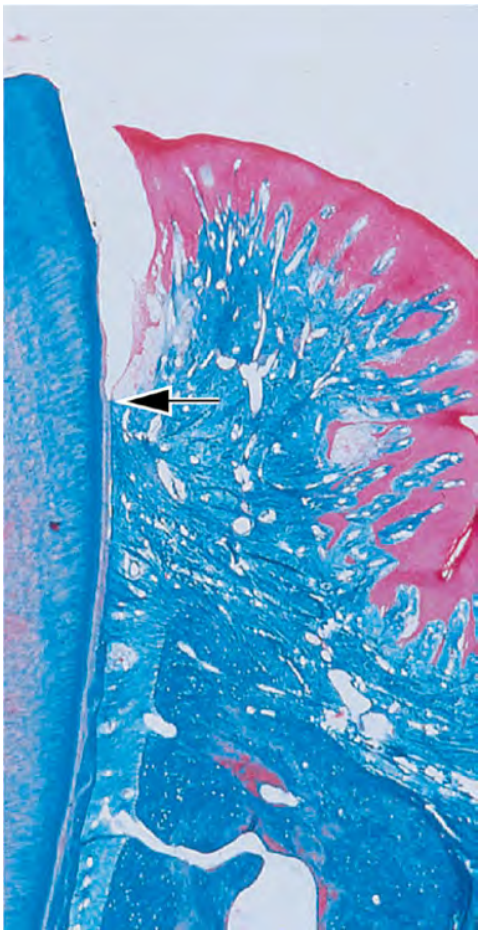


Fig. 38-3 Microphotograph of control specimen with a naturally existing periodontium. After 6 months of ligature-induced periodontitis, loss of attachment has occurred from the coronal cut tooth surface to the level indicated by the arrow.

Other long-term studies show that, if the patient participates in a professionally delivered supportive periodontal care program and maintains good oral hygiene, the regenerated attachment can be maintained long term (Christgau *et al*. 1997; Sculean *et al*. 2006, 2008; Eickholz *et al*. 2007; Slotte *et al*. 2007; Nickles *et al*. 2009; Pretzl *et al*. 2009; Nygaard-Østby *et al*. 2010).

Few investigations have looked at the long-term effects of periodontal regeneration on tooth survival. Cortellini and Tonetti (2004) performed a Kaplan–Mayer analysis of tooth survival following periodontal regenerative treatment in a sample of 175 patients followed up for 2–16 years (average 8 ± 3.4 years) in a specialist environment. In this study, 96% of teeth treated with periodontal regeneration survived. Of interest was the observation that tooth loss was observed among only the 32% of the population who smoked (tooth survival was 89% among smokers and 100% among non-smokers). CALs were located at the same level or coronal to the pretreatment levels in 92% of cases up to 15 years after treatment (Table 38-1, Fig. 38-4).

The potential clinical benefits of periodontal regeneration are best illustrated in a consecutive case series of strategic abutments severely compromised by the presence of deep intrabony defects with associated deep pockets, which were followed up for up to 8 years following regenerative treatment (Tonetti *et al*. 1996b; Cortellini *et al*. 1999b). At baseline, the periodontal defect rendered these teeth unsuitable as abutments to be included in a reconstruction. In all cases, periodontal regeneration with barrier membranes was able to change the clinical prognosis by providing both a 30% increase in radiographic bone support and shallow, maintainable PPD. These outcomes remained stable during the follow-up period (Fig. 38-5). A systematic review (Kao *et al*. 2015) concluded that

Table 38-1 Survival analysis of regenerated periodontal attachment over a 16-year follow-up period in 175 subjects treated with periodontal regeneration. In this survival analysis, the event is represented by clinical attachment level (CAL) loss of ≥2 mm from the level of attachment obtained at completion of healing 1 year after regeneration. No substantial recurrence of periodontitis (CAL loss) was observed in 92% of treated cases who participated in a secondary prevention program.

Time at risk (years)	Number of CAL loss ≥2 mm	Censored	Effective sample size	Conditional probability of CAL loss (%)	Survival (%)
0–2	2	0	175	1.1	100
2–4	3	0	166	1.7	98.9
4–6	2	0	155	1.2	97.1
6–8	1	55	119	0.7	96
8–10	0	47	70.5	0	95.3
10–12	2	16	41	3.5	95.3
12–14	0	25	24.5	0	92
14–16	0	21	8	0	92
16	0	1	0.5	0	92

Source: Cortellini & Tonetti (2004). Reproduced with permission from John Wiley & Sons.

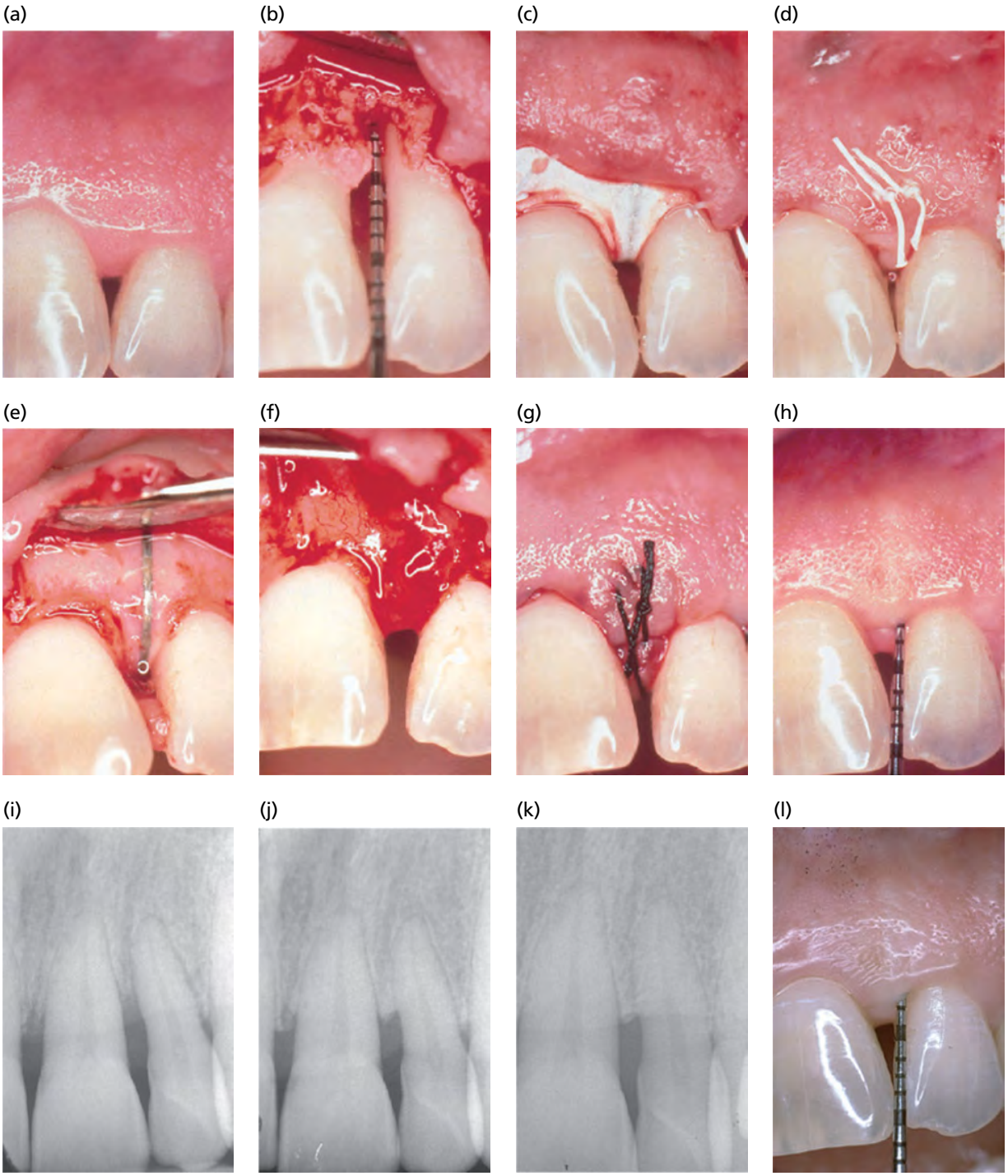


Fig. 38-4 (a, b) Left maxillary lateral incisor with a deep interproximal intrabony defect on the mesial surface. (c) Flaps are raised according to the modified papilla preservation technique, and a titanium-reinforced barrier membrane is placed over the defect. (d) By coronal displacement of the flap and preservation of the interdental papilla, the membrane is completely covered. (e, f) After 6 weeks of uneventful postoperative healing, the membrane was removed and (g) the newly formed tissue was completely covered. (h) At 1 year, residual probing pocket depth was 2 mm and no buccal or interdental recession had occurred. (i) Baseline radiograph showed radiolucency approaching the apex of the tooth, but after 1 year the intrabony defect is resolved and some supracrestal bone apposition seems to have occurred (j). Radiograph taken at 6 years confirms the supracrestal bone regeneration (k) and the clinical image showed the integrity of the interdental papilla with optimal preservation of the esthetic appearance (l).

improvements in clinical parameters obtained with periodontal regeneration are maintainable up to 10 years, even in severely compromised teeth, consistent with a favorable/good long-term prognosis.

A recent long-term randomized controlled trial (RCT) demonstrated that clinical benefits from periodontal regeneration can be maintained up to 20 years (Cortellini *et al*. 2017). In this study, survival of the regenerated teeth in well-maintained patients was 100% compared with 85.7% in the flap control group. Flap-treated sites had greater odds ratios (OR) for recurrences and higher costs of re-intervention than regenerated sites over a 20-year follow-up period with supportive periodontal care (SPC). Residual

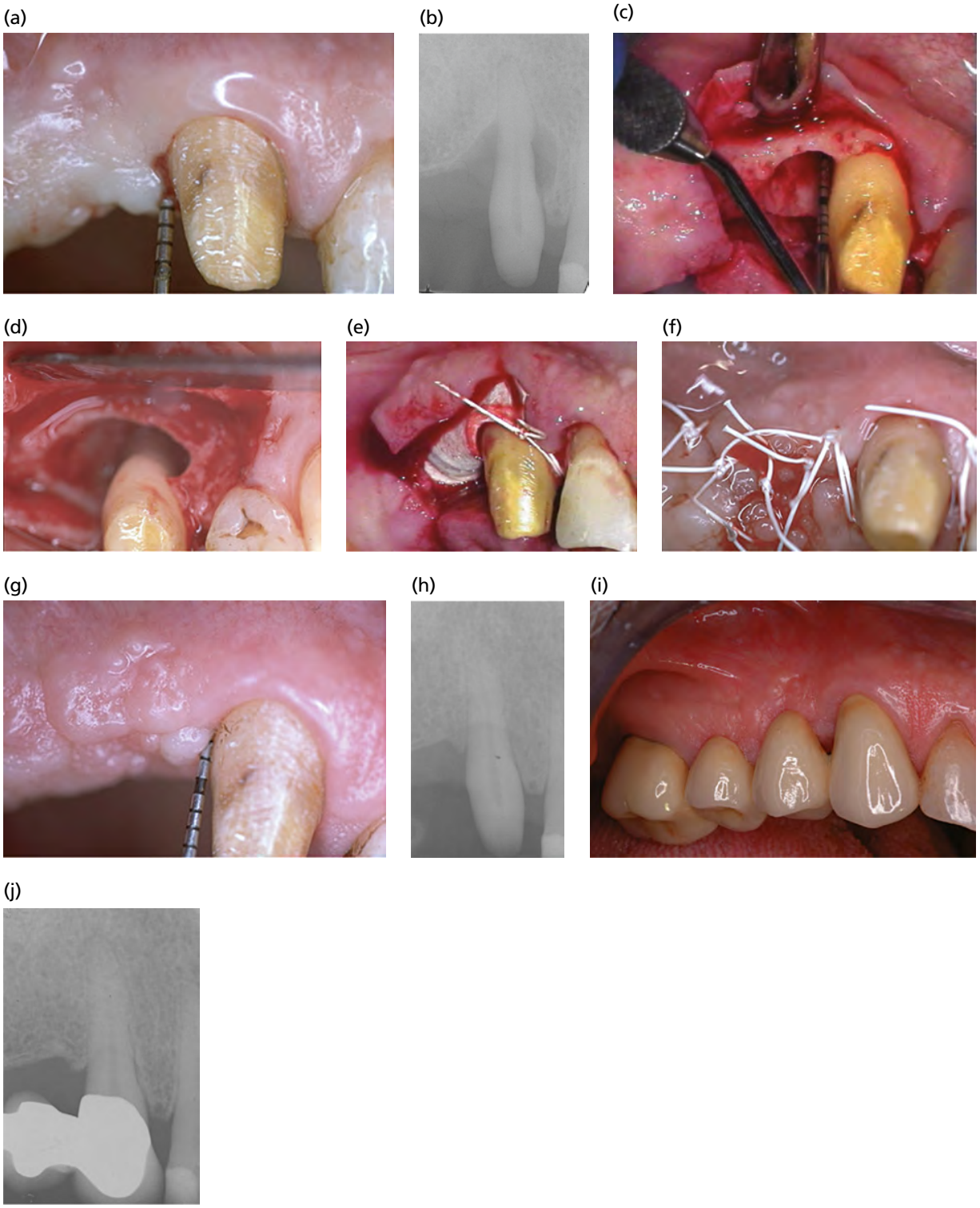


Fig. 38-5 Clinical benefits of periodontal regeneration. Patient presented with periodontally compromised mesial abutment of the bridge: a 10-mm pocket was associated with a 10-mm intrabony defect extending on three of the four surfaces of the tooth (a–d). A barrier membrane was positioned and secured around the root of the tooth (e). Primary closure with internal mattress sutures was achieved (f) and maintained during the healing period. At 1 year, periodontal probing showed a shallow maintainable pocket (3 mm) (g) and the complete resolution of the defect (h). Clinical and radiographic stability of the outcome is shown 10 years following regenerative therapy (i, j): stability of the gingival margin, shallow pockets, good esthetics, and good periodontal support for the abutment are evident.

pocket depth at 1 year, more frequently detected in the flap-treated sites, was significantly correlated with the number of recurrences ($P = 0.002$).

A randomized controlled clinical trial reported 88% survival at 10 years of "hopeless" teeth treated with periodontal regeneration (Cortellini *et al*. 2020b). The control group was treated with extraction and replacement of hopeless teeth with implant or teeth supported reconstructions. Complication-free survival was not significantly different: 6.7–9.1 years for

periodontal regeneration and 7.3–9.1 years for extraction and replacement ($P = 0.788$). Recurrence analysis showed that the 95% confidence interval of the costs was significantly lower for periodontal regeneration compared with extraction and replacement throughout the whole 10-year period. Patient-reported outcomes and oral health-related quality-of-life measurements improved in both groups. The authors concluded that periodontal regeneration can change the prognosis of hopeless teeth and is a less costly alternative to tooth extraction and replacement. The complexity of the treatment limits widespread application to the most complex cases but provides powerful proof of principle for the benefits of periodontal regeneration in deep intrabony defects.

A few studies have evaluated the long-term prognosis for furcation defects treated with regenerative therapy. Sixteen mandibular class II furcation defects, following coronal flap positioning and citric acid root biomodification with and without implantation of demineralized freeze-dried bone allografts (DFDBAs), were determined to be completely resolved with bone fill assessed by re-entry surgery. They were re-evaluated after 4–5 years (Haney *et al*. 1997), when 12 of the 16 sites exhibited recurrent class II furcations and all 16 sites demonstrated probable buccal furcation defects. The investigators concluded that these findings question the long-term stability of bone regeneration in furcations following coronally advanced flap procedures. A similar benefit has been reported following use of combination therapy (barrier membranes and DFDBA) in teeth compromised by class II furcation defects (Bowers *et al*. 2003): 92% of the class II defects were either closed or transformed into class I and thus at lower risk of tooth loss 1 year after therapy (McGuire & Nunn 1996a, b). A recent systematic review (Jepsen *et al*. 2020) investigated the clinical performance of regenerative periodontal surgery in the treatment of furcation defects versus open flap debridement (OFD) and compared different regenerative modalities. Authors concluded that regenerative surgery of class II furcations is superior to OFD. The likelihood of obtaining furcation closure or conversion to class I is significantly higher (OR = 20.91; 90% CI = 5.81, 69.41) for regenerative techniques than for OFD. Treatment modalities involving bone replacement graft are associated with higher performance.

The long-term stability of mandibular furcation defects regenerated following GTR alone or in combination with root surface biomodification with citric acid and bone grafting was also evaluated by McClain and Schallhorn (1993). Of the 57% of the furcation defects that were assessed as completely filled at 6 and 12 months, only 29% were completely filled after 4–6 years. However, 74% of the furcations treated with GTR in combination with the placement of DFDBA were completely filled at both the short- and long-term evaluation, suggesting that the results obtained with the combined procedure were more stable over time. Long-term results of GTR treatment of mandibular class II furcations with expanded polytetrafluoroethylene (e-PTFE) membranes were also reported by Machtei *et al*. (1996). The teeth were followed up for 4 years and compared with non-furcated molars. Improvements assessed in vertical (V-CAL) and horizontal CAL (H-CAL) after treatment were also maintained after 4 years, suggesting that changes obtained in class II furcation defects by GTR are stable. Only 9% of the treated defects were unstable, which was similar to the percentage observed for non-furcated molars. Good oral hygiene, as reflected in low plaque scores and elimination of periodontal pathogens, was closely related to the long-term stability. On the basis of these results, it was concluded that furcation defects treated with membrane barriers can be maintained in health for at least 4 years, provided good oral hygiene and frequent recall visits are established. Dannewitz *et al*. (2016), in a 10-year follow-up study, concluded that long-term retention of molars is possible. With active periodontal therapy, followed by supportive periodontal therapy, even teeth with an initial bone loss of more than 60% and/or through-and-through furcations can usually be retained for more than 10 years. Patient-related factors influencing molar loss are: age, female gender, smoking, and diabetes, while among tooth-related factors, class III furcation involvement, initial bone loss, endodontic treatment, and residual PPD at T1 played a significant role.

The survival rate of furcated teeth treated with regenerative therapy has been investigated in a few studies. Yukna and Yukna (1997) reported a 100% survival rate after an average observation period of 6.6 years in 26 mandibular and maxillary furcated molars treated with synthetic bone graft and coronally advanced flap. Eickholz and Hausmann (2002) reported a 100% survival rate after 60 months in 10 mandibular and 10 maxillary furcated molars treated with barriers. A survival rate of 98.1% was reported by Dannewitz *et al*. (2006) after a 107-month observation period of 29 maxillary and 24 mandibular furcated molars treated with GTR. Eickholz *et al*. (2006) reported an 83.3% survival rate after 10 years in 18 mandibular and maxillary molars treated with barriers.

Summary: Several clinical studies addressing the long-term effects of periodontal regeneration show that, if the patient participates in a professionally delivered supportive periodontal care program and maintains good oral hygiene, the regenerated attachment can be maintained long term. Risk factors for attachment loss are those associated with disease recurrence: poor compliance with supportive periodontal care, poor oral hygiene, and cigarette smoking. In addition, most treated teeth affected by intrabony defects or furcation involvement can be maintained over long periods of time provided proper supportive periodontal and home care is undertaken.

Evidence for clinical efficacy and effectiveness

Questions of efficacy relate to the added benefit of a treatment modality under ideal experimental conditions (such as those of a highly controlled research center environment). Effectiveness, on the other hand, relates to the benefit that can be achieved in a regular clinical setting where the procedure is likely to be performed in relation to morbidity and adverse events. Besides efficiency considerations, both evidence for efficacy and effectiveness need to be available in order to provide support for the adoption of a novel approach in clinical practice.

The clinical efficacy of periodontal regenerative procedures has been extensively evaluated in randomized controlled clinical trials that have compared the regenerative procedure with a standard approach. To limit sample size and study duration, these trials have utilized surrogate outcomes – CAL changes, decrease in PPD, furcation closure or radiographic measurements – rather than changes in tooth survival. These surrogate outcomes, however, are considered to be adequate proxies of the true outcome represented by tooth survival: persistence of deep pockets or furcation involvement are associated with a higher risk of periodontal breakdown and tooth extraction.

The majority of clinical trials have been small single-center studies. The evidence from these studies has been summarized in meta-analyses performed on data retrieved by systematic reviews of the published literature. In 2002, 2003, and 2008, the European Workshop on Periodontology and the Workshop on Emerging Technologies in Periodontics provided much of the systematic assessment of the evidence for currently available technologies. These include the use of barrier membranes (GTR), bone replacement grafts (BRGs), and biologically active regenerative materials, as well as the application of combination therapy. The clinical evidence must be interpreted in the context of the biologic mechanisms and evidence for regeneration discussed in Chapter 21.

The evidence for clinical efficacy of barrier membranes has been assessed in the systematic reviews and meta-analyses performed by Needleman *et al*. (2002, 2006), Jepsen *et al*. (2002), Murphy and Gunsolley (2003), and Kinaia (2011).

For intrabony defects, 26 controlled trials with 867 intrabony defects were included (Murphy & Gunsolley 2003). The application of barrier membranes resulted in an additional CAL gain of >1 mm compared with that with an access flap approach control (Fig. 38-6). A more recent meta-analysis (Needleman *et al*. 2006) was performed on 17 RCTs (16 studies testing GTR alone and two testing GTR + bone substitutes). For CAL change, the mean difference between GTR and OFD was 1.22 mm (95% CI random effects 0.80–1.64) and for GTR + bone substitutes was 1.25 mm (95% CI 0.89–1.61). The authors highlighted that GTR showed a significant benefit when comparing the numbers of sites failing to gain 2 mm of attachment, with a risk ratio of 0.54 (95% CI random effects 0.31–0.96). The number needed to treat (NNT) for GTR to achieve one extra site gaining 2 mm or more of attachment over OPD was therefore eight (95% CI 5–33), based on an incidence of 28% of sites in the control group failing to gain 2 mm or more of attachment. For baseline incidences in the range of the control groups of 3% and 55%, the NNT would be 71 and four, respectively. The authors concluded that GTR has a greater effect on probing measures of periodontal treatment than OPD, including improved attachment gain, reduced PPD, less increase in gingival recession, and more gain in hard tissue probing

	Barrier	Reference	SD/SE date provided	Test barrier	n1	n2	Effect	n total	*P* value
	Collagen	Quteish 1992	N	Hum coll	16	16	0.703	32	0.050
	Collagen	Blumenthal 1990	Y	Bov coll	10	10	0.706	20	0.117
	Collagen	Al-Arrayed 1995	N	Hum coll	11	11	0.743	22	0.085
Random	**Collagen (3)**				**37**	**37**	**0.716**	**74**	**0.004**
	e-PTFE	Nygaard-Østby 1996	Y	e-PTFE	15	13	0.121	28	0.744
	e-PTFE	Zybutz 2000	Y	e-PTFE	14	14	0.388	28	0.300
	e-PTFE	Pontoriero 1999	N	e-PTFE	10	10	0.691	20	0.124
	e-PTFE	Kilic 1997	Y	e-PTFE	18	18	0.796	36	0.020
	e-PTFE	Kim 1996	Y	e-PTFE	19	18	1.030	37	0.003
	e-PTFE	Cortellini 1995	Y	e-PTFE	15	15	1.153	30	0.003
	e-PTFE	Tonetti 1996	Y	e-PTFE	15	15	1.153	30	0.003
	e-PTFE	Cortellini 1995	Y	e-PTFE-TR	15	15	1.816	30	0.000
	e-PTFE	Cortellini 1996	Y	e-PTFE	12	12	2.545	24	0.000
Random	**e-PTFE (9)**				**133**	**130**	**1.014**	**263**	**0.000**
	Polymeric	Ratka-Kruger 2000	Y	PLA	16	16	–0.077	32	0.824
	Polymeric	Mayfield 1998	Y	PLA	22	22	0.109	44	0.714
	Polymeric	Cortellini 2001	Y	PGA	55	55	0.458	110	0.017
	Polymeric	Brathall 1998	Y	PLA/PGA	9	9	0.476	18	0.305
	Polymeric	Tonetti 1998	Y	PLA/PGA	69	69	0.552	138	0.001
	Polymeric	Zybutz 2000	Y	PLA	15	15	0.563	30	0.124
	Polymeric	Cortellini 1998	Y	PLA	23	23	0.786	46	0.009
	Polymeric	Pontoriero 1999	Y	PLA	10	10	0.879	20	0.055
	Polymeric	Pontoriero 1999	N	PLA/PGA	10	10	1.005	20	0.031
	Polymeric	Sculean 2001	N	PLA/PGA	14	14	1.046	28	0.008
	Polymeric	Joly 2002	Y	PLA/PGA	10	10	1.915	20	0.000
	Polymeric	Cortellini 1996	Y		12	12	2.221	24	0.000
Random	**Polymeric (12)**				**265**	**265**	**0.700**	**530**	**0.000**
	Random combined (24)				435	432	0.811	867	**0.000**

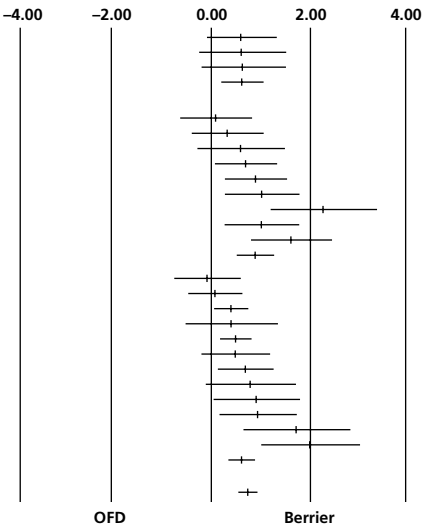


Fig. 38-6 Meta-analysis of intrabony defect studies examining open flap debridement versus guided tissue regeneration (GTR) with barrier, using clinical attachment level (CAL) gain as an outcome variable. Bov coll, bovine collagen; e-PTFE, expanded polytetrafluoroethylene; Hum coll, human collagen; OFD, open flap debridement; PLA, polylactic acid; PLA/PGA, polylactic/polyglycolic acid; TR, titanium-reinforced. (Source: Murphy & Gunsolley 2003. Reproduced with permission from John Wiley & Sons.)

at re-entry surgery. However, there was marked variability between the studies and the clinical relevance of these changes is unknown.

For class II furcation defects, 15 controlled trials with 376 involved teeth were included (Murphy & Gunsolley 2003). Membrane application resulted in additional vertical and horizontal (depth of the furcation involvement) CAL gains (Fig. 38-7). A meta-analysis of re-entry studies on the treatment of class II molar furcation involvement (Kinaia *et al*. 2011) was performed on 13 controlled clinical trials. There was a significant improvement for bioresorbable versus non-bioresorbable membranes mainly in vertical bone fill (0.77–0.33 mm; 95% CI 0.13–1.41). Non-bioresorbable membranes showed significant improvement in vertical probing reduction (0.75–0.31 mm; 95% CI 0.14–1.35), attachment gain (1.41–0.46 mm; 95% CI 0.50–2.31), horizontal bone fill (1.16–0.29 mm; 95% CI 0.59–1.73), and vertical bone fill (0.58–0.11 mm; 95% CI 0.35–0.80) over OFD. Bioresorbable membranes showed significant reduction in vertical probing depth (0.73–0.16 mm; 95% CI 0.42–1.05), attachment gain (0.88–0.16 mm; 95% CI 0.55–1.20), horizontal bone fill (0.98–0.12 mm; 95% CI 0.74–1.21), and vertical bone fill (0.78–0.19 mm; 95% CI 0.42–1.15) over OFD. These data alone, however, did not present conclusive evidence of efficacy as the possibility of bias arising from a possible tendency to report studies with positive results could not be ruled out. Multicenter studies were designed to assess efficacy conclusively. These were performed in a private practice environment in order to assess also the generalizability of the benefit to this specific setting (effectiveness). The results of large prospective multicenter studies in private practice settings (Tonetti *et al*. 1998, 2004b; Cortellini *et al*. 2001) conclusively support the additional benefit of membranes in improving CAL in intrabony defects, and thus their efficacy and effectiveness. More limited evidence is also available for combination therapy (BRG + barrier membranes) in furcation defects (Bowers *et al*. 2003).

The efficacy of BRG materials has been assessed in two systematic reviews (Trombelli *et al*. 2002; Reynolds *et al*. 2003). As these two systematic reviews used significantly different criteria for study inclusion, their results do not fully overlap. Trombelli *et al*. (2002), who included only controlled studies that reported changes in CAL as the primary outcome, concluded that there was insufficient evidence to support the clinical use of BRG materials in intrabony defects, since: (1) there was significant heterogeneity among the included studies; (2) the size of the adjunctive effect was small; and (3) there were differences that did not allow pooling of results obtained with different materials. In the other meta-analysis for intrabony defects, 27 controlled trials with 797 intrabony defects were included (Reynolds *et al*. 2003). The application of BRG resulted in an additional CAL gain of 0.5 mm compared with an access flap approach control (Fig. 38-8). Greater additional benefits from the application of BRG were observed whenever hard tissue measurements (bone fill or defect resolution) were utilized as outcome measures.

For furcation defects, the lack of consistent comparisons did not allow a meaningful assessment of the potential benefits of the use of BRGs alone (Reynolds *et al*. 2003). No large multicenter trials have provided definitive support for efficacy and/or effectiveness of the use of BRGs.

The evidence for clinical efficacy of biologically active regenerative materials has been summarized in meta-analyses for enamel matrix derivatives (EMDs) (Trombelli *et al*. 2002; Giannobile & Somerman 2003; Esposito *et al*. 2009; Koop *et al*. 2012), for growth factors (Darby & Morris 2013), and for platelet concentrate (Del Fabbro *et al*. 2011) in the treatment of intrabony defects only.

The outcomes of eight studies including 444 defects have indicated that EMD application provides additional benefits of a magnitude of 0.75 mm in terms of CAL gain (Giannobile & Somerman 2003). These data are in accordance with those of a large practice-based multicenter trial that demonstrated both efficacy and effectiveness of EMDs in intrabony defects (Tonetti *et al*. 2002). The meta-analysis by Esposito *et al*. (2009) included 13 trials. A meta-analysis including nine

	Barrier	Reference	Location	SD/SE data provided	n1	n2	Effect	n total	*P* value
	Collagen	Wang 1994	Mand	Y	12	12	0.516	24	0.204
Random	**Collagen (1)**				**12**	**12**	**0.516**	**24**	**0.228**
	e-PTFE	Pontoriero 1995	Max	N	8	8	0.000	16	1.000
	e-PTFE	Lekovic 1989	Mand	Y	12	12	0.026	24	0.949
	e-PTFE	Pontoriero 1995	Max	N	10	10	0.190	20	0.663
	e-PTFE	Pontoriero 1995	Max	N	10	10	0.759	20	0.093
	e-PTFE	Metzler 1991	Max	Y	17	17	1.172	34	0.001
	e-PTFE	Pontoriero 1988	Mand	Y	21	21	1.450	42	0.000
	e-PTFE	Avera 1998	Max	Y	8	8	9.115	16	0.000
Random	**e-PTFE (7)**				**86**	**86**	**0.930**	**172**	**0.025**
	Por coll	Flanary 1991	Mixed	Y	19	19	0.857	38	0.011
	Peristeum	Lekovic 1991	Mand	Y	15	15	2.943	30	0.000
Random	**Other (2)**				**34**	**34**	**1.856**	**68**	**0.080**
Random	**Combined (10)**				**132**	**132**	**1.063**	**264**	**0.001**

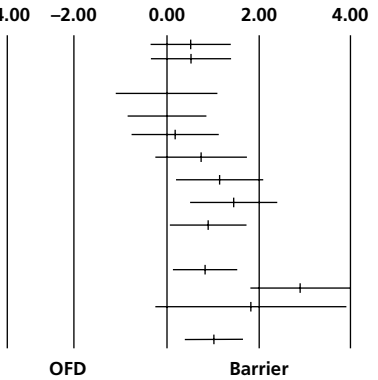


Fig. 38-7 Forest plot of furcation defect studies examining open flap debridement (OFD) versus guided tissue regeneration with barrier, using horizontal open probing attachment gain as an outcome variable. e-PTFE, expanded polytetrafluoroethylene; Mand, mandibula; Max, maxilla. (Source: Murphy & Gunsolley 2003. Reproduced with permission from John Wiley & Sons.)

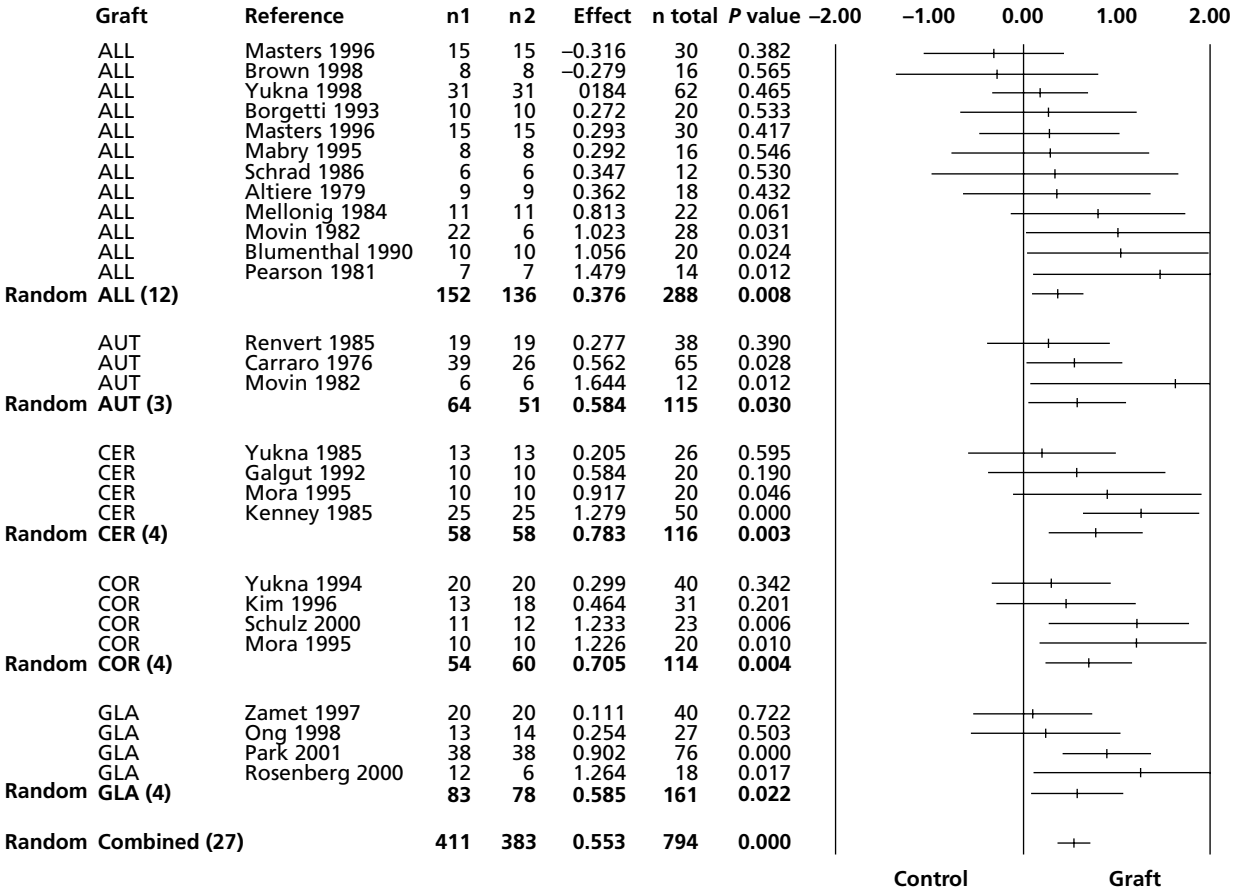


Fig. 38-8 Final meta-analysis of clinical attachment level in randomized controlled clinical studies comparing bone replacement graft to open flap debridement in the treatment of intrabony defects. ALL, allograft; AUT, autograft; CER, calcium phosphate (hydroxyapatite) ceramic; COR, coralline calcium carbonate; GLA, bioactive glass. (Source: Reynolds *et al*. 2003. Reproduced with permission from John Wiley & Sons.)

trials showed that EMD-treated sites displayed statistically significant CAL improvements (mean difference 1.1 mm; 95% CI 0.61–1.55) and PPD reduction (0.9 mm; 95% CI 0.44–1.31) when compared with placebo- or control-treated sites, although a high degree of heterogeneity was found. Approximately nine patients needed to be treated (NNT) for one to gain 2 mm or more probing attachment level (PAL) over the control group, based on a prevalence in the control group of 25%. No differences in tooth loss or esthetic appearance as judged by the patients were observed. When evaluating only trials at a low risk of bias in a sensitivity analysis (four trials), the effect size for PAL was 0.62 mm (95% CI 0.28–0.96), which was <1.1 mm for the overall result.

A more recent meta-analysis (Koop *et al*. 2012) on 20 RCTs showed a significant additional gain in CAL of 1.30 mm of EMD-treated sites compared with OFD, ethylenediaminetetra-acetic acid (EDTA), or placebo (Fig. 38-9).

The systematic review by Darby and Morris (2013) reported a meta-analysis on two studies on the use of recombinant human platelet-derived growth factor-BB (rhPDGF-BB). Sites treated with rhPDGF-BB had greater CAL gain of around 1 mm, a greater percentage bone fill of around 40%, and an increased rate of bone growth of around 2 mm compared with sites treated with an osseoconductive control, beta-tricalcium phosphate (β-TCP).

Del Fabbro *et al*. (2011) in a meta-analysis on 10 studies reported a significantly greater CAL gain in cases treated with platelet-rich plasma (PRP) compared with control sites (mean adjusted percentage difference 5.50%; 95% CI 1.32–9.67%; $P = 0.01$). The mean weighted CAL gain difference was 0.50 mm (95% CI 0.12–0.88 mm).

Combination therapy has been explored in two recent meta-analyses. Trombelli and Farina (2008) evaluated the clinical effects of bioactive agents when used in addition to OFD either alone or in association with grafts and/or barrier membranes. The authors concluded that there was evidence to support the use of EMDs either alone or in combination with grafts to effectively treat intraosseous defects and the additional use of a graft seems to enhance the clinical outcome of EMDs; the combined use of rhPDGF-BB and P-15 with a graft biomaterial has shown beneficial effects in intraosseous defects; contrasting results were reported for PRP and graft combinations. Tu *et al*. (2010) explored the additional treatment effect of barriers or bone grafts to EMDs in 28 studies. EMD plus bone grafts and EMD plus membranes attained

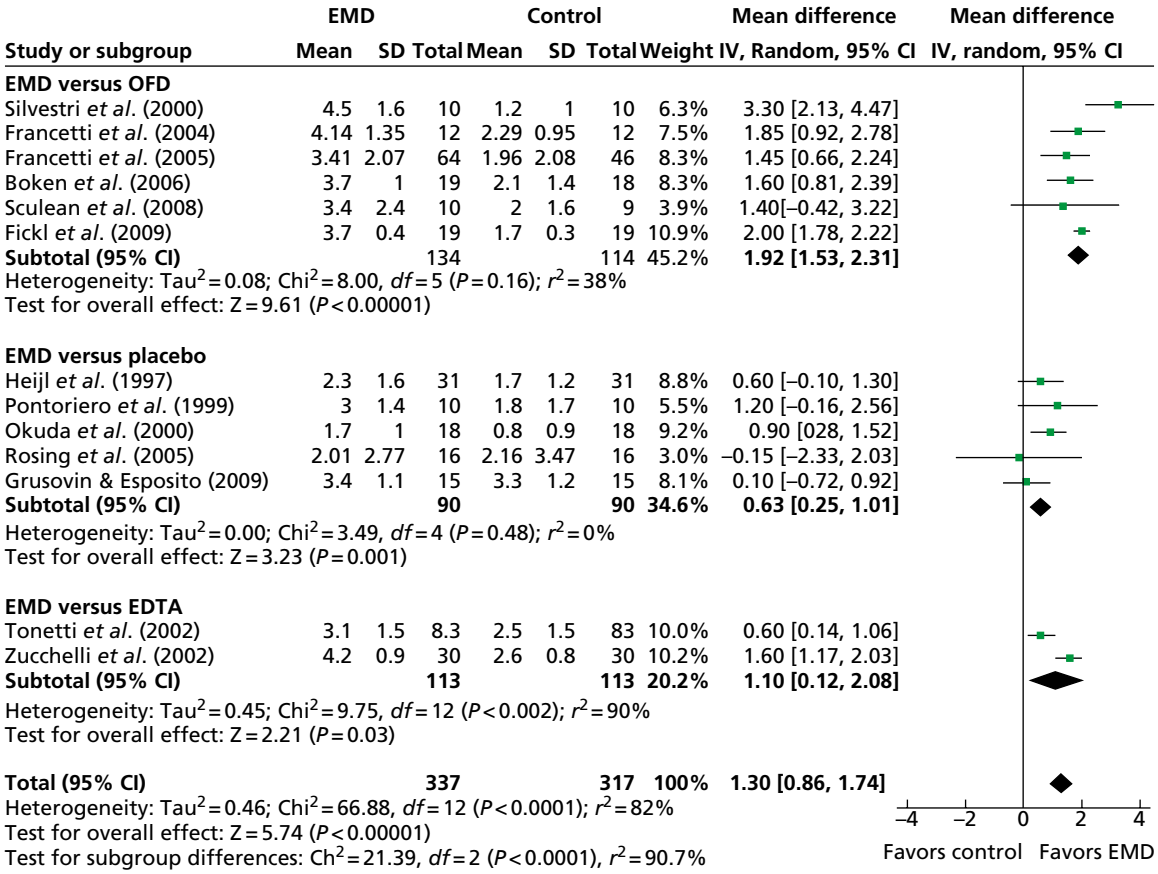


Fig. 38-9 Meta-analysis of intrabony defect studies. Comparison of enamel matrix derivatives (EMDs) versus control: change in clinical attachment level after 1 year. CI, confidence interval; EDTA, ethylene–diamine–tetra-acetic acid; IV, inverse variance; Total, number of patients. (Source: Koop *et al*. 2012. Reproduced with permission from John Wiley & Sons.)

0.24 mm and 0.07 mm more PPD reduction than EMD alone, respectively. EMD plus bone grafts and EMD plus membranes attained 0.46 mm and 0.15 mm more CAL gain, respectively. When different types of bone grafts and barrier membranes were treated separately, EMD with bovine bone grafts showed greater treatment effects. The authors concluded that there was little evidence to support the additional benefits of EMDs in conjunction with other regenerative materials.

Comparative studies between different regenerative approaches have been analyzed in a systematic review by Esposito *et al*. (2009) including six studies. The authors did not find any difference between EMDs and barriers in terms of CAL gain and PPD reduction. These data are supported by two large practice-based multicenter trials (Silvestri *et al*. 2003; Sanz *et al*. 2004). The Sanz *et al*. (2004) study, however, reported a significantly higher prevalence of complications in the barrier-treated group compared with the EMD-treated one. More recently, Tu *et al*. (2012) compared GTR, EMDs, and their use in conjunction with other regenerative materials with a Bayesian network meta-analysis of 53 RCTs. The authors found small differences between regenerative therapies which were non-significant statistically and clinically. GTR and GTR-related combination therapies achieved greater PPD reduction than EMDs and EMD-related combination therapies. Combination therapies achieved slightly greater CAL gain than the use of EMDs or GTR alone. The authors concluded that combination therapies performed better than single therapies, but the additional benefits were small. The same conclusions were reached by Koop *et al*. (2012).

Recent systematic reviews have confirmed the potential for clinical improvements of different regenerative materials. Kao *et al*. (2015) concluded that biologics (EMD and rhPDGF-BB plus b-tricalcium phosphate), demineralized freeze-dried bone allograft and GTR with membranes are superior to OFD procedures in improving clinical parameters in the treatment of intrabony defects. Nibali *et al*. (2020) concluded that all regenerative procedures provided adjunctive benefit in term of CAL gain (1.34 mm; 0.95–1.73) compared with OFD alone. Both EMD and GTR were superior to OFD alone in improving CAL (1.27 mm; 0.79–1.74 mm and 1.43 mm; 0.76–2.22 respectively), although with moderate–high heterogeneity. Among biomaterials, the addition of deproteinized bovine bone mineral (DBBM) improved the clinical outcomes of both GTR with resorbable barriers and EMD. Papillary preservation flaps enhanced the clinical outcomes.

Patient, defect, and tooth prognostic factors

The results reported in the meta-analyses discussed in the previous section indicate that clinical improvements beyond those from flap surgery can be obtained by treating periodontal defects with regenerative therapies, but they also suggest a great variability in clinical outcomes among the different studies. In addition, it is apparent from the results that the complete resolution of the intrabony component of the defect and of the horizontal component of a furcation is observed in only a minority of sites. Regeneration, in fact, is an advanced healing event that occurs when the systemic and local conditions are favorable and when therapy is properly applied. A significant "center effect" was consistently observed in five randomized multicenter studies (Tonetti *et al*. 1998, 2003, 2004a; Cortellini *et al*. 2001; Sanz *et al*. 2004). The center variability, defined as the difference in CAL between the best and the worst center, had a highly significant impact on the outcomes, greater than the impact of the tested regenerative materials (Table 38-2).

The observed variability among centers may depend on differences in the enrolled patients in terms of socioeconomic background, form of periodontal disease, response to therapy, and persistence of specific pathogens; or differences in clinical experience, surgical skills, and clinical organization of the clinicians. In addition, a series of prognostic factors associated with the clinical outcomes has been identified using multivariate approaches (Tonetti *et al*. 1993a, 1995, 1996a; Cortellini *et al*. 1994; Machtei *et al*. 1994; Falk *et al*. 1997; Cortellini & Tonetti 2000b). The main sources of clinical variability are patient-, defect-, and surgery-associated factors (Cortellini & Bowers 1995; Cortellini & Tonetti 2000a). Attention has focused on some important patient, defect, and tooth factors.

Patient factors

Periodontal infection

Periodontal regeneration does not treat periodontitis, but rather is an approach for regenerating defects that have developed as a result of periodontitis. Therefore, appropriate periodontal treatment should always be completed before periodontal regeneration is initiated. In this context, that is in patients who have undergone a cycle of cause-related periodontal therapy to the satisfaction of the treating clinician, evidence suggests that the level of control of periodontitis achieved before a periodontal regenerative procedure is initiated is associated with outcomes: the persistence of poor plaque control, high levels of bleeding upon probing, as well as the persistence of high loads of total bacteria or of specific microbial pathogens (or complexes of pathogens) have all been associated in a dose-dependent manner with poor clinical outcomes (Tonetti *et al*. 1993a, 1995; Cortellini *et al*. 1994, 1995a, b; Machtei *et al*. 1994, 2003; Silvestri *et al*. 2003; Heitz-Mayfield *et al*. 2006).

The level of self-performed plaque control has a great and dose-dependent effect on the outcome of periodontal regeneration. Better CAL gains were observed in patients with optimal levels of plaque control as compared with those in patients with less ideal oral hygiene (Cortellini *et al*. 1994, 1995a, b; Tonetti *et al*. 1995, 1996a). Patients with plaque on <10% of the tooth surfaces (full-mouth plaque score [FMPS]) had a gain of CAL which was 1.89 mm greater than that observed in patients with a FMPS of >20% (Tonetti *et al*. 1995).

Although not formally tested for efficacy in randomized trials, achieving high levels of plaque control and suppression of the pathogenic microflora through behavioral intervention and intensive antiinfective periodontal therapy are generally advocated before proceeding with periodontal regeneration. Furthermore, some proof of principle investigations

Table 38-2 Outcomes of regression analyses performed to explain variability in terms of clinical attachment gain at 1 year.

	Tonetti *et al*. (1998)	**Cortellini *et al*. (2001)**	**Tonetti *et al*. (2002)**	**Sanz *et al*. (2004)**	**Tonetti *et al*. (2004b)**
No. of patients	143	113	166	67	120
Treatment	Bioresorbable barriers vs flap	Bioresorbable barriers vs flap	EMD vs flap	EMD vs bioresorbable barriers	Bioresorbable barriers + filler vs flap
Treatment effect[a]	0.6 mm	1.0 mm	0.5 mm	0.8	0.8
Center effect[b]	2.4 mm	2.1 mm	2.6 mm	2.6	2.8

[a] Treatment effect = added clinical benefit on top of control treatment.
[b] Center effect = clinical outcomes of the best center versus the worst center. EMD, enamel matrix derivative.

have assessed the adjunctive effect of using an antibiotic locally delivered within the wound area or in the regenerative material (Yukna & Sepe 1982; Sanders *et al*. 1983; Machtei *et al*. 2003; Stavropoulos *et al*. 2003). Results showed consistently better outcomes in the groups that received the systemic/local antibiotic. At present, however, no regenerative device with enhanced antimicrobial activity is commercially available. Local contamination of the defect-associated pocket should be as low as possible (Heitz-Mayfield *et al*. 2006). Presence of BoP (i.e. bacteria) should be controlled with additional gentle root planing and eventually with the additional use of local antimicrobials (Tunkel *et al*. 2002; Hanes & Purvis 2003).

Smoking

A retrospective study found that cigarette smokers displayed significantly impaired regenerative outcomes compared with non-smokers (Tonetti *et al*. 1995). Data showed that cigarette smoking was associated with reduced CAL gains. The CAL gain in subjects smoking more than 10 cigarettes/day was 2.1 ± 1.2 mm versus 5.2 ± 1.9 mm in non-smokers (Tonetti *et al*. 1995). Thereafter, a series of investigations has confirmed that cigarette smoking displays a dose-dependent detrimental effect on CAL gains in intrabony defects (Cortellini *et al*. 1995b, 2001; Falk *et al*. 1997; Trombelli *et al*. 1997, 1998; Ehmke *et al*. 2003; Stavropoulos *et al*. 2004) and furcations (Luepke *et al*. 1997; Bowers *et al*. 2003; Machtei *et al*. 2003). A meta-analysis (Patel *et al*. 2012) concluded that smoking has a negative effect on bone regeneration after periodontal treatment. Patients should be advised that their smoking habit may result in poorer bone regeneration after periodontal treatment. Although no formal evidence is available, it is generally suggested that smoking cessation counseling should be initiated in the context of cause-related periodontal therapy, and that patients who are unable to quit the habit should be informed of the possibility of reduced outcomes and of the need to abstain from smoking during the perioperative and early healing period.

Other patient factors

It has been suggested that other patient factors, such as age, genetics, systemic conditions or stress levels, may be associated with suboptimal regenerative outcomes. In the light of lack of evidence, however, no action is required with the exception of considering the patient characteristics that represent a contraindication to surgery (e.g. uncontrolled diabetes or unstable, severe diseases).

Clinical relevance of patient factors

The data discussed above indicate that patient factors play an important role in regenerative periodontal therapy (Fig. 38-10). Some of these factors can be modified by appropriate interventions in some patients. These interventions should be performed before periodontal regenerative therapy. Whenever modification is not possible, reduced outcomes in terms of extent and predictability should be considered.

Defect factors

Type of defect

With the currently available periodontal regenerative technologies, there is no evidence that suprabony (horizontal) defects, supracrestal components of intrabony defects, or class III furcation involvements can be predictably treated with regenerative approaches. This limitation is also true for interdental craters, thus limiting the type of defects that can be treated to intrabony defects and class II furcation defects.

Morphology of the defect

Defect morphology plays a major role in healing following periodontal regenerative treatment of intrabony defects (Papapanou & Tonetti 2000). This was demonstrated in studies showing that the depth and width of the intrabony component of the defect influenced the amount of CAL and bone gained at 1 year.

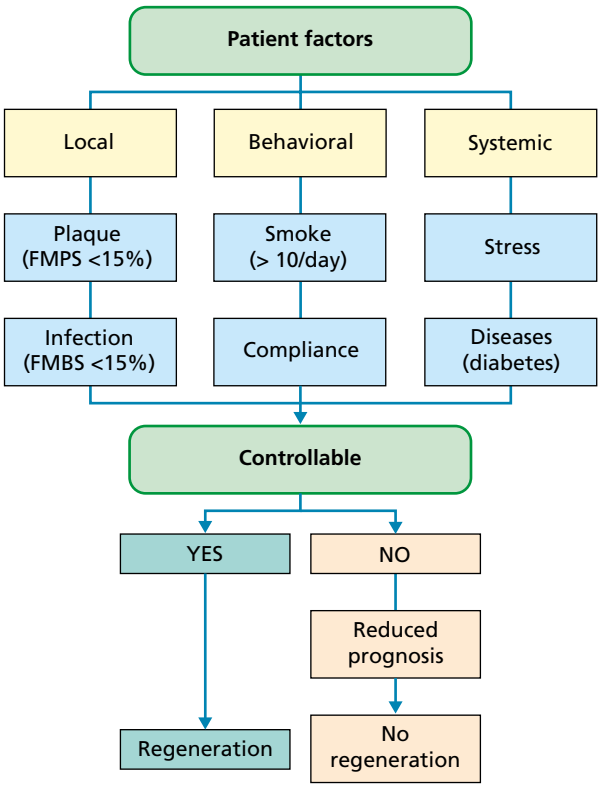


Fig. 38-10 Patient selection criteria. It can be seen that control of local, behavioral, and systemic patient characteristics may improve the treatment outcomes. FMPS, full mouth plaque score; FMBS, full mouth bleeding score. (Source: Adapted from Cortellini & Bowers 1995. Reproduced with permission from John Wiley & Sons.

The deeper the defect, the greater was the amount of clinical improvements (Tonetti *et al*. 1993a, 1996a; Garrett *et al*, 1988; Ehmke *et al*. 2003; Silvestri *et al*. 2003).

In a controlled study, however, it was demonstrated that deep and shallow defects have the "same potential" for regeneration (Cortellini *et al*. 1998). Deep defects (>3 mm) resulted in larger linear CAL gain than shallow defects (3.7 ± 1.7 mm versus 2.2 ± 1.3 mm), but the percentage of CAL gain as related to the baseline defect depth was similar in deep (76.7 ± 27.7%) and in shallow (75.8 ± 45%) defects.

Another important morphologic characteristic of the defect is the *width* of the intrabony component, measured as the angle that the bony wall of the defect forms with the long axis of the tooth (Steffensen & Weber 1989). Wider defects have been associated with reduced CAL and bone gain at 1 year (Tonetti *et al*. 1993a, 1996a; Garrett *et al*. 1988). In a study on 242 intrabony defects treated with membranes, Cortellini and Tonetti (1999) demonstrated that defects with a radiographic angle of ≤25° gained consistently more attachment (1.6 mm on average) than defects with an angle of ≥37°. Two follow-up studies addressed the significance of the baseline radiographic angle of the intrabony defect following the use of either EMDs (Tsitoura *et al*. 2004) or a combination of BRG with a barrier membrane (Linares *et al*. 2006). The impact of the width of the baseline radiographic angle was confirmed for the non-space-making biologic mediator, but not for the more stable combination therapy. These data are consistent with the notion that the choice of the regenerative technology may partially overcome negative morphologic characteristics of intrabony defects. An earlier secondary analysis of a controlled clinical trial using titanium-reinforced membranes (Tonetti *et al*. 1996a) indicated that the relevance of defect morphology parameters may be diminished with the use of supported membranes.

It was also shown that the number of residual bony walls was related to the outcomes of various regenerative approaches (Goldman & Cohen 1958; Schallhorn *et al*. 1970). This issue as related to GTR therapy was addressed in three investigations (Selvig *et al*. 1993; Tonetti *et al*. 1993a, 1996a). In one study, the reported 1-year mean CAL gain was 0.8 ± 0.3 mm. This gain corresponded to the depth of the three-wall intrabony component of the defect (Selvig *et al*. 1993). In contrast, in the other two investigations, CAL gain was not related to the defect configuration in terms of one-wall, two-wall, and three-wall subcomponents (Tonetti *et al*. 1993a, 1996a). A total of 70 defects were examined in these two latter studies, utilizing a multivariate approach. The treatment resulted in mean attachment gains of 4.1 ± 2.5 mm and 5.3 ± 2.2 mm, and it was observed that the most coronal portion of the defects, which is the most susceptible to negative influences from the oral environment, was often incompletely filled with bone, irrespective of whether these were one-wall, two-wall, or three-wall defects.

Thus, these studies questioned the impact of the number of residual bony walls of the defect on the clinical outcomes of periodontal regeneration with membranes and suggested that location of the one-wall subcomponent (the one most likely to be the most superficial) may have acted as a confounder in other studies and be an important predictor of the outcomes. The number of walls was not significant when titanium barriers (Tonetti *et al*. 1996a) or combination therapy (Tonetti *et al*. 2004a, b) were used, but were significant when bioresorbable barriers (Falk *et al*. 1997; Silvestri *et al*. 2003) and EMDs were used (Tonetti *et al*. 2002; Silvestri *et al*. 2003). In particular, a secondary analysis of a multicenter trial showed that, in intrabony defects, the added benefit of EMDs was greater in three-wall defects compared with one-wall defects (Tonetti *et al*. 2002, 2004a).

These data also questioned the suitability of the gel formulation of EMDs for the treatment of defects with a non-supporting anatomy (wide defects with missing bony walls). More recently, however, two studies demonstrated a reduced impact of the number of residual bony walls and of defect width on the outcomes obtained with EMDs when a minimally invasive surgical technique (MIST) was used (Cortellini *et al*. 2008; Cortellini & Tonetti 2009a). This finding clearly differs from the evidence discussed previously of a strong impact of the defect anatomy in terms of residual bony walls and defect width on the clinical outcomes observed in previous studies in which EMDs were used under conventional large and intrinsically less stable papilla preservation flaps (Tonetti *et al*. 2002, 2004a).

Tooth factors

The endodontic status of the tooth has been suggested as a potential relevant factor in periodontal therapy. Emerging evidence (see Chapter 41) indicates that root canal-treated teeth may respond differently to periodontal therapy. A clinical study of 208 consecutive patients with one intrabony defect each demonstrated that properly performed root canal treatment does not negatively affect the healing response and the long-term stability of deep intrabony defects treated with membranes (Cortellini & Tonetti 2000b).

Tooth mobility has long been considered an important factor for periodontal regeneration (Sanders *et al*. 1983). A multivariate analysis of a multicenter controlled clinical trial demonstrated that tooth hypermobility was negatively and dose-dependently associated with the clinical outcomes of regeneration (Cortellini *et al*. 2001). Although significant, the size of the effect was small, within the range of physiologic mobility. Another secondary analysis of three previously reported trials assessed the regenerative outcomes for hypermobile teeth (Trejo & Weltman 2004). This report indicated that teeth with baseline

mobility amounting to <1 mm horizontally could be successfully treated with periodontal regeneration. Although no intervention trial has been performed to date, these results are generally considered supportive of an approach that does not base the prognosis of the tooth or the regenerative procedure on tooth mobility, but rather considers splinting hypermobile teeth before periodontal regenerative surgery.

Conclusion: Based on these results, it can be concluded that deep and narrow intrabony defects at either vital or endodontically treated teeth are the ones in which the most significant and predictable outcomes can be achieved with GTR treatment. Number of walls and width of the defect are influential when non-supportive biomaterials are used. The influence of defect anatomy appears to be reduced to some extent when a more stable flap design is applied. Severe, uncontrolled dental hypermobility (Miller class II or higher) may impair the regenerative outcomes. Significant clinical improvements can be expected only in patients with optimal plaque control, with reduced levels of periodontal contamination, and who are non-smokers.

Factors affecting the clinical outcomes in furcations

Significant evidence has demonstrated that treatment of maxillary class II furcations and maxillary and mandibular class III furcation involvements with regeneration is unpredictable, while clinical improvements can be expected for mandibular class II furcations. The great variability in clinical outcomes following treatment of mandibular class II furcations with regeneration is probably related to the factors discussed relative to intrabony defects.

Regarding tooth/defect factors, it was shown that first and second mandibular molars and buccal and lingual furcations respond equally well to GTR treatment (Pontoriero *et al*. 1988; Machtei *et al*. 1994). It was also demonstrated that the preoperative horizontal pocket depth directly correlates with the magnitude of attachment gain and bone formation in the furcation area (Machtei *et al*. 1993, 1994; Horwitz *et al*. 2004). The deeper the baseline horizontal pocket, the greater the H-CAL and bone gain. The anatomy of the furcations in terms of height, width, depth, and volume, however, did not correlate with the clinical outcome (Machtei *et al*. 1994). Horwitz *et al*. (2004) demonstrated that a long root trunk, a wide furcation entrance, and a furcation fornix coronal to the alveolar crest have negative influences on the success of therapy. Anderegg *et al*. (1995) demonstrated that sites with a gingival thickness of >1 mm exhibited less gingival recession postsurgery than sites with a gingival thickness of <1 mm. Bowers *et al*. (2003) reported that increases in presurgical PAL-H were associated with monotonic decreases in the percentage of sites demonstrating complete clinical closure, with only 53% of lesions of ≥5 mm responding with complete closure. Similarly, significant reductions in the frequency of clinical closure were associated with increases in the distance between the roof of the furcation and the crest of the bone, roof of the furcation and base of the defect, and depth of the horizontal defect and the divergence of the roots. The authors concluded that the highest frequency of clinical furcation closure was observed in early class II defects. Tsao *et al*. (2006a) treated class II furcations in lower molars with either OFD alone or with additional use of bone graft or bone graft plus a collagen barrier. Among the anatomic factors, only the baseline vertical depth was found to affect the clinical outcomes in terms of vertical CAL gain. The most influential factor was the type of surgical treatment: the regenerative procedures performed better than the flap alone.

Relevance of the surgical approach

At the beginning of the 1980s, the need to modify standard periodontal surgical procedures to favor periodontal regeneration became apparent. In particular, the need to preserve soft tissues in order to attempt primary closure of the interdental space to contain grafts or coronally advanced flaps to cover furcation entrances led to the development of specific flap designs for periodontal regeneration (Takei *et al*. 1985; Gantes & Garret 1991).

In fact, graft exfoliation and membrane exposure with consequent bacterial contamination during healing represented the major complications of periodontal regenerative procedures at the time. Membrane exposure was reported to be a major complication with a prevalence of 50–100% (Becker *et al*. 1988; Cortellini *et al*. 1990, 1993a; Selvig *et al*. 1992, 1993; Murphy 1995a; De Sanctis *et al*. 1996a, b; Falk *et al*. 1997; Trombelli *et al*. 1997; Mayfield *et al*. 1998). Cortellini *et al*. (1995c, d) reported that the prevalence of membrane exposure could be greatly reduced with the use of access flaps specifically designed to preserve the interdental tissues (modified papilla preservation technique) (Fig. 38-11).

Many studies have shown that the exposed membranes are contaminated with bacteria (Selvig *et al*. 1990, 1992; Grevstad & Leknes 1992; Machtei *et al*. 1993; Mombelli *et al*. 1993; Tempro & Nalbandian 1993; Nowzari & Slots 1994; Novaes *et al*. 1995; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). Contamination of exposed non-bioresorbable as well as bioresorbable membranes was associated with lower PAL gains in intrabony defects (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). The impaired clinical results in some studies were associated with high counts of bacteria and with the presence of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* (Machtei *et al*. 1994; Nowzari & Slots 1994; Nowzari *et al*. 1995).

Bacterial contamination of the regenerative biomaterials may occur during surgery, but also during the postoperative healing phase. Bacteria from the

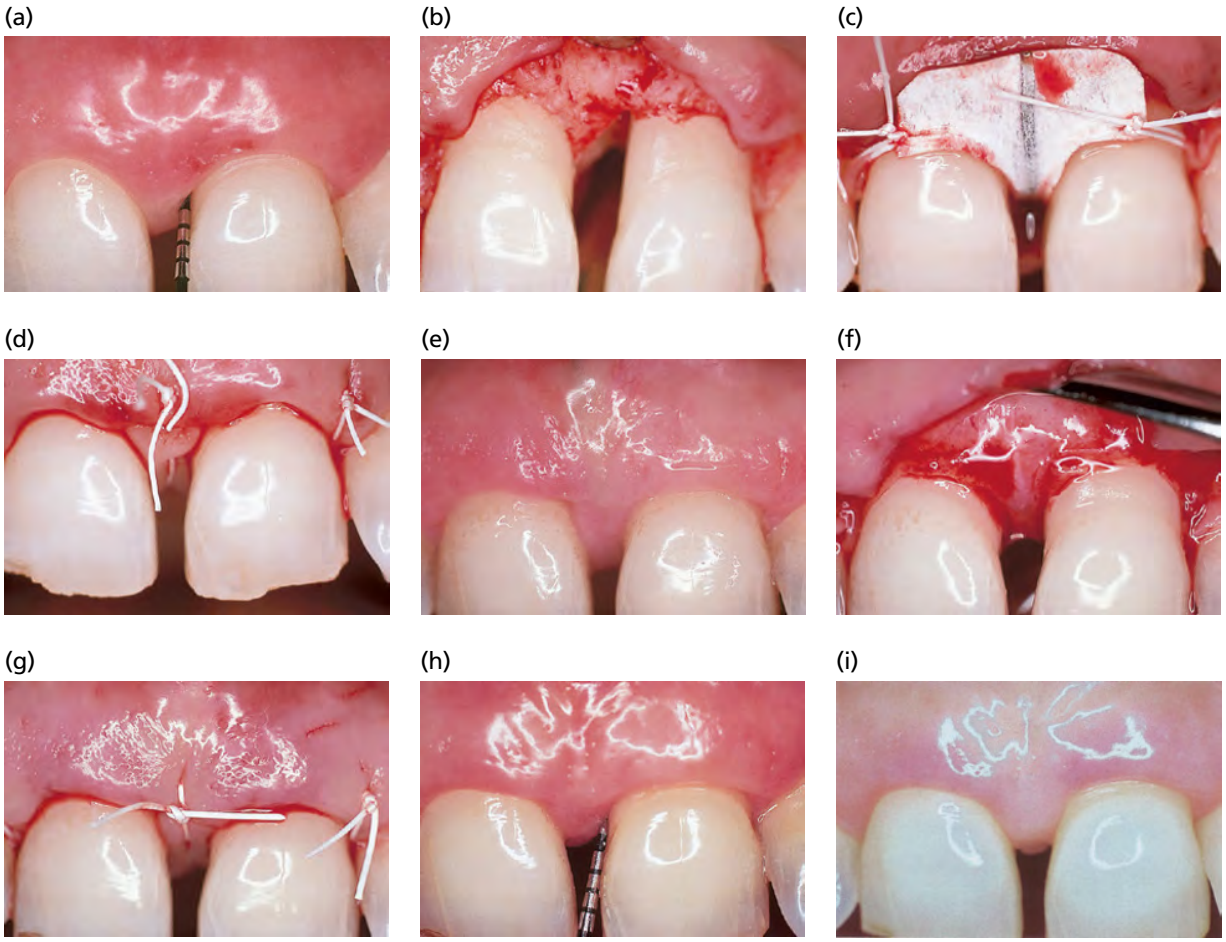


Fig. 38-11 (a) Left maxillary central incisor with a 10-mm pocket depth and 11 mm of clinical attachment loss on the mesial surface. A diastema is present between the two central incisors. (b) Full thickness buccal and palatal flaps have been raised and an intrabony defect can be seen. The interdental papilla has been incised on the buccal aspect and elevated with the palatal flap (modified papilla preservation technique). (c) Titanium-reinforced e-PTFE barrier membrane has been placed and fixed close to the level of the cementoenamel junction. (d) Membrane is completely covered. This primary closure has been obtained by preserving the interdental papilla and by coronal displacement of the buccal tissue flap. (e) At 6 weeks, the membrane is completely covered with healthy tissue. (f) After membrane removal at 6 weeks, dense newly formed tissue is evident in the defect and in the supracrestal space maintained by the titanium-reinforced membrane. (g) Newly formed tissue is completely covered by the raised and well-preserved tissue flaps. (h) Clinical photograph after 1 year showed a 4-mm residual pocket depth. A gain of clinical attachment of 6 mm was recorded, and no recession had occurred compared with baseline. (i) Ten-year clinical photograph showing the optimal preservation of the interdental tissues.

oral cavity may colonize the implanted biomaterials. Frequently, this results in recession of the gingival tissues, which allows colonization of the material further apically. The significance of bacterial contamination was addressed in an investigation in monkeys (Sander & Karring 1995). The findings of this study showed that new attachment and bone formation occurred consistently when bacteria were prevented from invading the membrane and the wound during healing.

In order to prevent wound infection, some investigators have administered systemic antibiotics to patients before and during the first weeks after membrane application (Demolon *et al*. 1993; Nowzari & Slots 1994). However, despite the application of systemic antibiotics, postoperative wound infection related to implanted barrier membranes was noted. This indicates that either the drug administered is not directed against the microorganisms responsible for the wound infection, or that the drug does not reach the infected site at a concentration sufficiently high enough to inhibit the target microorganisms. An improved effect on periodontal healing after GTR in association with local application of metronidazole was reported by Sander *et al*. (1994). Twelve patients each with two similar intrabony defects participated in this intraindividual study. Metronidazole in a gel form was placed in the test defects and on the membrane prior to wound closure, while the control defects were treated with a membrane alone. Six months following membrane removal the medium gain in PAL, presented as a percentage of the initial defect depth, was 92% for the test defects versus 50% for the control defects. Other clinical parameters, like plaque index, BoP, PPD reduction, and recession of the gingival margin, were similar in the test and control sites. Although local or systemic antibiotics may reduce the bacterial load on exposed membranes,

they seem ineffective in preventing the formation of a microbial biofilm (Frandsen *et al*. 1994; Nowzari *et al*. 1995). In addition to the erythema and swelling related to such infection of the wound, more severe postoperative complications such as suppuration, sloughing or perforation of the flap, membrane exfoliation, and postoperative pain have been reported (Murphy 1995a, b).

Another important issue associated with the clinical results is the coverage of the regenerated tissue after removal of a non-bioresorbable membrane. Many authors have reported that the frequent occurrence of a gingival dehiscence over the membrane is likely to result in insufficient protection of the interdental regenerated tissue (Becker *et al*. 1988; Selvig *et al*. 1992; Cortellini *et al*. 1993a; Tonetti *et al*. 1993a). Exposure of the regenerated tissue to the oral environment introduces the risk of mechanical and infectious insults that in turn may prevent complete maturation of the regenerated tissue into a new connective tissue attachment. In fact, incomplete coverage of the regenerated tissue was associated with reduced attachment and bone gain at 1 year (Tonetti *et al*. 1993a). The positioning of a saddle-shaped free gingival graft over the regenerated interdental tissue (Fig. 38-12) was suggested to offer better coverage and protection than a dehiscent gingival flap (Cortellini *et al*. 1995a). In this randomized controlled study (Cortellini *et al*. 1995a) more gain of attachment was observed in the 14 sites where a free gingival graft was positioned after membrane removal (5.0 ± 2.1 mm), than in the 14 sites where conventional protection of the regenerated tissue was accomplished (3.7 ± 2.1 mm).

The systematic assessment of the relevant factors associated with variability of periodontal regenerative outcomes performed at the beginning of the 1990s (Tonetti *et al*. 1993a, 1995, 1996a; Machtei *et al*. 1994; Falk *et al*. 1997) provided further evidence that surgical factors had a great impact on regeneration and led the way to the development of procedures specifically designed for periodontal regeneration. In general, the development of new procedures was aimed at complete tissue preservation in order to achieve and maintain primary closure on top of the applied regenerative material during the critical stages of healing and to save space for blood clot formation and maturation. Specifically, flap designs attempted to achieve passive primary closure of the flap combined with optimal wound stability. In fact, basic and clinical research indicate that, among many, absolute requirements for regeneration include the presence of space for the formation of the blood clot at the interface between the flap and root surface (Haney *et al*. 1993; Sigurdsson *et al*. 1994, Cortellini *et al*. 1995b, c; Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al*. 2004), the stability of the blood clot to maintain a continuity with the root surface and thereby prevent the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993), and protection of the soft tissue of the treated area to avoid bacterial contamination (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b; Sanz *et al*. 2004).

Development of periodontal regenerative medicine in the last 25 years has followed two distinct, though totally interlaced, paths. The interest of researchers has so far focused on regenerative materials and products on the one hand and on novel surgical approaches on the other hand.

Surgical approach to intrabony defects

Papilla preservation flaps

The modified papilla preservation technique (MPPT) was developed in order to increase the space for regeneration and to achieve and maintain primary closure of the flap in the interdental area (Cortellini *et al*. 1995c, d). This approach combines special soft tissue management with the use of a self-supporting titanium-reinforced membrane capable of maintaining a supra-alveolar space for regeneration. The MPPT allows primary closure of the interdental space, resulting in better protection of the membrane from the oral environment (Cortellini *et al*. 1995d). The technique involves the elevation of a full-thickness palatal flap which includes the entire interdental papilla. The buccal flap is mobilized with vertical and periosteal incisions, coronally positioned to cover the membrane, and sutured to the palatal flap through a horizontal internal crossed mattress suture over the membrane. Primary closure between the flap and the interdental papilla is obtained with a second internal mattress suture. Representative cases are shown in Figs. 38-4 and 38-11.

In a randomized controlled clinical study of 45 patients (Cortellini *et al*. 1995c), significantly greater attachment gain was obtained with the MPPT (5.3 ± 2.2 mm) in comparison with either conventional GTR (4.1 ± 1.9 mm) or flap surgery (2.5 ± 0.8 mm), demonstrating that a modified surgical approach can result in improved clinical outcomes. In this study, 100% of the sites were closed on top of a titanium-reinforced membrane and 73% remained closed for up to 6 weeks, when the barrier membrane was removed. This study provided proof of principle of the benefit of specific flap designs for periodontal regeneration. The MPPT has been successfully applied in multicenter randomized clinical trials designed to test the generalizability of the added benefits of regenerative approaches in deep intrabony defects (Tonetti *et al*. 1998, 2002, 2004b; Cortellini *et al*. 2001).

A meta-analysis (Murphy & Gunsolley 2003) showed the existence of a trend associating better clinical outcomes with flap designs and closing techniques considered conducive to the achievement and maintenance of primary closure of the flap (Figs. 38-13, 38-14). A similar trend was observed by

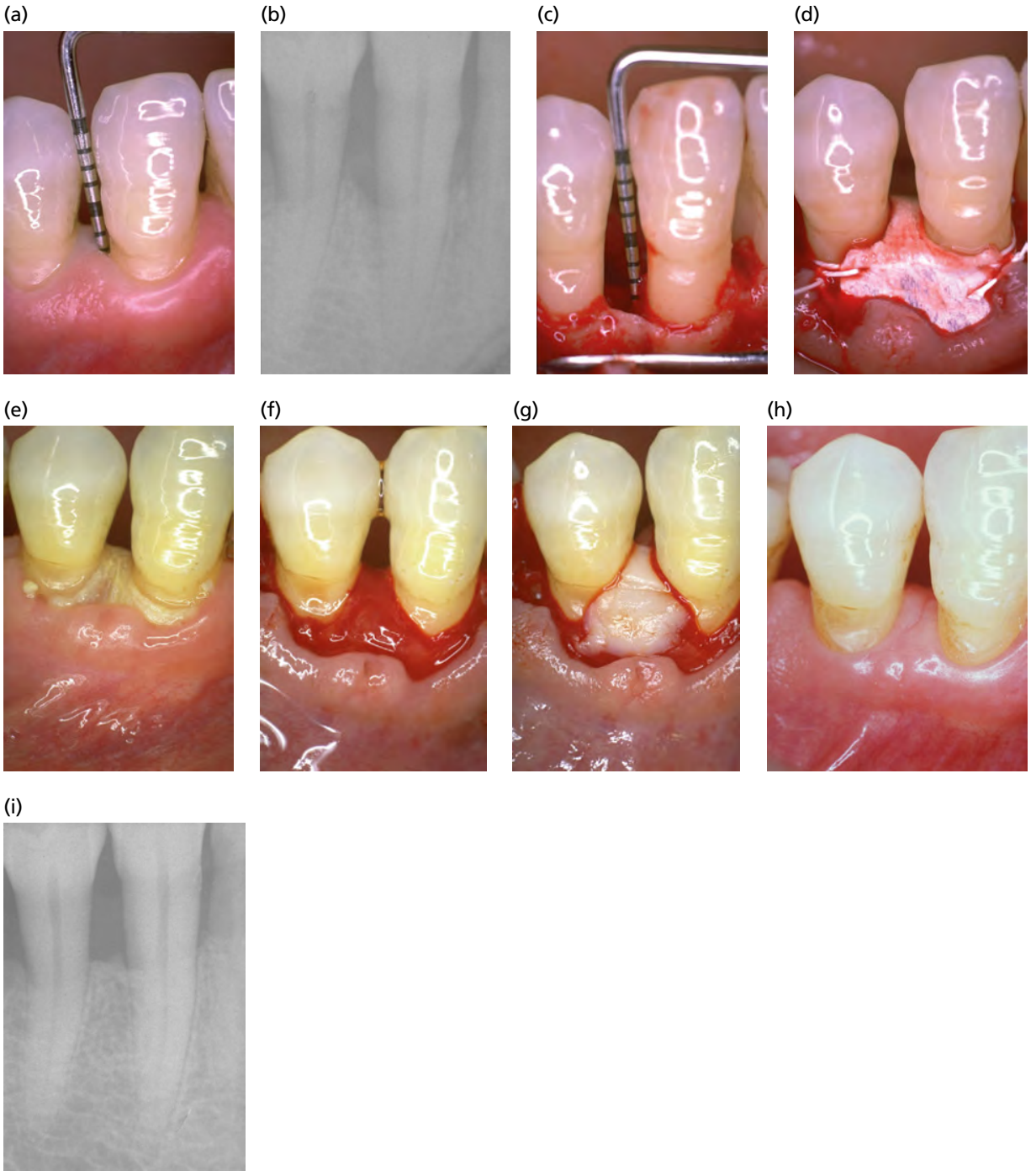


Fig. 38-12 Clinical case illustrating the management of the most common complication following application of a non-bioresorbable barrier membrane: membrane exposure and consequent loss of interdental soft tissue. Upon completion of cause-related periodontal therapy, regenerative periodontal surgery was performed to resolve a deep pocket associated with a deep intrabony defect (a, b). The 7-mm intrabony defect was accessed with a modified papilla preservation flap (c) and a non-bioresorbable barrier membrane was placed (d). Primary closure with multilayered sutures was obtained, but 5 weeks after surgery, the membrane became exposed to the oral cavity (e). Upon membrane removal (f), a newly regenerated tissue completely filled the space below the membrane, but inadequate soft tissue was available to completely cover the regenerated tissue in the interdental space. In order to protect the maturation of this tissue, a saddle-shaped interdental free gingival graft was harvested from the palate and shaped to precisely fit the interdental area (g). The graft healed well on the highly vascularized recipient bed and allowed good healing of the interdental tissues. Nine years after completion of therapy, the clinical and radiographic outcomes show healing with shallow probing depths and elimination of the defect (h, i).

Graziani *et al*. (2011) in their meta-analysis of flap surgery studies, where papilla preservation flaps performed better than conventional flap surgery.

The reported MPPT can be successfully applied in sites where the interdental space width is at least 2 mm at the most coronal portion of the papilla. When interdental sites are narrower, the reported technique is difficult to apply. In order to overcome this problem, a different papilla preservation procedure (the simplified papilla preservation flap [SPPF]) has been

proposed for narrow interdental spaces (Cortellini *et al*. 1999a). This approach includes an oblique incision across the defect-associated papilla, starting from the buccal angle of the defect-associated tooth and continuing to the mid-interdental part of the papilla at the adjacent tooth under the contact point. In this way, the papilla is cut into two equal parts of which the buccal part is elevated with the buccal flap and the lingual part with the lingual flap. In the cited study, 100% of the narrow interdental papillae could be closed on top of bioresorbable barriers, and 67% maintained primary closure over time, resulting in 4.9 ± 1.8 mm of CAL gain. This approach has been successfully applied in different multicenter RCTs designed to test the generalizability of the added benefits of using barrier membranes on deep intrabony defects (Tonetti *et al*. 1998, 2002, 2004b; Cortellini *et al*. 2001).

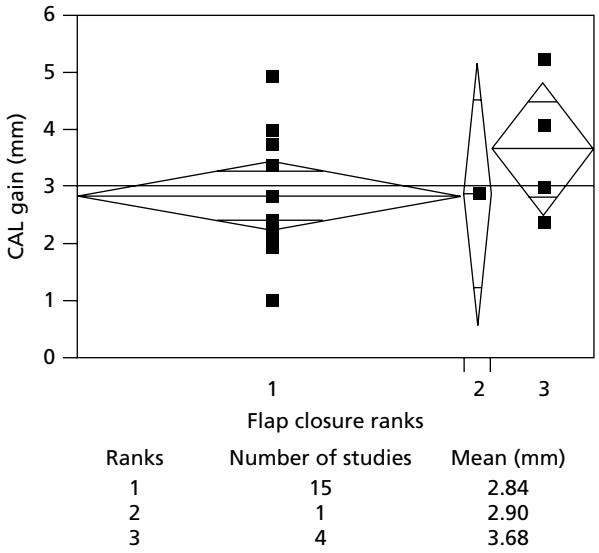
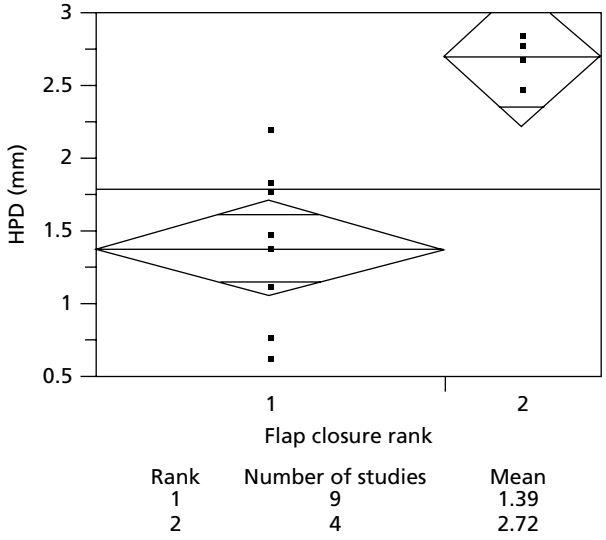


Fig. 38-13 Means of intrabony defect studies examining the relationship between flap closure technique ranking and gain in clinical attachment level (CAL) (in mm) considering only e-PTFE barrier types. Groupings were not statistically different from one another. (Source: Murphy & Gunsolley 2003. Reproduced with permission from John Wiley & Sons.)

In the cited studies, GTR therapy of deep intrabony defects performed by different clinicians on various patient populations resulted in both greater amounts and improved predictability of CAL gain than access flap alone. The issue of soft tissue manipulation to obtain stable protection of the regeneration site has been further explored by applying a microsurgical approach in the regenerative therapy of deep intrabony defects (Fig. 38-15). In a patient cohort study of 26 patients with 26 intrabony defects treated with papilla preservation techniques, primary closure on the barrier was obtained in 100% of the cases and maintained over time in 92.3% of the sites (Cortellini & Tonetti 2001). Treatment resulted in large CAL gain (5.4 ± 1.2 mm) and minimal gingival recession (0.4 ± 0.7 mm). Thus, the improved vision and better soft tissue handling improved the predictability of periodontal regeneration.

Today, the use of papilla preservation flap designs and closure techniques has become the standard approach for regenerative periodontal surgery. In a recent meta-analyses, Graziani *et al*. (2012) and Nibali *et al*. (2020) concluded that papillary preservation flaps enhanced the clinical outcomes of both access flap and regenerative surgery. The consensus panel of the XVI European Workshop in Periodontology *recommended* the use of specific flap designs with maximum preservation of interdental soft tissue such as papilla preservation flaps for the regenerative treatment of residual deep pockets associated with an intrabony defect (Sanz *et al*. 2020). The panel also *recommended* limiting flap elevation, under some specific circumstances, to optimize wound stability



	Difference	t test	DF	Prob > |t|
Estimate	−1.3319	−7.014	10.538	<0.0001
Standard error	0.1899			
Lower 95%	−1.9277			
Upper 95%	−0.7361			

Fig. 38-14 Regression analysis of furcation defect studies examining the relationship between flap closure technique ranking and the reduction (in mm) in horizontal probing depth (HPD). Groups 1 and 2 are statistically different from one another. (Source: Murphy & Gunsolley 2003. Reproduced with permission from John Wiley & Sons.)

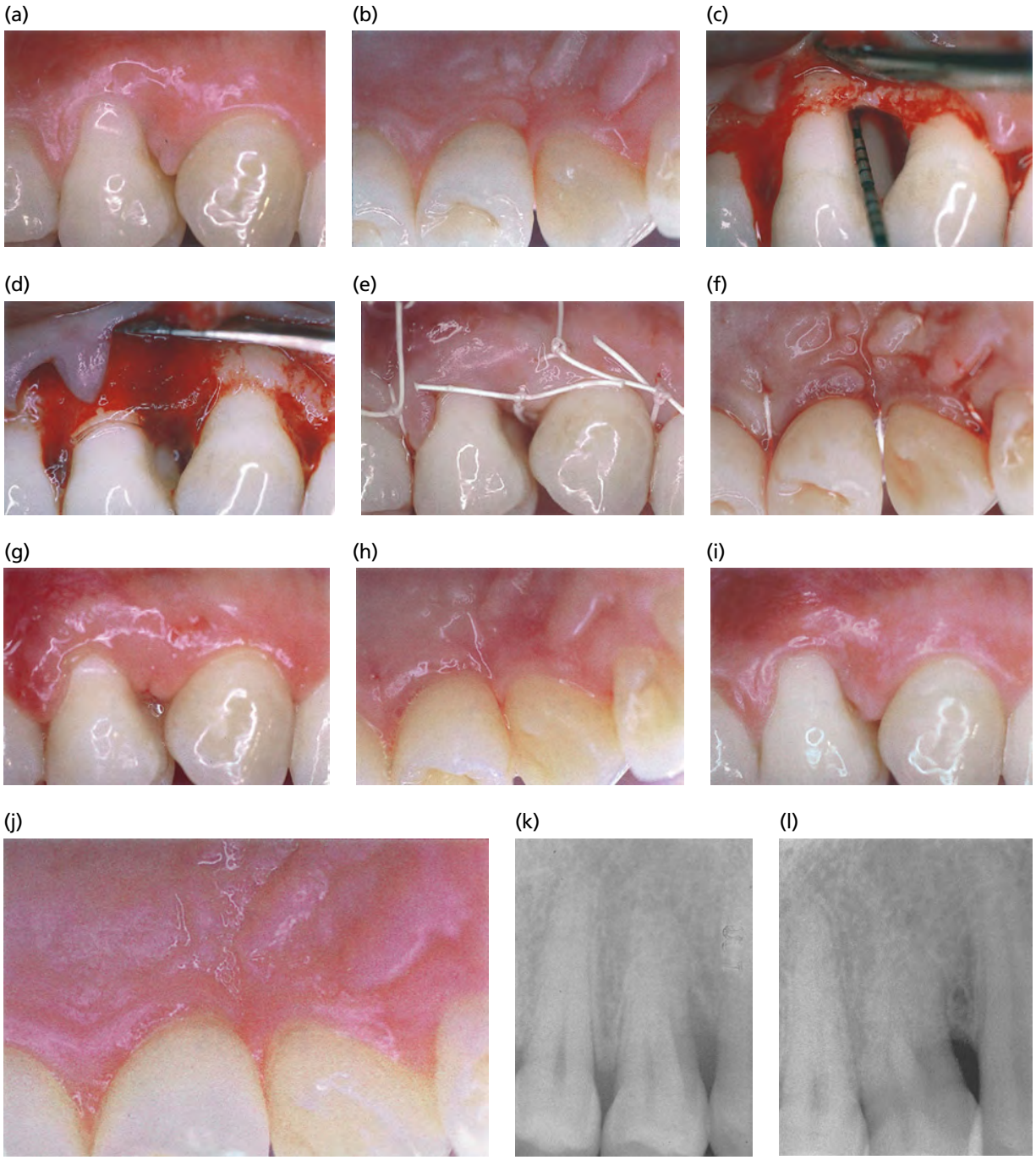


Fig. 38-15 (a) Right first maxillary premolar with a 7-mm pocket on the mesial surface. The interdental space (b) is very narrow (>2 mm), and is accessed with a simplified papilla preservation flap using a microsurgical approach (operative microscope and microsurgical instruments). The 5-mm deep intrabony defect (c) is covered with a bioresorbable barrier membrane (d). Primary closure of the flap over the membrane (e, f) is maintained over time (g, h). After 1 year, the interdental papilla is completely preserved and the residual pocket depth is 3 mm (i, j). The radiograph taken at baseline (k) compared with that taken 1 year after treatment (l) shows that the intrabony defect has healed completely.

and reduce morbidity according to the principles of minimally invasive surgery, that will be discussed in the next paragraphs.

Modified papilla preservation technique

The rationale for developing this technique was to achieve and maintain primary closure of the flap in the interdental space over the membrane (Cortellini *et al*. 1995d) (Figs. 38-16, 38-17, 38-18). Access to the interdental defect is achieved with a horizontal incision traced in the buccal keratinized gingiva at the base of the papilla and connected to mesiodistal buccal intrasulcular incisions. After elevation of a full-thickness buccal flap, the residual interdental tissues are dissected from the neighboring teeth and the underlying bone, and elevated towards the palatal aspect. A full-thickness palatal flap, including the interdental papilla, is elevated and the interdental defect exposed. Following debridement of the defect,

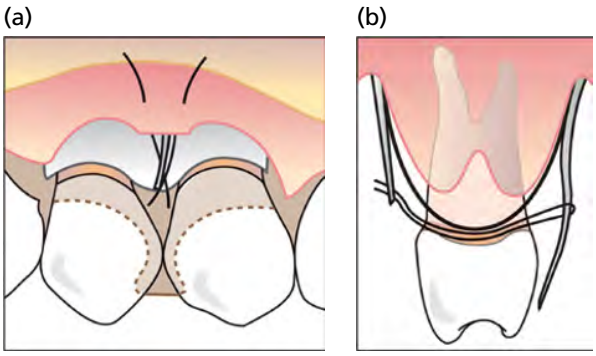


Fig. 38-16 Suture to obtain coronal positioning of the buccal flap: schematic illustration of the crossed horizontal internal mattress suture between the base of the palatal papilla and the buccal flap immediately coronal to the mucogingival junction. Note that the suture crosses above the titanium reinforcement of the membrane. (a) Buccal view; (b) mesiodistal view. (Source: Cortellini *et al*. 1995d. Reproduced with permission from John Wiley & Sons.)

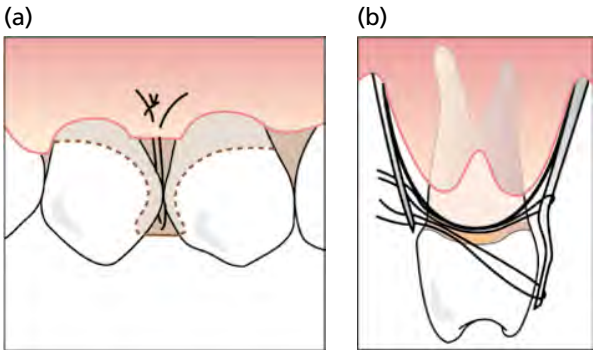


Fig. 38-17 Suture to obtain tension-free primary closure of the interdental space: schematic illustration of the vertical internal mattress suture between the most coronal portion of the palatal flap (which includes the interdental papilla) and the most coronal portion of the buccal flap. (a) Buccal view; (b) mesiodistal view. (Source: Cortellini *et al*. 1995d. Reproduced with permission from John Wiley & Sons.)

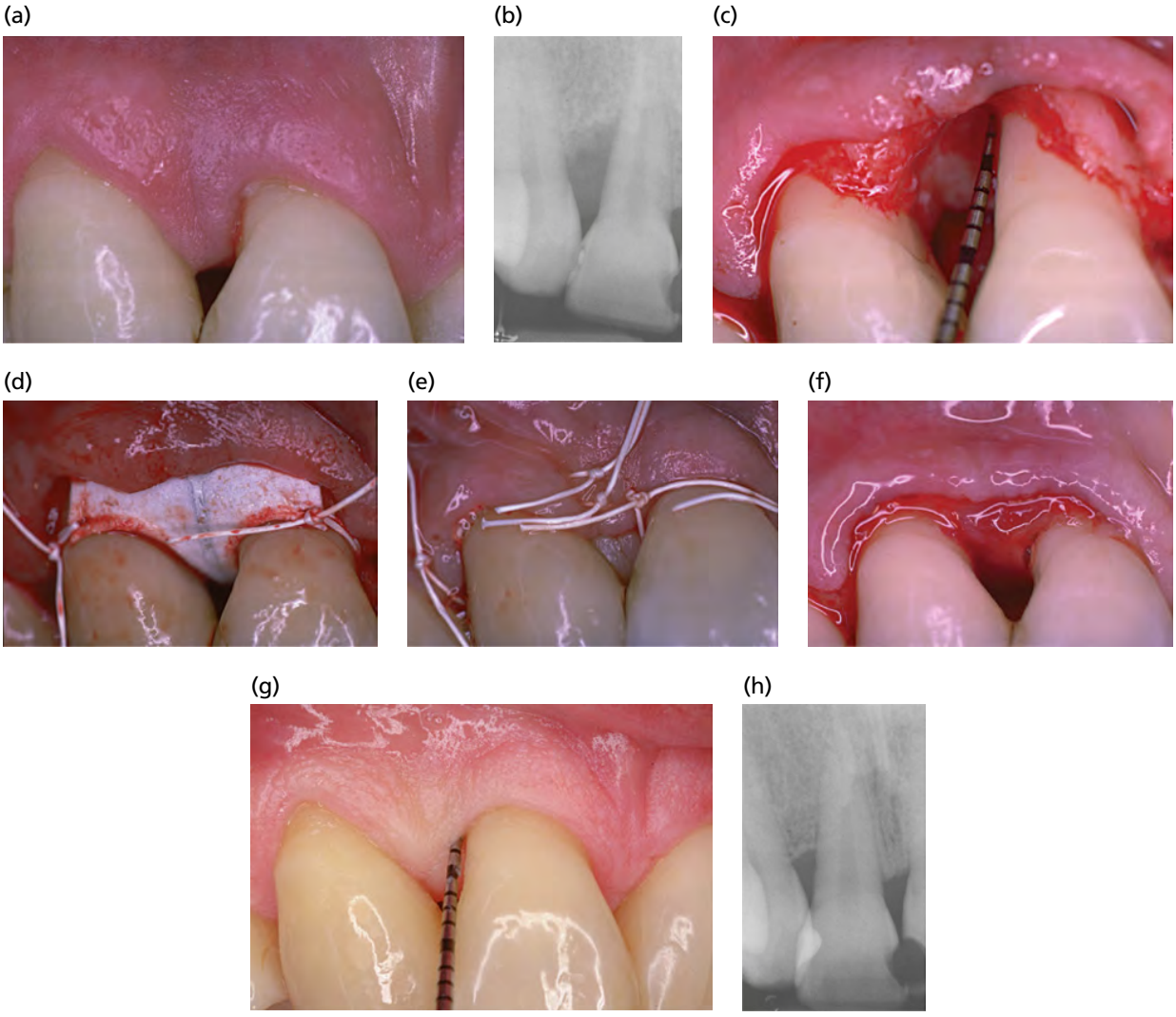


Fig. 38-18 Clinical case illustrating the modified papilla preservation technique (MPPT) used to completely close the interdental space above a barrier membrane. Following completion of initial cause-related therapy, an 8-mm pocket associated with 2 mm of recession of the gingival margin was present on the distal aspect of the central incisor (a). A wide intrabony defect was detectable on the radiograph (b). Defect was accessed with the MPPT, keeping the whole interdental tissue connected with the palatal flap. A 7-mm intrabony defect was uncovered (c). Following root debridement, a titanium-reinforced barrier membrane was positioned (d). Primary closure of the interdental space was obtained by suturing back the papilla preservation flap using a multilayered suturing technique aimed at coronal advancement of the flap, complete relief of wound tension, and good flap stability (e). Six weeks later, the same flap was elevated in order to remove the membrane that had remained completely submerged for the whole time. New tissue filled the space maintained beneath the membrane (f). Following completion of healing (1 year), a 3-mm probing depth and fill of the intrabony defect were observed. The results were maintained over time as indicated by the clinical and radiographic appearance 6 years after regeneration (g, h).

the buccal flap is mobilized with vertical and periosteal incisions, when needed.

This technique was originally designed for use in combination with self-supporting barrier membranes. In fact, the suturing technique requires a supportive (or supported) membrane to be effective (Figs. 38-16, 38-17). To obtain primary closure of the interdental space over the membrane, a first suture (horizontal internal crossed mattress suture) is placed beneath the mucoperiosteal flaps between the base of the palatal papilla and the buccal flap. The interdental portion of this suture hangs on top of the membrane, allowing the coronal displacement of the buccal flap. This suture relieves all the tension in the flaps. To ensure primary passive closure of the interdental tissues over the membrane, a second suture (vertical internal mattress suture) is placed between the buccal aspect of the interdental papilla (i.e. the most coronal portion of the palatal flap, which includes the interdental papilla) and the most coronal portion of the buccal flap. This suture is free of tension.

An alternative type of suture to close the interdental tissues has been proposed by Dr Lars Laurell. This modified internal mattress suture starts from the external surface of the buccal flap, crosses the interdental area, and runs through the lingual flap at the base of the papilla. The suture runs back through the external surface of the lingual flap and the internal surface of the buccal flap, about 3 mm distant from the first two bites. Finally, the suture is passed through the interdental area above the papillary tissues, passed through the loop of the suture on the lingual side, and brought back to the buccal side, where it is tied. This suture is very effective in ensuring stability and primary closure of the interdental tissues.

In a randomized controlled clinical study of 45 patients (Cortellini *et al*. 1995c), significantly greater PAL was gained with the MPPT (5.3 ± 2.2 mm) in comparison with either conventional GTR (4.1 ± 1.9 mm) or access flap surgery (2.5 ± 0.8 mm), demonstrating that a modified surgical approach can result in improved clinical outcomes. The sites accessed with the MPPT showed primary closure of the flap in all but one case, and no gingival dehiscence until membrane removal in 73% of the cases.

This surgical approach has also been used in combination with non-supported bioresorbable barrier membranes (Cortellini *et al*. 1996c), with positive results. CAL gains at 1 year were 4.5 ± 1.2 mm. In all the cases, primary closure of the flap was achieved and about 80% of the sites maintained primary closure over time (Fig. 38-19). It should be underlined, however, that the horizontal internal crossed mattress suture most probably caused an apical displacement of the interdental portion of the membrane, thereby reducing the space for regeneration.

The MPPT can be successfully applied in conjunction with a variety of regenerative materials, including biologically active materials such as EMDs (Tonetti *et al*. 2002) (Fig. 38-20) or growth factors and BRGs (Fig. 38-21) (Tonetti *et al*. 2004b; Cortellini & Tonetti 2005).

The surgical access of the interdental space with the MPPT is technically very demanding, but it has been reported to be very effective and applicable to wide interdental spaces (>2 mm at the interdental tissue level), especially in the anterior dentition. In properly selected cases, large attachment gain and consistent reduction of PPD associated with no or minimal recession of the interdental papilla can be consistently expected. It is, therefore, indicated in cases in whom esthetics are particularly important.

Simplified papilla preservation flap

To overcome some of the technical problems encountered with the MPPT (difficult application in narrow interdental spaces and in posterior areas, suturing technique not appropriate for use with non-supportive barriers), a different approach, the SPPF (Figs. 38-15, 38-22) was subsequently developed (Cortellini *et al*. 1999a).

This simplified approach to the interdental papilla includes a first incision across the defect-associated papilla, starting from the gingival margin at the buccal-line angle of the involved tooth and extending to the mid-interdental portion of the papilla under the contact point of the adjacent tooth. This oblique incision is carried out by keeping the blade parallel to the long axis of the teeth in order to avoid excessive thinning of the remaining interdental tissues. The first oblique interdental incision is continued intrasulcularly in the buccal aspect of the teeth neighboring the defect. After elevation of a full-thickness buccal flap, the remaining tissues of the papilla are carefully dissected from the neighboring teeth and the underlying bone crest. The interdental papillary tissues at the defect site are gently elevated along with the lingual/palatal flap to fully expose the interdental defect. Following defect debridement and root planing, vertical releasing incisions and/or periosteal incisions are performed, when needed, to improve the mobility of the buccal flap. After application of a barrier membrane, primary closure of the interdental tissues above the membrane is attempted in the absence of tension, with the following sutures:

1. A first horizontal internal mattress suture (offset mattress suture) is positioned in the defect-associated interdental space running from the base (near to the mucogingival junction) of the keratinized tissue at the mid-buccal aspect of the tooth not involved with the defect to a symmetrical location at the base of the lingual/palatal flap. This suture rubs against the interdental root surface, hangs on the residual interdental bone crest, and is anchored to the lingual/palatal flap. When tied, it allows the coronal positioning of the buccal flap. Importantly, this suture, lying on the interdental bone crest,

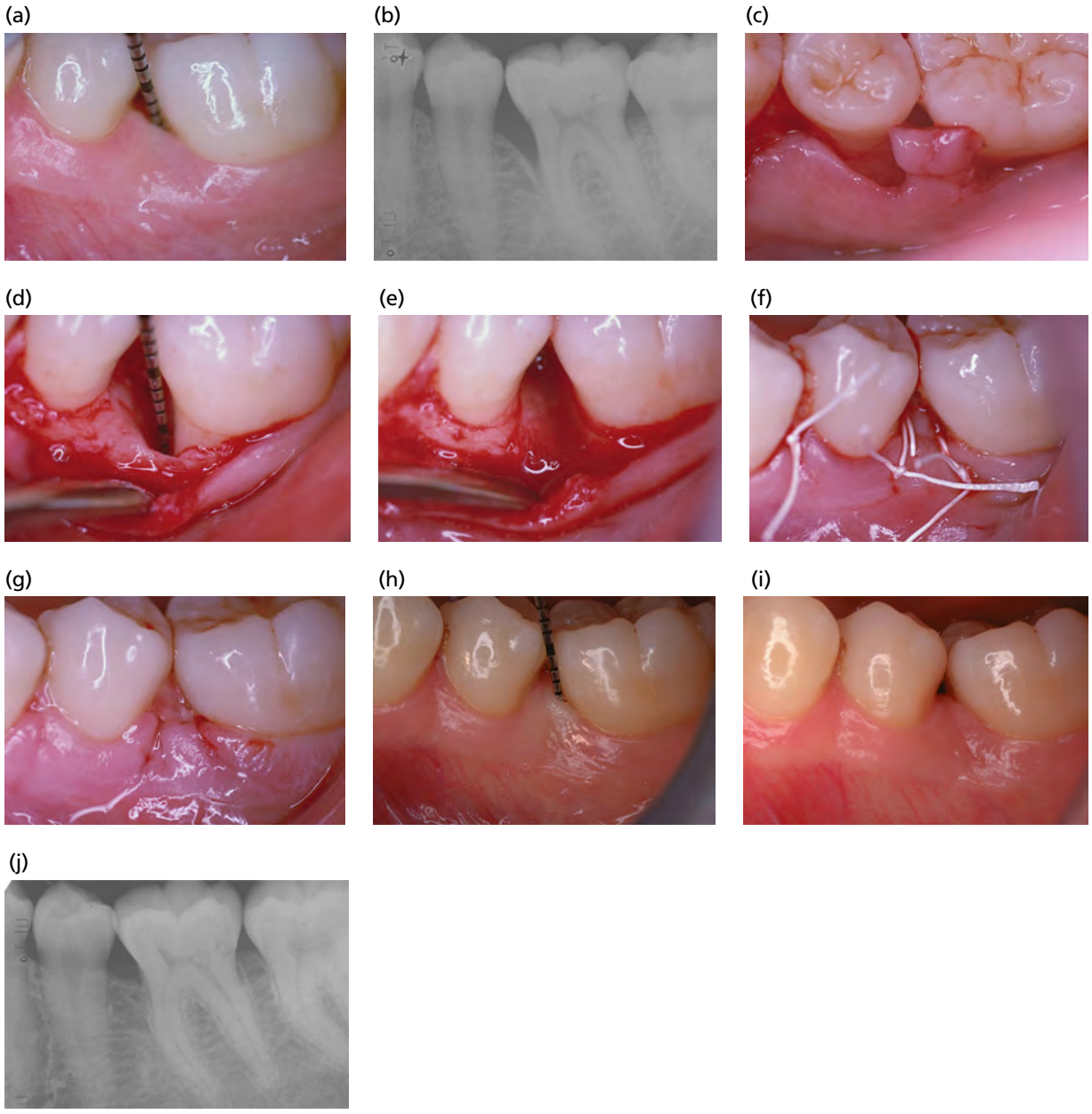


Fig. 38-19 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) to a case treated with a bioresorbable barrier membrane. An 8-mm pocket associated with an intrabony defect persisted on the mesial aspect of the lower first molar following completion of initial cause-related therapy (a, b). The defect was accessed with the MPPT. Note the papilla preserved attached to the lingual flap (c) as well as the presence of a 7-mm intrabony defect (d). Following root debridement, a bioresorbable barrier membrane was positioned and secured around the root of the tooth with bioresorbable sutures (e). Primary closure of the interdental space was obtained with multilayered sutures (f) and was fully maintained at the 1-week suture removal appointment (g). At 6 years, probing depths were 2–3 mm, the soft tissue profile was conducive to optimal self-performed oral hygiene measures, and the radiograph showed elimination of the defect (h–j).

does not cause any compression at the mid-portion of the membrane, therefore preventing its collapse into the defect.

2. The interdental tissues above the membrane are then sutured to obtain primary closure with one of the following approaches: one interrupted suture whenever the interdental space is narrow and the interdental tissues thin; two interrupted sutures when the interdental space is wider and the interdental tissues thicker; an internal vertical/oblique mattress suture when the interdental space is wide and the interdental tissues are thick.

Special care has to be paid to ensure that the first horizontal mattress suture relieves all the tension in the flaps, and to obtain primary passive closure of the interdental tissues over the membrane with the second suture. When tension is observed, the sutures should be removed and the primary passive closure attempted again.

This approach has been preliminarily tested in combination with bioresorbable barrier membranes in a case series of 18 deep intrabony defects (Cortellini *et al*. 1999a). The average CAL gain observed at 1 year was 4.9 ± 1.8 mm. In all the cases

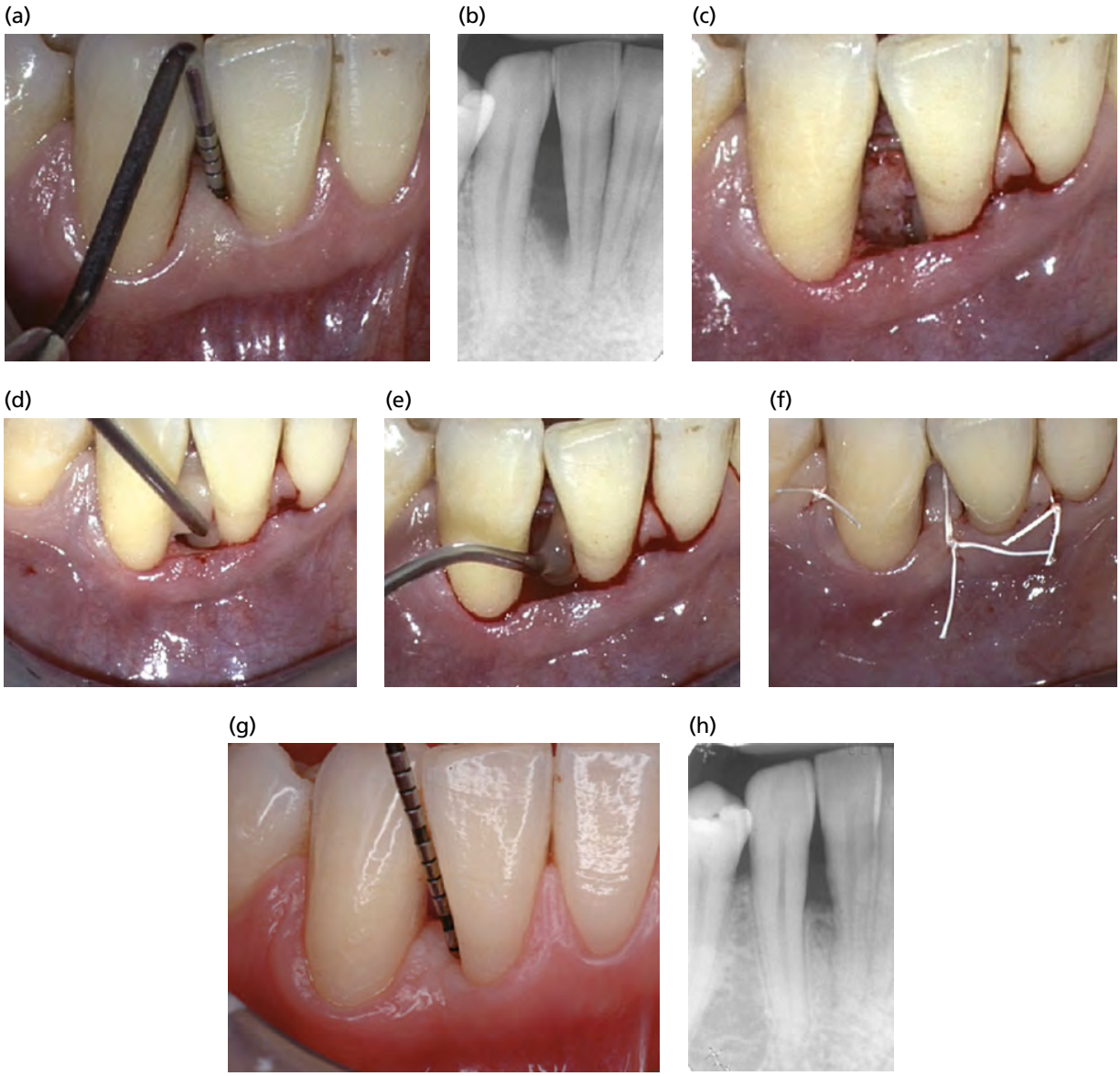


Fig. 38-20 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) in conjunction with the application of enamel matrix derivatives (EMDs). (a) A 10-mm pocket was detectable on the distal aspect of the lower lateral incisor following successful completion of initial cause-related therapy. (b) The radiograph showed the presence of a deep intrabony defect extending to the apical third of the root. The defect was accessed with the MPPT (c) with limited mesial and distal extension of the flap. Following careful debridement, the root was conditioned with an EDTA gel according to the manufacturer's instructions for the application of EMDs (d). After rinsing and drying of the defect and root surface, the EMD gel was applied to the root surface and to fill the defect (e), and flaps were sutured with a multilayer technique to achieve primary closure in the absence of tension (f). (g, h) One year following regenerative surgery, shallow pockets and radiographic resolution of the defect were apparent.

it was possible to obtain primary closure of the flap over the membrane, and 67% of the sites maintained primary closure over time. This approach was tested in a multicenter controlled randomized clinical trial involving 11 clinicians from seven different countries and a total of 136 defects (Tonetti *et al*. 1998). The average CAL gain observed at 1 year in the 69 defects treated with the SPPF and a bioresorbable barrier membrane was 3 ± 1.6 mm. More than 60% of the treated sites maintained primary closure over time. It is important to underline that these results were obtained by different clinicians treating different populations of patients and defects, including those with narrow spaces and involving the posterior areas of the mouth. The SPPF was successfully applied in conjunction with a variety of regenerative materials, including biologically active materials such as EMDs (Tonetti *et al*. 2002) (Fig. 38-23) and BRG (Fig. 38-24) (Cortellini & Tonetti 2004; Tonetti *et al*. 2004b).

Minimally invasive surgical technique (MIST)

More recently there has been a growing interest in a friendlier, patient-oriented surgery and clinical investigators have focused their interest on the development of less invasive approaches. Harrel and Rees

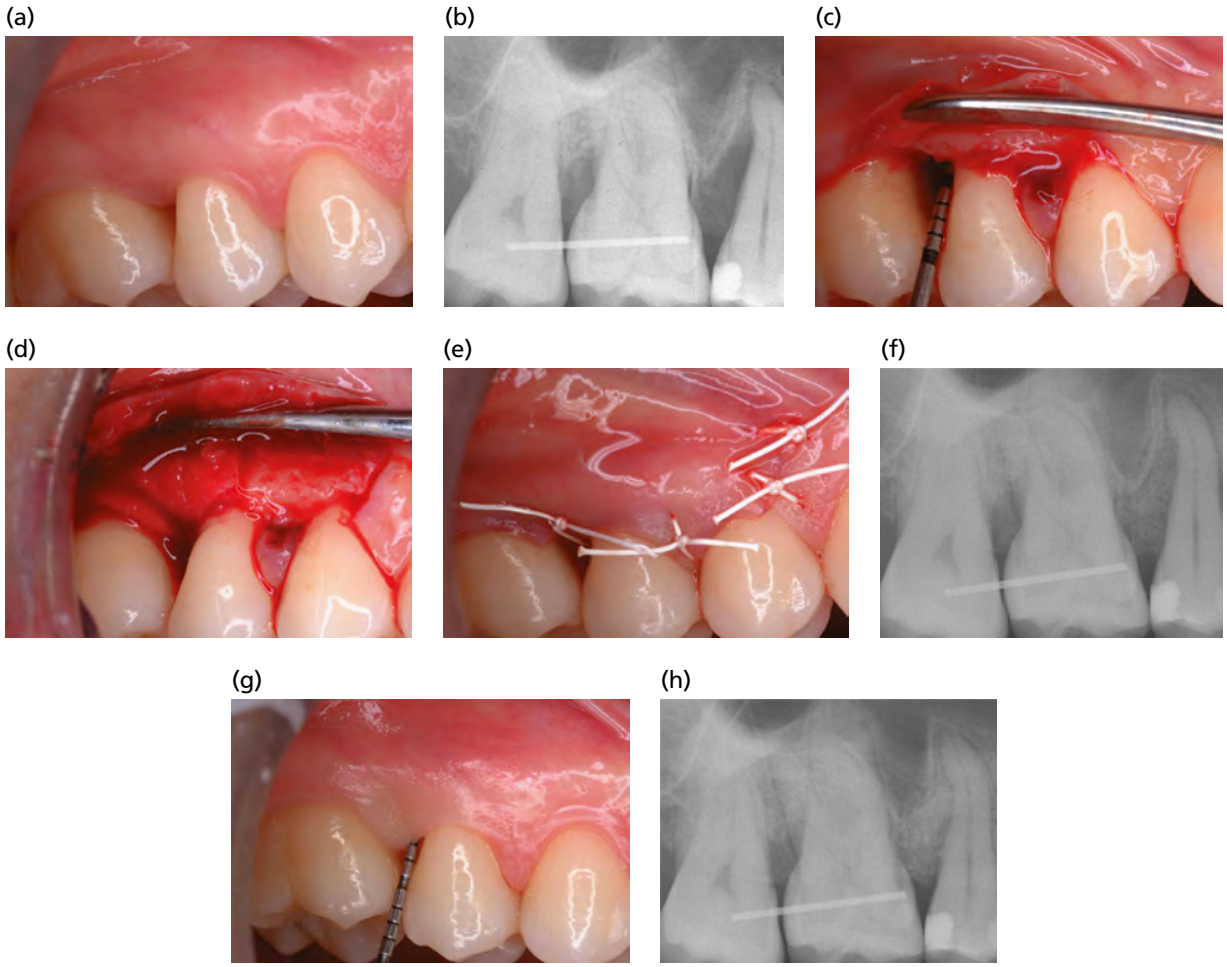


Fig. 38-21 Clinical case illustrating the application of the modified papilla preservation technique (MPPT) in conjunction with a bone replacement graft (BRG) in combination with a bioresorbable membrane. After completion of initial cause-related therapy, a 9-mm pocket associated with an intrabony defect was present on the distal aspect of the upper second premolar (a, b). The defect reached the apical portion of the root and had a 9-mm intrabony component (c). Following careful root debridement, a bioresorbable membrane was adapted to the local anatomy and was positioned to contain the defect. A BRG was subsequently inserted under the membrane to provide additional support for the membrane and for the soft tissues (d). Primary closure was achieved with a single internal mattress suture (e). The control radiograph taken upon completion of the surgery showed the presence of the radio-opaque BRG in the defect (f). At 1-year follow-up, a 3-mm probing depth associated with resolution of the intrabony component of the defect was apparent (g, h). Note that the radio-opaque BRG particles are still detectable but appear embedded in newly formed mineralized tissue.

(1995) proposed the minimally invasive surgery (MIS) approach with the aim of producing minimal wounds, minimal flap reflection, and gentle handling of the soft and hard tissues (Harrel & Nunn 2001; Harrel *et al*. 2005). In order to provide even greater wound stability and to further limit patient morbidity, a papilla preservation flap can be used in the context of a minimally invasive, high-power magnification-assisted surgical technique (Cortellini & Tonetti 2007a). Such a minimally invasive approach is particularly suited for treatment in conjunction with biologically active agents such as EMDs or growth factors and/or grafting materials.

The defect-associated interdental papilla is accessed either with the SPPF (Cortellini *et al*. 1999a) or the MPPT (Cortellini *et al*. 1995d). The SPPF is performed whenever the width of the interdental space is 2 mm or narrower, while the MPPT is applied at interdental sites wider than 2 mm. The interdental incision (SPPF or MPPT) is extended to the buccal and lingual aspects of the two teeth adjacent to the defect. These incisions are strictly intrasulcular to preserve all the height and width of the gingiva, and their mesiodistal extension is kept to a minimum to allow the coronoapical elevation of a very small full-thickness flap with the objective of exposing just 1–2 mm of the defect-associated residual bone crest. When possible, only the defect-associated papilla is accessed and vertical releasing incisions are avoided. With these general rules in mind, different clinical pictures can be encountered in different defects.

The shortest mesiodistal extension of the incision and the minimal flap reflection occurs when the intrabony defect is a pure three-wall, or has shallow two- and/or one-wall subcomponents allocated entirely in the interdental area. In these instances, the mesiodistal incision involves only the defect-associated papilla and part of the buccal and lingual

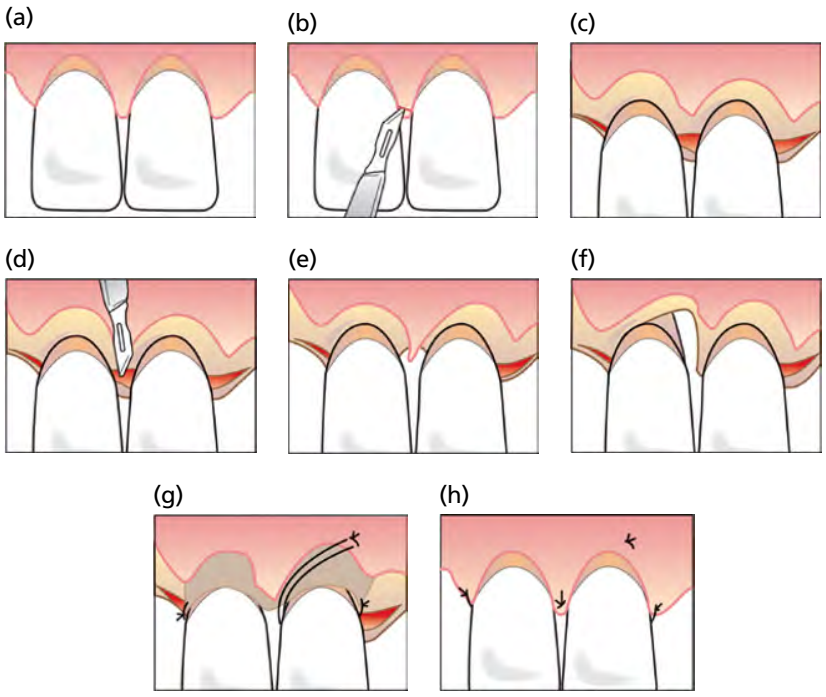


Fig. 38-22 (a) Presurgical appearance of the area to be accessed with a simplified papilla preservation flap (SPPF). The defect is located on the mesial aspect of the maxillary right lateral incisor. (b) First oblique incision in the defect-associated papilla begins at the gingival margin of the mesiobuccal line angle of the lateral incisor. The blade is kept parallel to the long axis of the tooth and reaches the mid-point of the distal surface of the central incisor just below the contact point. (c) First oblique incision continues intrasulcularly in the buccal aspect of the lateral and central incisors, extending to the adjacent papillae, and a buccal full-thickness flap is elevated to expose 2–3 mm of bone. Note the defect-associated papilla is still in place. (d) Buccolingual horizontal incision at the base of the papilla is as close as possible to the interproximal bone crest. Care is taken to avoid a lingual/palatal perforation. (e) Intrasulcular interdental incisions continue in the palatal aspect of the incisors to the adjacent partially dissected papillae. A full-thickness palatal flap including the interdental papilla is elevated. (f) Intrabony defect following debridement. Note the position of the bone crest on the distal aspect of the central incisor. (g) Membrane is positioned to cover the defect and 2–3 mm of remaining bone and secured to neighboring teeth. A horizontal internal mattress suture runs from the base of the keratinized tissue at the mid-buccal side of the central incisor to a symmetric location at the base of the palatal flap. This suture causes no direct compression of the mid-portion of the membrane, preventing its collapse into the defect. (h) Primary closure and complete coverage of the membrane are obtained. (Source: Cortellini *et al*. 1999a. Reproduced with permission from John Wiley & Sons.)

aspects of the two teeth neighboring the defect. The full-thickness flap is elevated minimally, just enough to expose the buccal and lingual bone crest delineating the defect in the interdental area (Fig. 38-25).

A larger coronoapical elevation of the full-thickness flap is necessary when the coronal portion of the intrabony defect has a deep two-wall component. The coronoapical extension of the flap is kept to a minimum at the aspect where the bony wall is preserved (either buccally or lingually), and extends more apically at the site where the bony wall is missing (lingually or buccally), the objective being to reach and expose 1–2 mm of the residual bone crest (Fig. 38-26).

When a deep one-wall defect is approached, the full-thickness flap is elevated to the same extent on both the buccal and the lingual aspects.

When the position of the residual buccal/lingual bony wall(s) is very deep and difficult or impossible to reach with the previously described minimal incision of the defect-associated interdental space, the flap(s) is (are) further extended mesially or distally and one extra interdental space is involved to obtain a larger flap reflection. The same approach is used when the bony defect also extends to the buccal or the palatal side of the involved tooth, or when it involves the two interdental spaces of the same tooth (Fig. 38-27) or two approximal teeth (Fig. 38-28). In the latter instance, a second interdental papilla is accessed, either with an SPPF or an MPPT, according to the indication. Vertical releasing incisions are performed when flap reflection causes tension at the extremities of the flap(s). The vertical releasing incisions are always kept very short and within the attached gingiva (never involving the mucogingival junction). The overall aim of this approach is to avoid using vertical incisions whenever possible or to reduce their number and extent to a minimum when there is a clear indication for them. Periosteal incisions are never performed.

The defects are debrided with the combined use of mini-curettes and power-driven instruments, and the roots carefully planed. During the instrumentation, the flaps are slightly reflected and carefully protected with periosteal elevators and frequent saline irrigations. At the end of instrumentation, the biologically active agent is applied, and then the flaps are repositioned.

The suturing approach in most instances consists of a single modified internal mattress suture at the defect-associated interdental area to achieve primary closure

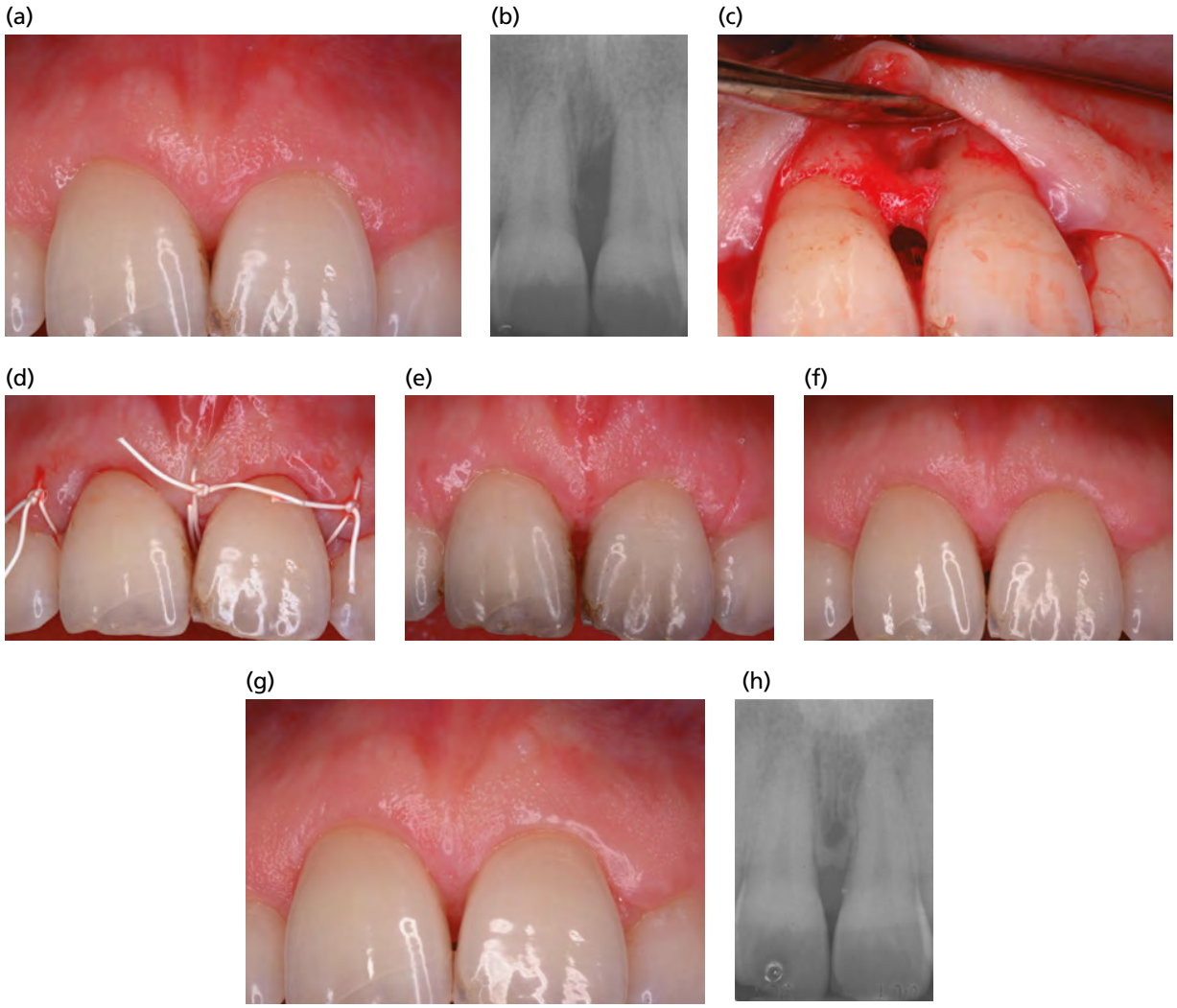


Fig. 38-23 Clinical case illustrating the clinical application of the simplified papilla preservation flap (SFFP) in conjunction with the application of a biologically active regenerative material (enamel matrix derivatives [EMDs] in gel form). At re-evaluation following completion of successful initial cause-related therapy, an 8-mm pocket was detected on the mesial palatal aspect of the left central incisor (a). An angular defect was evidenced on a periapical radiograph (b). The complex anatomy of the defect was apparent following access to the defect with the modified papilla preservation technique (MPPT): a buccal fenestration was apparent with the majority of the defect extending palatally to the apical third of the root (c). Following application of the EMDs, primary closure of the flap was achieved with a multilayered suture (d). At the 1-week suture removal appointment, excellent maturation of the soft tissue healing was apparent (e). At 6 months, a well-represented interdental papilla was present thanks to both the papilla preservation approach and the presence of a bony bridge that assisted in soft tissue support, in spite of the gel formulation of the EMDs (f). Clinical and radiographic outcomes at 1 year showed preservation of excellent esthetics and elimination of the defect (g, h). Probing depths were in the 2–3 mm range.

of the papilla in the absence of any tension (Cortellini & Tonetti 2001, 2005). When a second interdental space has been accessed, the same suturing technique is used to obtain primary closure in this area. Vertical releasing incisions are sutured with simple passing sutures. The buccal and lingual flaps are repositioned at their original level, without any coronal displacement to avoid any additional tension in the healing area.

All the surgical procedures can be performed with the aid of an operating microscope or magnifying loupes at a magnification of ×4 to ×16 (Cortellini & Tonetti 2001, 2005). Microsurgical instruments are utilized whenever needed as a complement to the normal set of periodontal instruments.

This approach has been preliminary tested in two case series with a total of 53 deep intrabony defects (Cortellini & Tonetti 2007a, b). One-year results showed clinically significant improvements (CAL gain of 4.8 ± 1.9 mm with 88.7 ± 20.7% clinical resolution of the defect) and greatly reduced patient morbidity. The same approach was successfully applied to multiple intrabony defects in 20 patients (Cortellini *et al*. 2008). The 44 treated defects gained on average 4.4 ± 1.4 mm of clinical attachment and 73% of defects showed CAL improvements of ≥4 mm. This corresponded to an 83 ± 20% resolution of the defect (15 defects were completely filled). Residual PPDs were 2.5 ± 0.6 mm. A minimal increase of 0.2 ± 0.6 mm in gingival recession between baseline and 1 year was recorded.

A recent controlled clinical study of 30 patients compared MIST plus EMD to MIST alone (Ribeiro

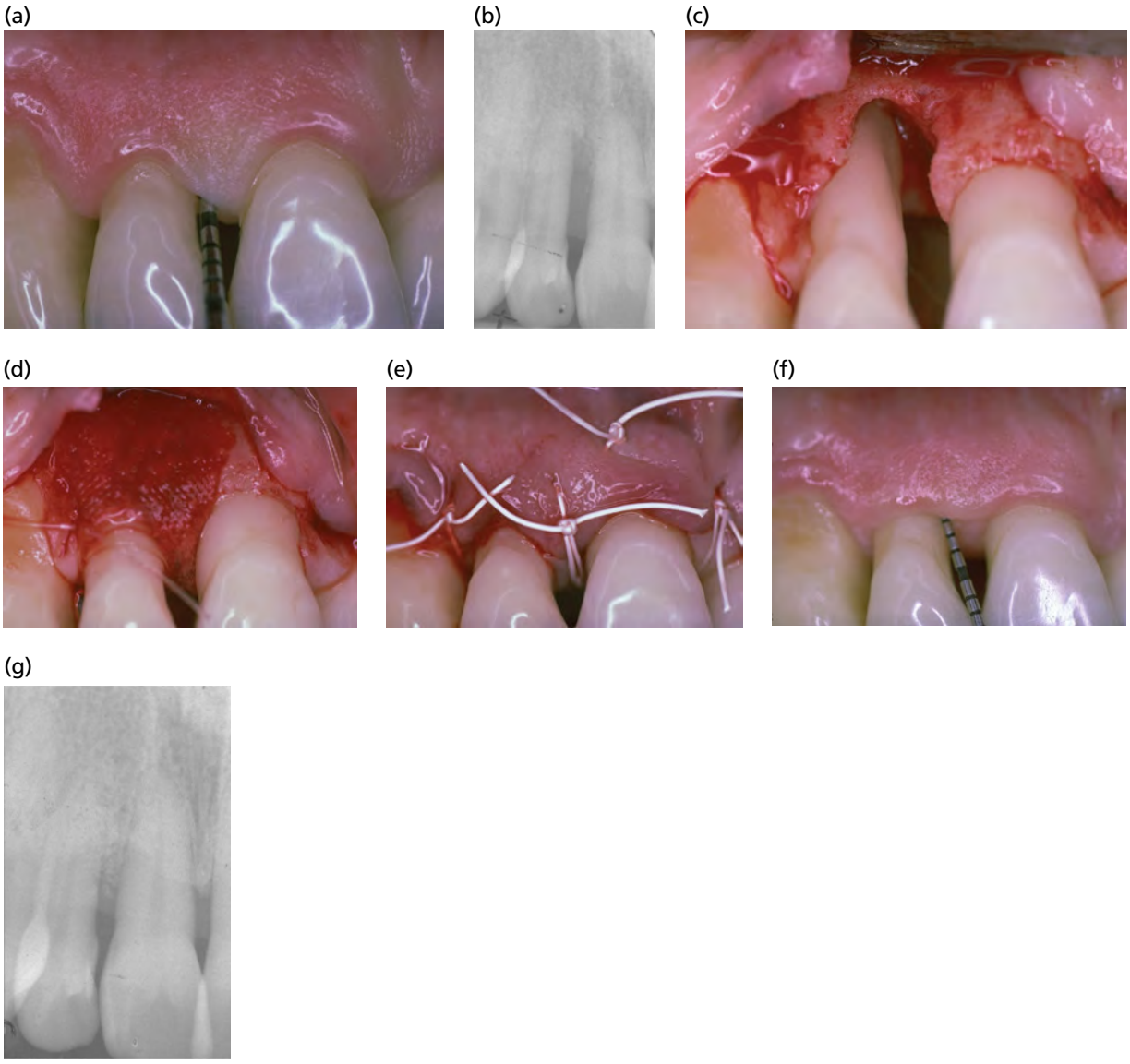


Fig. 38-24 Clinical case illustrating the application of the simplified papilla preservation flap (SPPF) in combination with a bioresorbable barrier membrane applied in combination with a bone replacement graft (BRG). At re-evaluation, a 9-mm pocket was detected on the mesial aspect of the lateral incisor (a). The radiograph showed the presence of a deep intrabony defect (b). Following access with a SPPF, a predominantly two-wall intrabony defect was exposed (c). After careful root instrumentation, a bioresorbable membrane was placed on top of a BRG (d). Primary closure of the flap was obtained with a multilayered suture approach (e). At 6 years, shallow probing depths were present (f); note the moderate increase in recession of the gingival margin. The radiograph at 6 years showed elimination of the defect but persistence of mineralized granules of the BRG embedded in the newly formed mineralized tissue (g).

et al. 2011a). The authors reported significant PPD reduction, CAL gain, and radiographic bone gain at 3 and 6 months in both groups. No differences were detected between therapies at any time point. It was concluded that the use of EMDs did not improve the outcome of the MIST for the treatment of intrabony defects.

Modified Minimally Invasive Surgical Technique (M-MIST)

A development of this technique, the modified minimally invasive surgical technique (M-MIST) (Cortellini & Tonetti 2009b) has been tested (Fig. 38-29). The M-MIST was designed especially to improve flap stability and to provide self-ability to maintain space for regeneration. The surgical approach consists of a tiny interdental access through which only a buccal triangular flap is elevated, while the papilla is left in place, connected to the root of the crest-associated tooth with its supracrestal fibers (see Fig. 38-5). Access to the defect is gained through the tiny buccal triangular flap: from the buccal "window", the soft tissue filling the defect (i.e. the so-called granulation tissues) is sharply dissected from the papillary supracrestal connective tissue and from the bony walls with a microblade, and removed with a mini-curette. Then, the root surface is carefully debrided with hand and mechanical instruments. The supracrestal fibers of the defect-associated papilla and the palatal tissues are left untouched. The minimal wound and

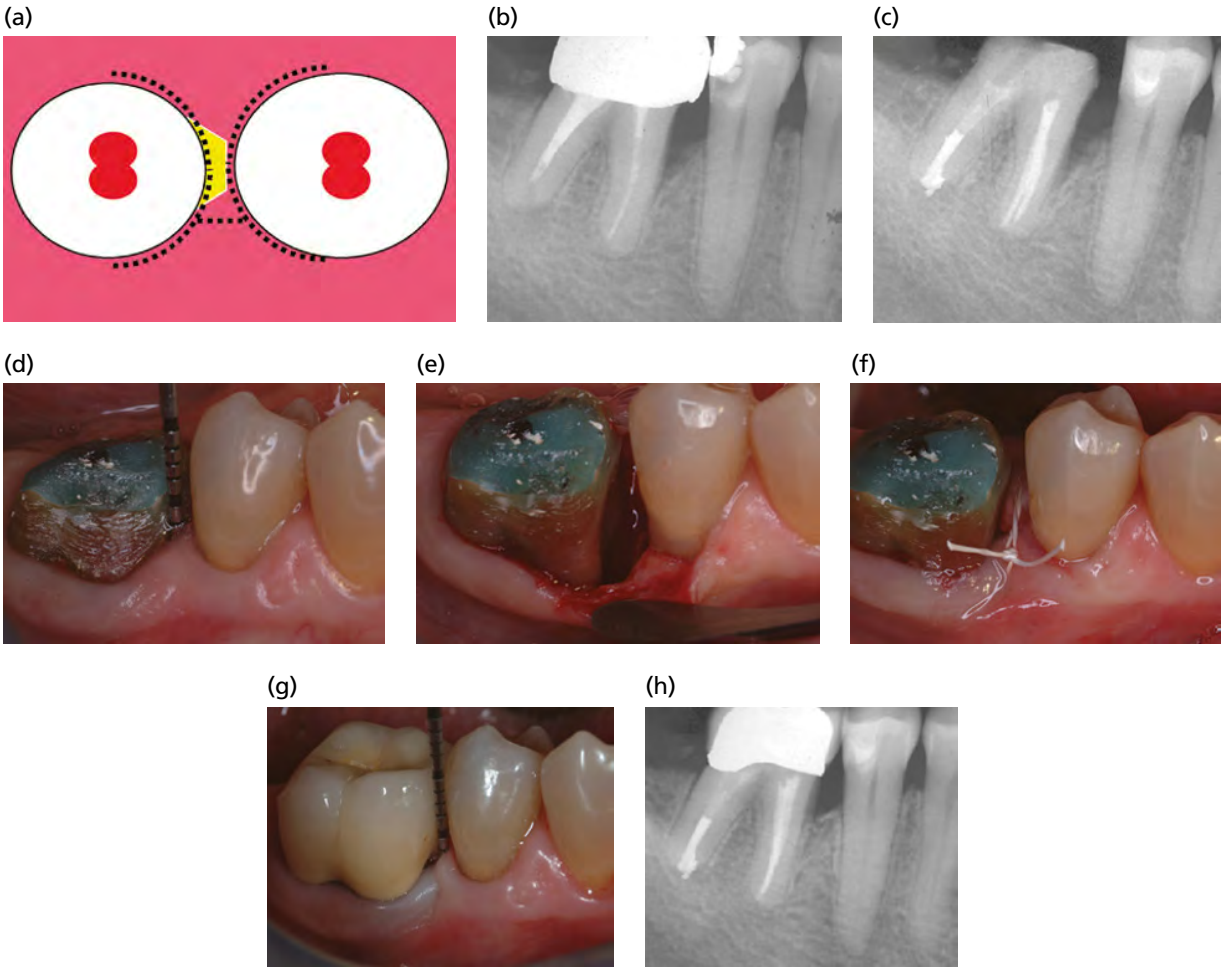


Fig. 38-25 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in an isolated interdental three-wall defect. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the interdental space associated with the defect. Mesiodistal extension of the flap was limited to the buccal aspect of the teeth adjacent to the defect in order to optimize wound stability (a). The baseline radiograph showed the presence of dental diseases (periapical infection and caries) that needed to be controlled during the initial cause-related phase of therapy (b). At re-evaluation, an 8-mm pocket associated with the presence of a deep intrabony defect was detected on the mesial aspect of the first molar (c, d). The defect was accessed in a minimally invasive fashion using the MPPT. The three-wall intrabony defect was exposed and carefully debrided (e). After application of enamel matrix derivatives, primary closure was obtained with a single modified internal mattress suture (f). One-year outcomes showed shallow probing depths and almost complete resolution of the defect (g, h).

the minimal flap elevation allows for preservation of most of the vessels providing the blood supply to the interdental tissues, with obvious advantages for the healing process of the interdental wound. This surgical approach with its novel design ensures self-support to the interdentally soft tissues through the "hanging" papilla, thereby enhancing space provision. The flap is extremely stable since most of the soft tissue around the bony defect is not incised or elevated, thereby enhancing blood clot stability. Minimal flap trauma, integrity of the blood supply, and absolute passivity in the suturing technique ensures primary closure of the interdental wound in the majority of the cases, thereby preventing bacterial contamination. The suturing approach is based on the use of a single internal modified mattress suture. Additional sutures can be applied to further increase primary closure, when needed. The reduced buccal access, however, means this approach is not applicable to very deep defects that involve the lingual side of a tooth for which the diseased root surface is not easily accessible for instrumentation from the small buccal window (Cortellini & Tonetti 2009b).

Recently, a three-arm randomized controlled clinical trial was designed to compare the clinical efficacy of the M-MIST alone versus M-MIST combined with EMD and EMD plus bone mineral derived xenograph (BMDX), in the treatment of isolated, interdental intrabony defects (Cortellini & Tonetti 2011). The study was performed on 45 deep isolated intrabony defects accessed with the M-MIST and randomly assigned to three experimental groups: 15 to M-MIST alone, 15 to M-MIST + EMD, and 15 to M-MIST + EMD–BMDX (Fig. 38-30). The differences between baseline and 1 year were statistically significant in the three groups for PPD reduction (P >0.0001, student t-test) as well as CAL gain (P >0.0001). Comparisons between the three groups showed no statistically

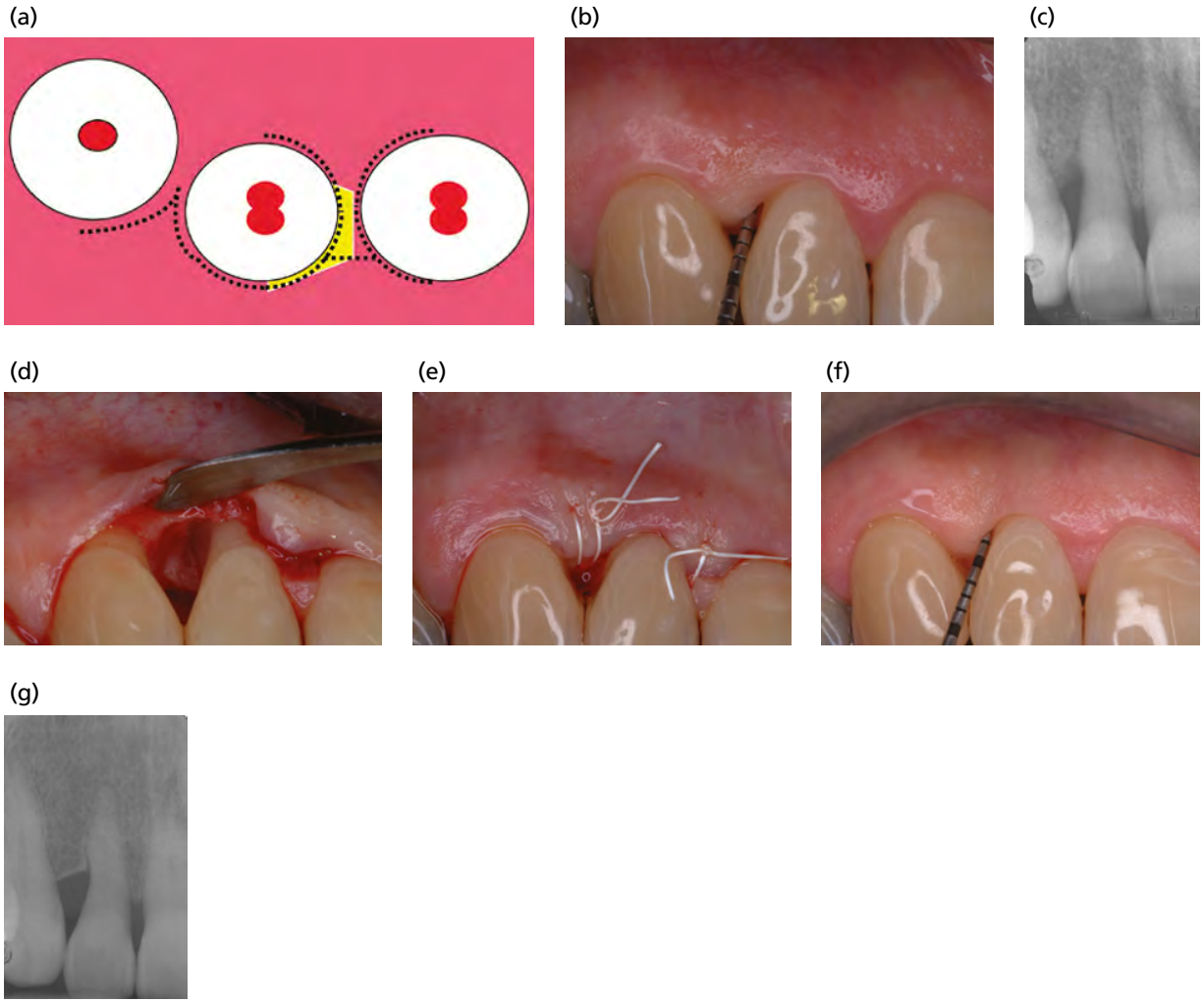


Fig. 38-26 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in an isolated interdental defect extending towards the buccal aspect of the tooth. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the interdental space associated with the defect. Mesiodistal extension of the flap was limited to the buccal aspect of the teeth adjacent to the defect and to the interdental aspect adjacent to the buccal extension of the defect in order to optimize wound stability (a). Following completion of successful initial cause-related therapy, a 6-mm pocket associated with an intrabony defect was detected on the distal aspect of the lateral incisor (b, c). The attachment loss extended to the buccal aspect of the lateral incisor, suggesting the need to obtain access to the buccal aspect of this tooth. The defect was therefore accessed with a minimally invasive approach using the MPPT to access the interdental area and extending the incision to the papilla between the lateral and central incisors to ensure adequate access to the defect (d). Primary closure was obtained with a modified internal mattress suture and a simple passing suture (e). One-year outcomes showed shallow probing depths, good preservation of the soft tissue heights, and resolution of the defect (f, g).

significant difference in any of the measured clinical outcomes. In particular, CAL gain of 4.1 ± 1.4 mm was observed in the M-MIST control group, 4.1 ± 1.2 mm in the EMD group, and 3.7 ± 1.3 mm in the EMD + BMDX group. The percentage radiographic bone fills of the intrabony component were 77 ± 19%, 71 ± 18%, and 78 ± 27%, respectively. This initial controlled study could detect a true difference in CAL of 0.96 mm between the treatment groups. However, the fact that the outcomes among the three groups could not be discriminated raises a series of hypotheses that focus on the intrinsic healing potential of a wound when ideal conditions are provided with the surgical approach. In other words, the outcomes of this study lay down the challenge to clinicians of possibly achieving substantial clinical improvements without the use of products or materials. An independent study (Trombelli *et al*. 2010) reported similar outcomes with no difference between a single flap approach (SFA) alone and SFA plus a bioresorbable barrier and hydroxyapatite. The study was conducted on 24 patients/defects. Authors reported five sites in the SFA + HA/GTR group showing incomplete closure at week 2, which resolved spontaneously. There were no statistically significant or clinically meaningful differences in mean (+/− SD) clinical attachment gain (4.7 +/−2.5 versus 4.4 +/− 1.5 mm), probing depth reduction (5.3 +/−2.4 versus 5.3 +/−1.5 mm), and gingival recession increase (0.4 +/−1.4 versus 0.8 +/−0.8 mm) between the SFA + HA/GTR and SFA groups. Mishra *et al*. (2013) evaluated the efficacy of the M-MIST alone versus M-MIST with local delivery of rhPDGF-BB gel in the treatment of 24 intrabony defects. Gain in CAL and

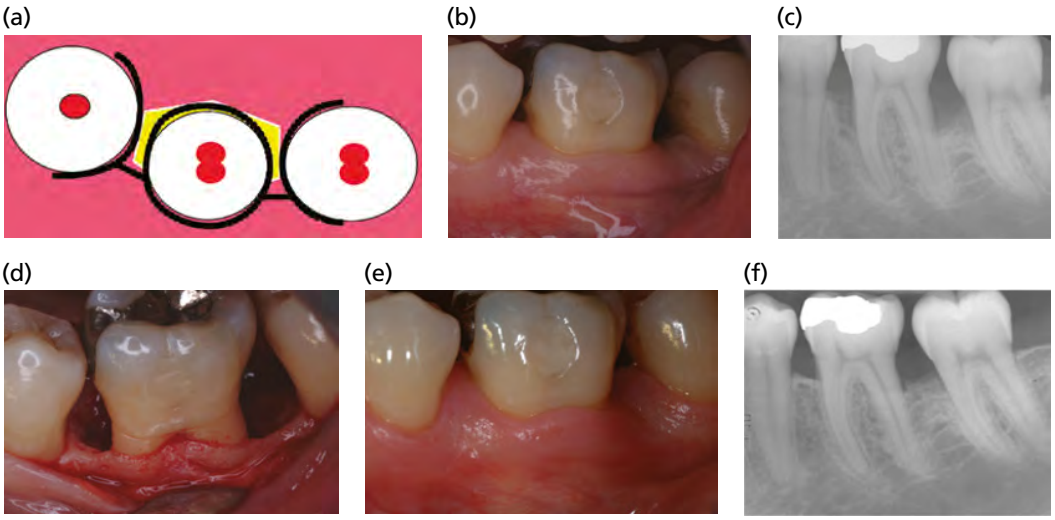


Fig. 38-27 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in intrabony defects involving both interdental spaces of the same tooth. The schematic diagram shows the extent of the incision performed according to the principles of the modified papilla preservation technique (MPPT) in the two interdental spaces associated with the defects. Mesiodistal extension of the flap was limited to the two interdental papillae associated with the defects (a) and reached the line angle of the two adjacent teeth in order to limit the loss of wound stability, while allowing adequate access to the defects. The clinical and radiographic appearance at baseline highlighted the good control of inflammation obtained following completion of initial cause-related therapy and the presence of deep mesial and distal pockets with associated intrabony defects (b, c). Both the mesial and distal defects were accessed with papilla preservation flaps, the defects were debrided, and the root surfaces were carefully instrumented (d). Following application of enamel matrix derivatives in the well-contained defects, primary closure of the flap was achieved by modified internal mattress sutures. At 1-year follow-up, shallow pockets, preservation of soft tissues, and elimination of the defects were apparent (e, f).

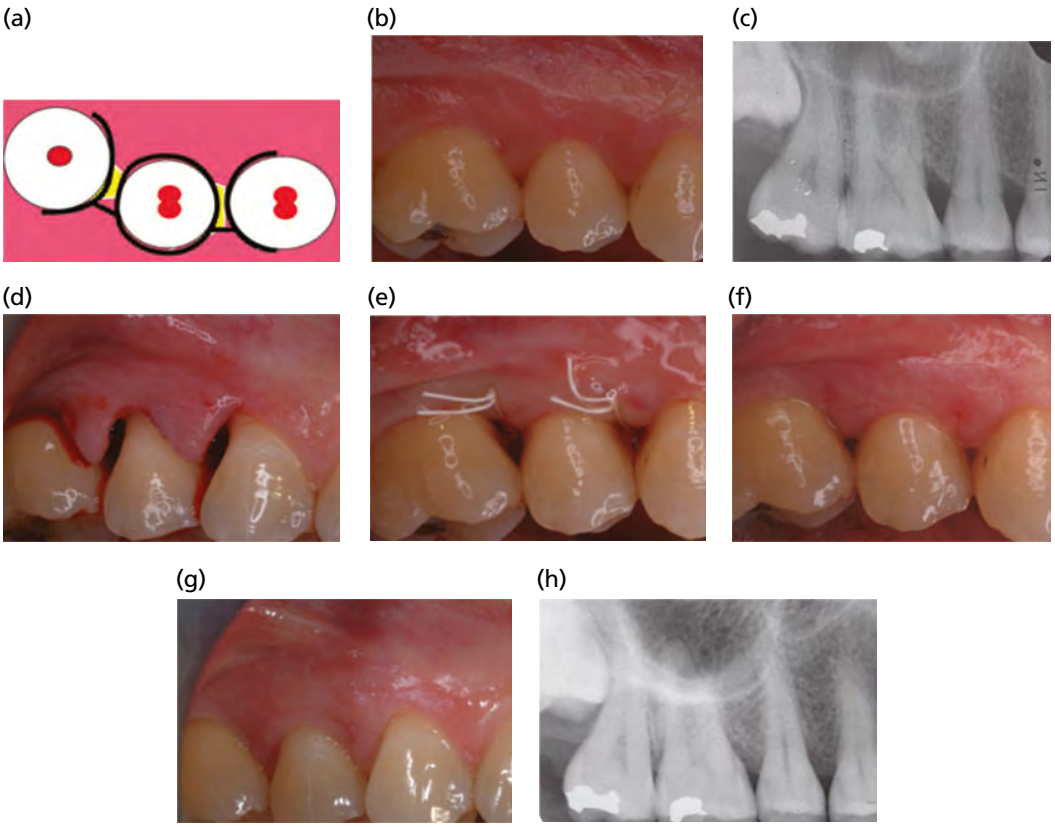


Fig. 38-28 Clinical illustration of the use of the minimally invasive surgical technique (MIST) in intrabony defects involving two adjacent teeth. The schematic diagram shows the extent of the incision performed according to the principles of the papilla preservation flaps in the two interdental spaces associated with the defects. Mesiodistal extension of the flap was limited to the two interdental papillae associated with the defects (a) and reached the line angle of the two adjacent teeth in order to limit the loss of wound stability and to limit flap extension. After successful initial cause-related therapy, two defects were present on the mesial aspect of the first molar and second premolar (b, c). Simplified papilla preservation flaps (SPPF) were used to access the defects (d). Incisions were stopped at the distal line angle of the first premolar and on the buccal aspect of the first molar. Root debridement and application of enamel matrix proteins in gel form were performed before primary closure of the flap with two modified internal vertical mattress sutures (e). Excellent early healing in the absence of pain or discomfort was evident at the 1-week suture removal (f). At 1-year follow-up, absence of inflammation, shallow probing depths, and resolution of the defects were evident (g, h).

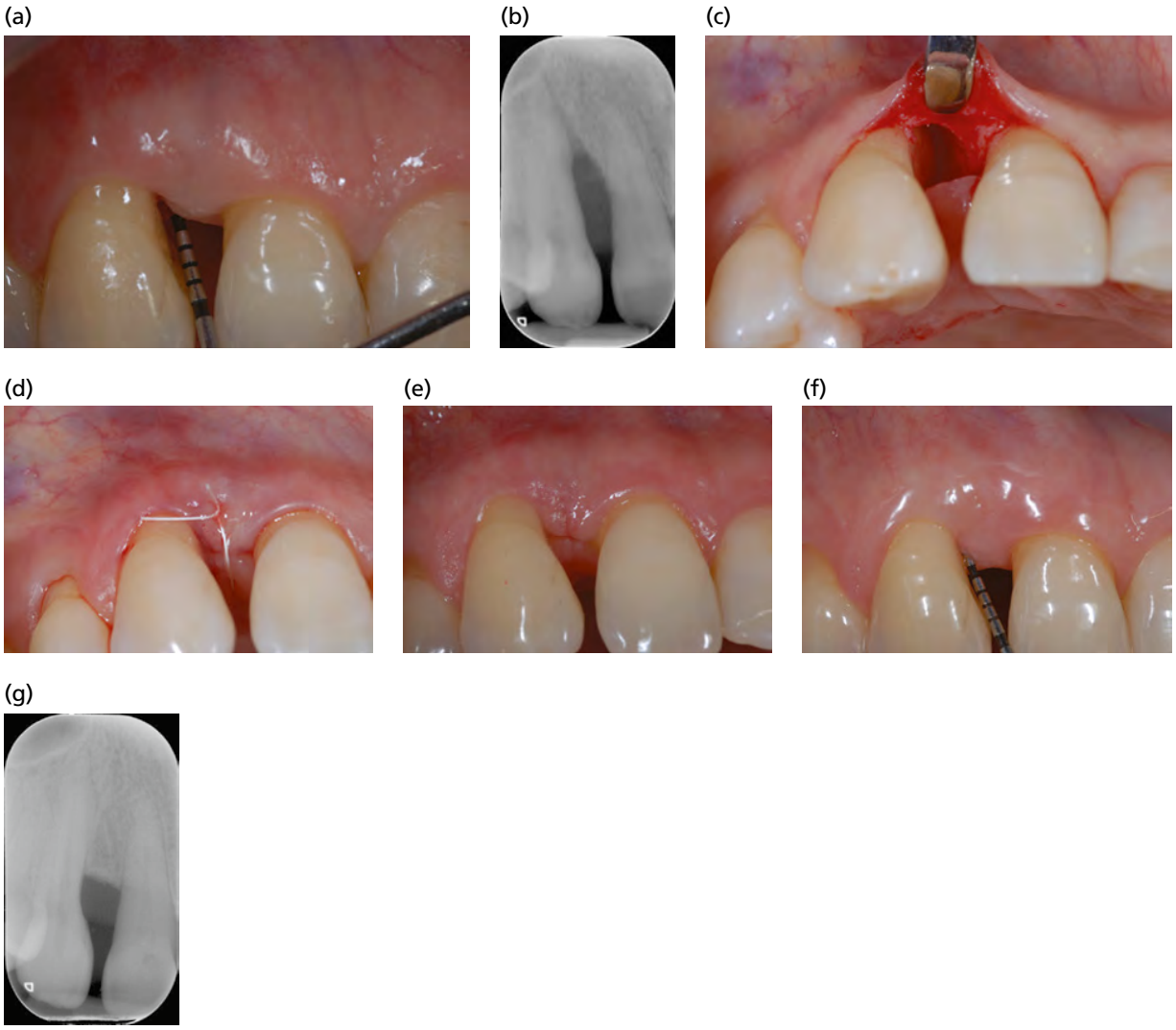


Fig. 38-29 Clinical case treated with the modified minimally invasive procedure (M-MIST). A 10-mm pocket mesial to the upper right cuspid (a) was associated with a deep intrabony defect reaching the mid third of the root (b). The area was accessed with the M-MIST procedure (c). The buccal flap was minimally elevated to the mid-buccal contour of the cuspid and the lateral incisor. The defect-associated interdental papilla was left untouched and the lingual flap was not elevated. The intrabony defect and the exposed root surface were instrumented through the small buccal surgical "window". A single modified internal mattress suture was positioned to close the area (d). No regenerative material was placed into the defect, leaving the natural blood clot alone to fill the intrabony component. Integrity of the primary closure of the wound was maintained after 1 week (e). One-year clinical photograph showed a 3-mm normal sulcus, associated with a 7-mm clinical attachment gain and no increase in gingival recession (f). One-year radiograph showed the complete resolution of the intrabony component of the defect (g).

linear bone growth was 3 ± 0.89 mm and 1.89 ± 0.6 mm in test group and 2.64 ± 0.67 mm and 1.85 ± 1.18 mm in control group, respectively, and did not show statistical significance. Authors concluded that the improvement in both groups could be attributed to the novel surgical technique rather than addition of rhPDGF-BB.

In a recent study, Schincaglia *et al*. (2015) reported similar clinical outcomes when treating intrabony defects with a flap based on the elevation of the defect associated papilla versus a flap designed to keep the papilla in place (SFA). The regenerative material applied was rhPDGF-BB and β-TCP. A recent systematic review on MIS applied to intrabony defects (Barbato *et al*. 2020) concluded that MIS represents a reliable treatment for isolated intrabony defect. Another meta-analysis (Liu *et al*. 2016) suggested no significant difference in treatment of intrabony defects between the MIS plus biomaterials group and the MIS alone group, indicating that it is important to take costs and benefits into consideration when a decision is made about a therapeutic approach.

Entire Papilla Preservation Technique (EPP)

Recently, a novel technique, the entire papilla preservation technique (EPP) has been proposed (Aslan *et al*. 2017a, b) for treatment of isolated intrabony defects. The EPP technique is a tunnel-like approach of the defect-associated interdental papilla (Fig 38-31). Following a buccal intracrevicular incision, a bevelled vertical releasing incision is performed in the buccal gingiva of the neighbouring interdental space and extended just beyond the mucogingival line to provide appropriate mechanical

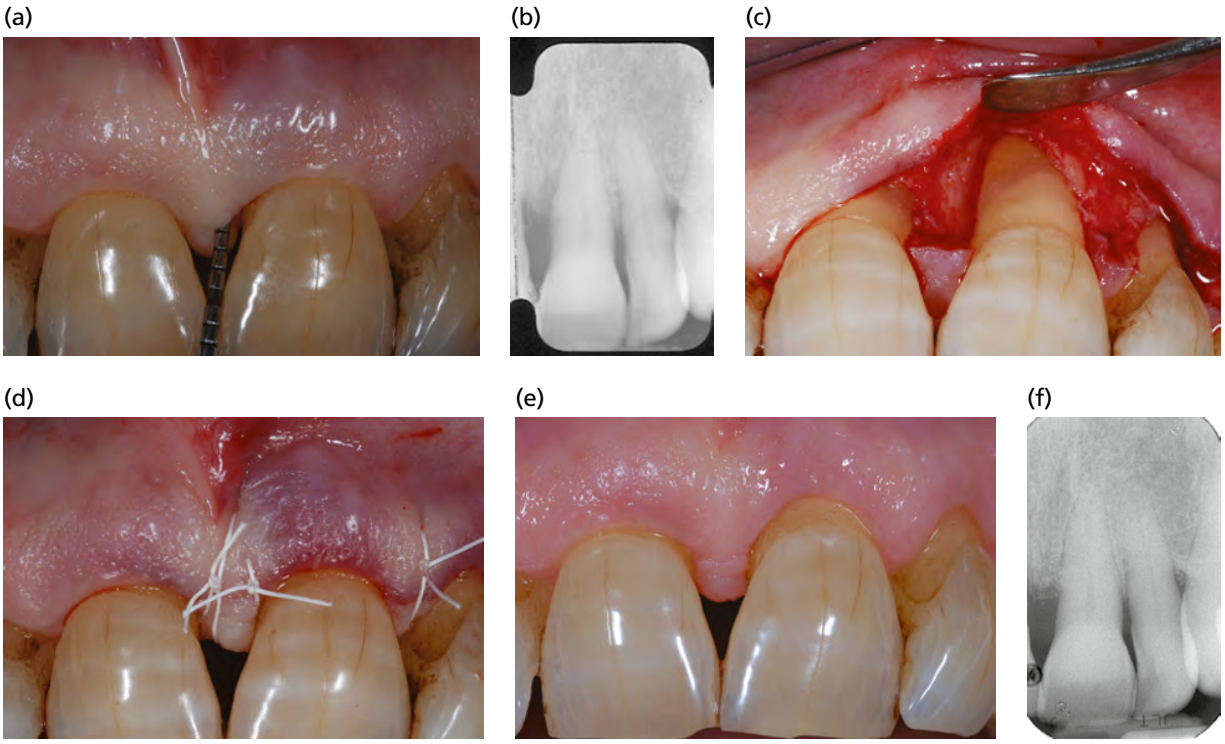


Fig. 38-30 Clinical case treated with the modified minimally invasive procedure (M-MIST) + enamel matrix derivatives (EMDs) + Bio-Oss®. A 7-mm attachment loss was associated with a 6-mm pocket depth at the mesial side of the left upper central incisor (a). The intrabony defect was evident on the baseline radiograph (b). The area was accessed with the M-MIST approach. The flap was extended to the distal interdental space to uncover the buccal bone dehiscence (c). The flap was sutured after positioning of EMDs and grafting material (d). Clinical photograph (e) and radiograph (f) at 1 year showed the resolution of the periodontal lesion.

access to the intrabony defect. A microsurgical periosteal elevator is used to elevate a buccal full-thickness mucoperiosteal flap extending from the vertical incision to the defect-associated papilla. A specifically designed angled tunnel elevator facilitates the interdental tunnel preparation under the papillary tissue. Utmost care is taken to elevate the full thickness of the interdental papilla up to the intact lingual bone crest. Granulation tissue is removed from the inner aspect of the defect-associated interdental papilla. Excessive thinning of the papilla must be avoided to avoid compromising the blood supply. The granulation tissue is then removed with a mini-curette and the root surface debrided and planed. Regenerative materials like EMD and/or bone substitutes can be placed into the intrabony defect. A collagen barrier can be utilized to contain the biomaterial. Sutures are applied for optimal wound closure of the surgical area. A recent RCT (Aslan *et al*. 2020) on 30 patients compared the EPP alone versus EPP and amelogenins. The authors reported 100% primary closure of the flap maintained through the early wound healing; a highly significant CAL gain of 6.3 ± 2.5 mm and PD reduction of 6.5 ± 2.65 mm was observed in the EPP + EMD group, while CAL gain and PD reduction were 5.83 ± 1.12 mm and 6.2 ± 1.33 mm, respectively in the EPP group. A slight statistically not significant increase in gingival recession of 0.2 ± 0.25 mm and 0.36 ± 0.54 mm was reported. EPP is an advanced flap procedure, based on the concepts of microsurgery and MIS, that requires competence and surgical skills and cannot be extended to any intrabony defect. The application of EPP is indicated in isolated interproximal intrabony defects. The ample involvement of the palatal side of a tooth makes this approach not applicable. It is a matter of fact that a 2-wall intrabony defect with a missing buccal bony wall and a relatively well-preserved lingual wall is the best indication for EPP.

Technical implications

The studies cited in the previous section propose three different minimally invasive approaches to intrabony defects (Cortellini 2012). The MIS (Harrel & Rees1995) and the MIST (Cortellini & Tonetti 2007a, b) include the elevation of the interdental papillary tissues to uncover the interdental space, gaining complete access to the intrabony defect; the M-MIST (Cortellini & Tonetti 2009a) in which the access to the defect is gained through the reflection of a small buccal flap, without elevation of the interdental papilla (Figs. 38-27, 38-28, 38-29, 38-30); the EPP that is based on a tunnel-like approach with no incision of the interdental papilla (Aslan *et al*. 2017a). The major problem to be overcome when applying MIS is the visibility and manipulation of the surgical field. This issue is clearly enhanced in the M-MIST and EPP approaches. High magnification and direct optimal illumination can help in solving the problem. Thereby, the adoption of magnifying devices, like loops or operating microscopes, are strongly recommended. Traditionally, dental surgeons are taught

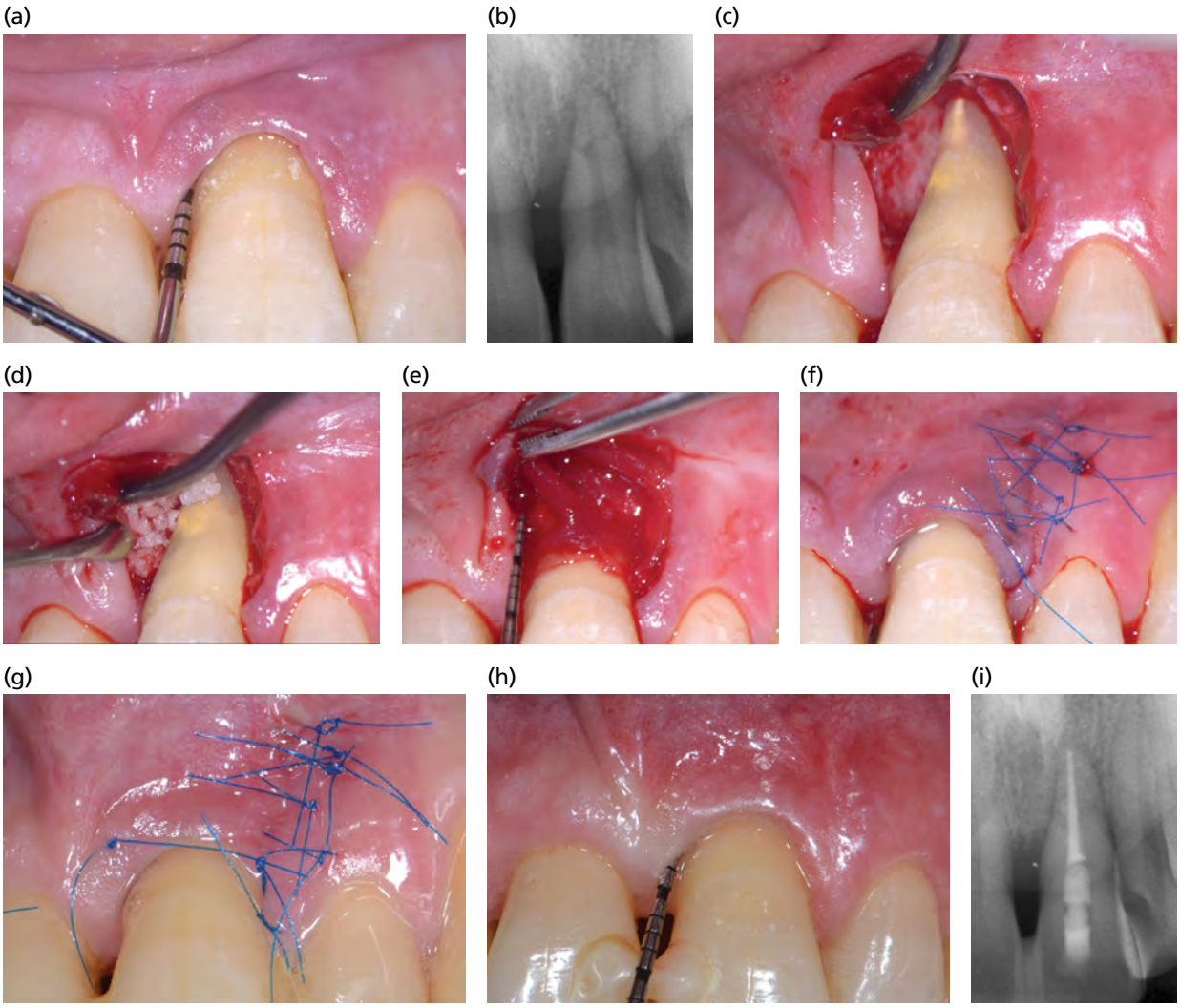


Fig. 38-31 Clinical case treated with the entire papilla preservation technique (EPP). Probing depth of 10 mm, with a 13 mm clinical attachment level (CAL) (a) is associated with bone destruction involving the apex (b). Access to the defect using the EPP technique by avoiding an incision over the defect-associated papilla (c). Note the osseous defect involving the apex. Application of bone substitutes to fill the defect (d). Application of a collagen membrane to cover the defect (e). Primary wound closure is obtained with microsurgical suturing technique (f). Primary closure maintained 7 days postoperatively, when sutures are removed (g). Clinical condition at 1-year examination. The probe indicates a 3 mm residual probing depth and 7 mm CAL gain (h), associated with the mineralization of the intrabony component of the defect (i). (Source: Courtesy Dr. Serhat Aslan.)

to raise large flaps to completely expose the area of interest. In reality, visibility of the defect is restricted by the residual bony walls that surround the defect. The elevation of a flap to the edge of the residual bony walls should therefore be sufficient to visualize the defect: over-reflection of the flaps does not increase defect visibility. However, the minimal flap reflection narrows the angle of vision and especially the light penetration into the surgical field. In addition, the soft tissue manipulation during instrumentation requires more care since the flaps, which are not fully reflected, lie very close to the working field. Use of small instruments, like small periosteal elevators and tiny tissue players, is mandatory for soft and hard tissue manipulation. Microblades, mini- or microcurettes, and miniscissors allow for full control over the incision, debridement, and refinement of the surgical area, and sutures from 6-0 to 8-0 are mandatory for wound closure.

Flap design for furcation involvement

Flap design for buccal and lingual mandibular and buccal maxillary class II furcations, the so-called "key hole", were described more than 20 years ago and have not been substantially modified since (Pontoriero *et al*. 1988; Andersson *et al*. 1994; Jepsen *et al*. 2004). Following intrasulcular incisions, a mucoperiosteal flap is raised at the buccal or lingual aspect of the alveolar process (Fig. 38-32). The root surfaces are carefully scaled and planed using hand and power-driven instruments and rotating, flame-shaped diamond burs. Remaining granulation tissue in the furcation area is carefully removed to expose the surface of the alveolar bone.

The regenerative material of choice (a non-bioresorbable or a bioresorbable barrier, a bone graft, a biologically active agent, or a combination approach) is positioned at the furcation area (Fig. 38-33). When

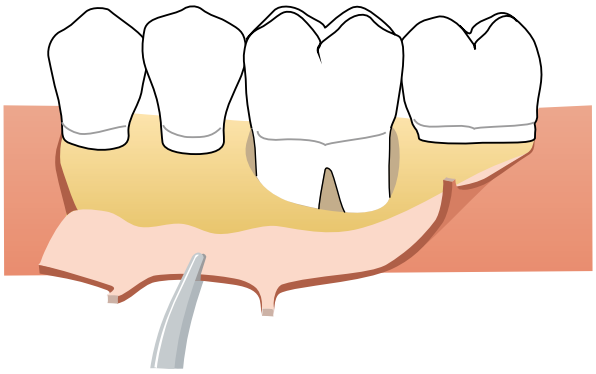


Fig. 38-32 Furcation involvement: step-by-step approach. Following marginal incisions and vertical releasing incisions on the buccal aspect of the jaw, buccal and lingual full-thickness flaps are elevated.

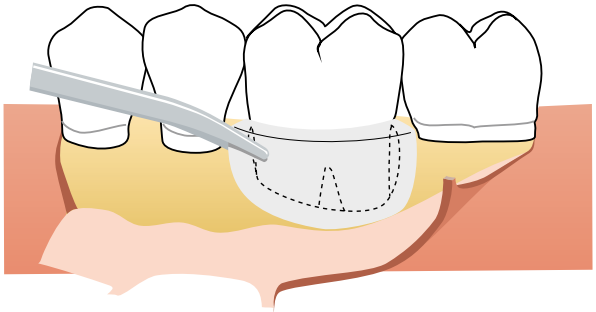


Fig. 38-33 Furcation involvement: step-by-step approach. The barrier material is placed in such a way that it completely covers the defect and extends over at least 3 mm of bone beyond the defect margin.

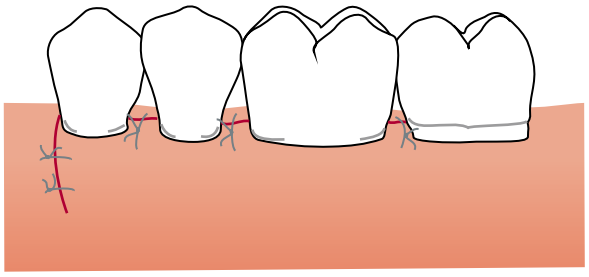


Fig. 38-34 Furcation involvement: step-by-step approach. The elevated tissue flaps are coronally displaced and sutured in such a way that the border of the barrier material is at least 2 mm below the flap margin.

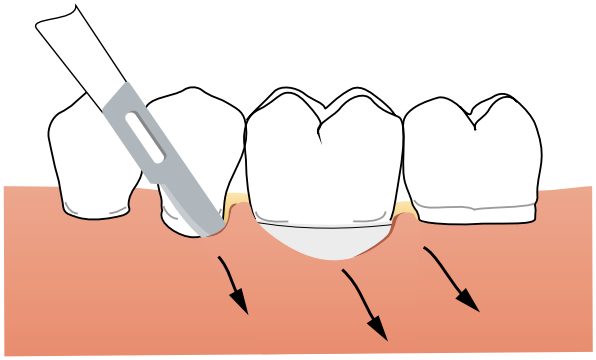


Fig. 38-35 Furcation involvement: step-by-step approach. In order to remove the barrier material, an incision is made extending one tooth mesially and distally to the border of the barrier. After reflecting the covering tissue flaps, the barrier can be removed without compromising the newly regenerated tissue.

a barrier is used, it is adjusted to cover the entrance (buccal or lingual) of the furcation area, the adjacent root surfaces (from the distobuccal/lingual line angle of the distal root to the mesiobuccal/lingual line angle of the mesial root), and a 4–5-mm wide surface of the alveolar bone apical to the bone crest. The membrane can be retained in position by sutures placed around the crown of the molar using a sling technique. When a graft is preferred, it is positioned to completely fill the furcation area and slightly overfill the entrance. Biologically active agents are delivered into the furcation area. A combination approach requires the positioning of different biomaterials according to the properties of each material.

Following placement of the regenerative material, the mucoperiosteal flap is repositioned to completely cover the furcation and the biomaterials (Fig. 38-34). A periosteal incision can be made, when needed, to coronally advance the flap. The flap is secured with interdental or sling sutures. The sutures are removed 7–15 days after surgery. When a non-bioresorbable barrier is positioned, a second surgical procedure to remove the barrier is performed after a healing period of about 6 weeks (Fig. 38-35).

The surgical technique has been carefully refined and revised by McClain and Schallhorn (2000). Their surgical technique is especially designed for combination therapy (barrier plus grafting material) and is based on a common core, modified as necessary for specific situations. This common core employs a sulcular incision full-thickness envelope flap with maximum retention of gingival and papillary tissues and sufficient exposure of the defect for adequate visualization and access for debridement. If recession has occurred and/or coronal flap positioning is required for membrane coverage, periosteal separation is also performed.

The defect is debrided and the root surface planed to remove plaque, accretions, enamel projections, and other root surface alterations (grooves, notches, caries, etc.) employing ultrasonic or sonic, hand and rotary (fine diamond and/or finishing burs) instrumentation. Odontoplasty and/or osteoplasty are performed if required for adequate access to the defect, including intraradicular or furcation fundus concavities, and/or for reduction of enamel projections. Adequate root preparation is considered critical to a successful outcome.

The bone graft is prepared (typically by DFDBA) in a dappen dish with hydration with sterile saline or local anesthetic solution and, if there is no contraindication, combined with tetracycline (125 mg/0.25 g of DFDBA). After mixing, the dappen dish is covered with a sterile, moistened gauze to prevent drying of the graft. The appropriate membrane is selected and trimmed to fit into the desired position, and then placed on sterile gauze. Care is taken to prevent

membrane contamination via contact with the lips, tongue, mucosa, or saliva.

The area is thoroughly cleansed and isolated, and the root surface at the regenerative site is treated with citric acid (pH 1) for 3 minutes using cotton pellets, with care taken to contain the solution to the root and bone surface. The pellets are removed and the site inspected for any residual cotton fibers prior to flushing it with sterile water or saline. Intramarrow penetration is then performed with a 1/4 round bur if a sclerotic bone surface exists in the graft site. The ligament surface is "scraped" with a periodontal probe to remove any eschar and to stimulate bleeding, and the DFDBA is packed firmly into the defect using an overfill approach, along with covering the root trunk and combination or confluent intrabony, dehiscence or horizontal/crestal osseous defects. The custom-made membrane is placed over the graft and secured as appropriate. After rechecking to be sure adequate graft material remains in the desired area, the flap is positioned to cover the membrane and secured with non-bioresorbable sutures (typically Gore sutures). Throughout the root conditioning and subsequent treatment to closure, the site remains isolated to avoid saliva contamination.

If a non-bioresorbable membrane is used, it is removed at 6–8 weeks postoperatively by employing minor flap reflection, de-epithelialization of the internal aspect of the flap adjacent to the membrane, gentle removal (peeling) of the membrane outward from the site, and flap positioning to cover the regenerated tissues as feasible. Closure with sutures is then accomplished with non-bioresorbable sutures.

Flap design for combined furcation and intrabony defects

Compromised molars are frequently characterized by the presence of deep pockets and by a pattern of periodontal breakdown that involves both apical and interradicular spread of attachment and bone loss. The anatomy of bone destruction, thereby, can result in a combination of horizontal breakdown in the furcation area and vertical breakdown around the single roots. The vertical extension of the periodontal breakdown seems to be an important predictor of survival of teeth with furcation involvement (Tonetti *et al*. 2017). Clinical studies have demonstrated the potential for clinical improvements of both the horizontal and vertical furcation components, reporting encouraging results (Jepsen *et al*. 2002). The peculiar anatomy of a combined furcation and intrabony defect requires a surgical approach which is different with respect to the traditional buccal or lingual flap for a key-hole defect. Cortellini *et al*. (2020a) proposed the application of papilla preservation flaps (PPF) following the positive experience with regeneration of intrabony components. The design of PPF is selected upon the width of the interdental space. A horizontal incision according to the principles of the MPPT (Cortellini *et al*. 1995d) is traced at the buccal aspect of the defect-associated papilla when the width of the interdental space is greater than 2 mm, while a diagonal incision is applied when the interdental space is 2 mm or narrower (SPPF; Cortellini *et al*. 1999). Flaps are designed to obtain adequate access to the defect limiting as much as possible flap extension and thus preserving optimal wound stability according to the concepts of MIS, as previously described for intrabony defects (Cortellini 2012) and as exemplified in Figs. 38-36 and 38-37. In particular, the choice of how far to extend the flap in a mesiodistal and buccolingual direction is dependent upon the anatomy of the combined bony and furcation defect. Whenever possible, only the full thickness buccal flap is elevated (M-MIST; Cortellini & Tonetti 2009b) and the defect/furcation debrided through the buccal window. When the defect extends toward the oral aspect of the tooth, the preserved papilla is elevated along with the full thickness lingual flap (MIST, MIS; Cortellini & Tonetti 2007a). The full thickness flaps are elevated to expose the crest of bone surrounding the intrabony defect and to gain access to the involved interradicular space. Vertical releasing incisions are traced only when needed to gain access. Defects and furcation area are thoroughly debrided with a combination of microcurettes and fine sonic tips. In the presence of furrows, the roof of the furcation is further instrumented with the aid of diamond tips mounted on a sonic device. Cleanliness of the furcation roof is carefully inspected at ×30 magnification with the aid of micromirrors. The exposed root surfaces can be treated with the application of EDTA gel for 2 minutes then carefully rinsed with sterile water. A single modified internal mattress suture (6-0 or 7-0 e-PTFE) is applied at the preserved papilla and left loose to keep the flaps reflected. EMD and/or bone substitutes can be applied in the defects and the sutures tightened to obtain passive primary closure of the flaps

A pilot study on 49 subjects with furcated molars and deep intrabony defects showed that significant clinical improvements can be achieved by applying periodontal regeneration in both maxillary and mandibular molars (Cortellini *et al*. 2020a). The benefits included improvement in vertical CALs, decrease in PPDs, and improvements in horizontal and vertical furcation involvement. These surrogate outcomes also translated into excellent tooth retention observed during the follow-up period. At 1 year, 100% of maxillary and 92% of mandibular molars showed improvements. Improvements were not observed in molars with baseline hypermobility: two mandibular molars with hypermobility were extracted at the 1-year follow up. Improvement in the vertical component was observed in 87.5% of maxillary and in 84.6% of mandibular molars. One-year improvements could be maintained over the 3–16-year follow-up. These results were obtained in cases with an interdental peak of bone coronal to the furcation roof

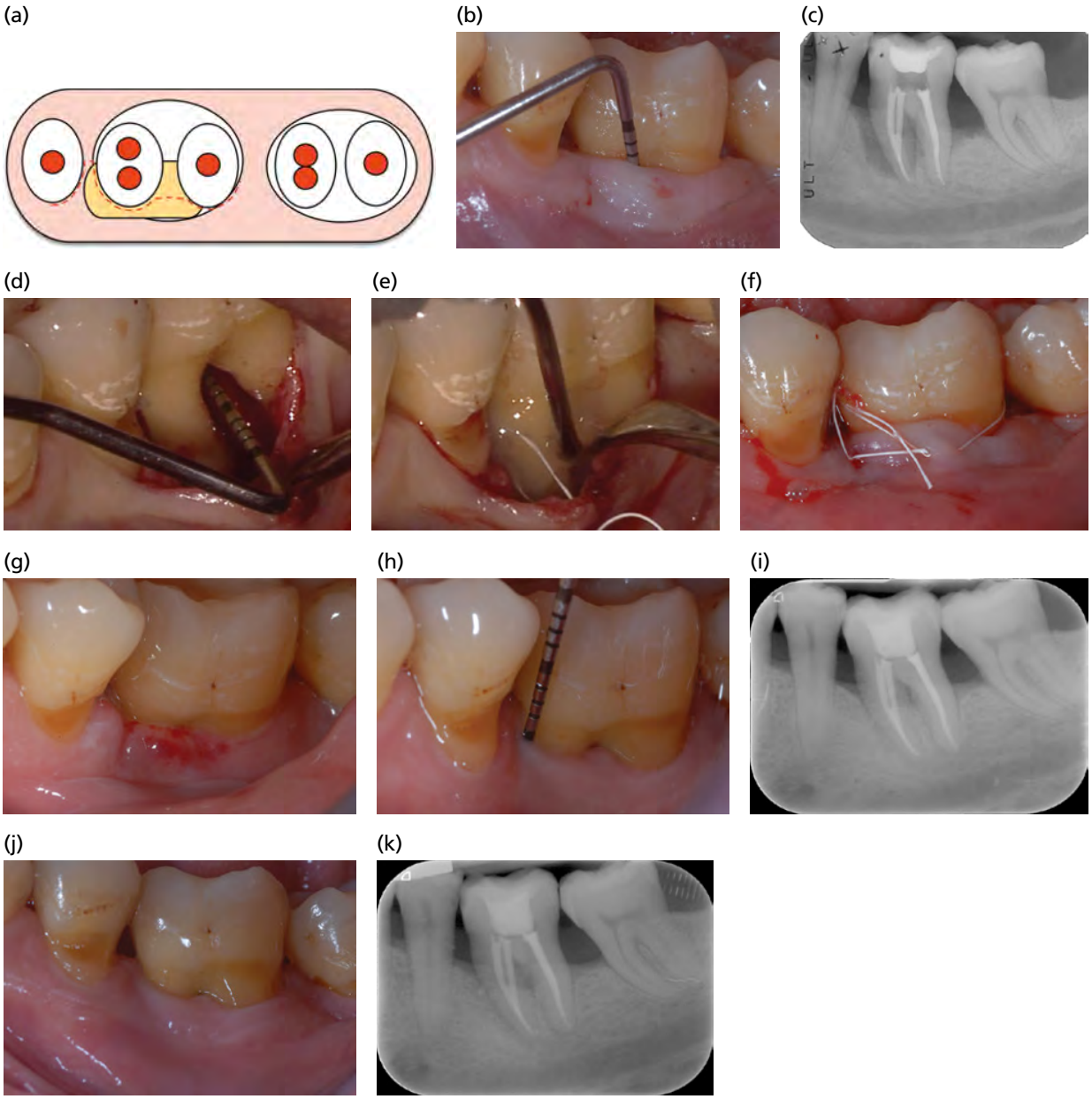


Fig. 38-36 Clinical illustration of the use of papilla preservation flap (PPF) and modified minimally invasive surgical technique (M-MIST) in a case presenting with a combined deep class II buccal furcation and intrabony defect involving the lower left first molar. The schematic diagram (a) shows the extent of the incision involving the mesial interdental space associated with the defects and the elevation of the sole buccal flap. Distal extension of the flap was limited to the buccal side of the distal root of the molar. A 12 mm pocket was detected before surgery (b) associated with a deep intrabony defect and a deep class II furcation (c, d). EMD was delivered on the debrided root surface (e) and the flap was closed with an internal mattress modified suture (f). One week after surgery, sutures were removed; primary intention closure of the wound was maintained (g). At 1 year a 4 mm probing depth and a class I shallow furcation involvement was detected (h, i). The clinical outcomes are maintained at 5-year follow up (j, k)

and gingival margin coronal to the furcation entrance in well-maintained and compliant subjects.

Postoperative regimen

The postoperative regimen prescribed to the patients is aimed at controlling wound infection or contamination as well as mechanical trauma to the treated sites. A meta-analysis indicated that differences in regenerative outcomes can be expected based on the postoperative care protocol: more frequent, intensive regimens were associated with better CAL gain in intrabony defects (Murphy & Gunsolley 2003) (Fig. 38-38). It generally includes the prescription of systemic antibiotics (doxycycline or amoxicillin) in the immediate postoperative period (1 week), 0.2 or 0.12% chlorhexidine mouth rinsing b.i.d. or t.i.d., and weekly professional tooth cleaning until the membrane is in place. Professional tooth cleaning consists of supragingival prophylaxis with a rubber cup and chlorhexidine gel. Patients are generally advised not to perform mechanical oral hygiene and not to chew in the treated area.

Non-bioresorbable membranes are removed 4–6 weeks after placement, following elevation of partial-thickness flaps. Patients are re-instructed to

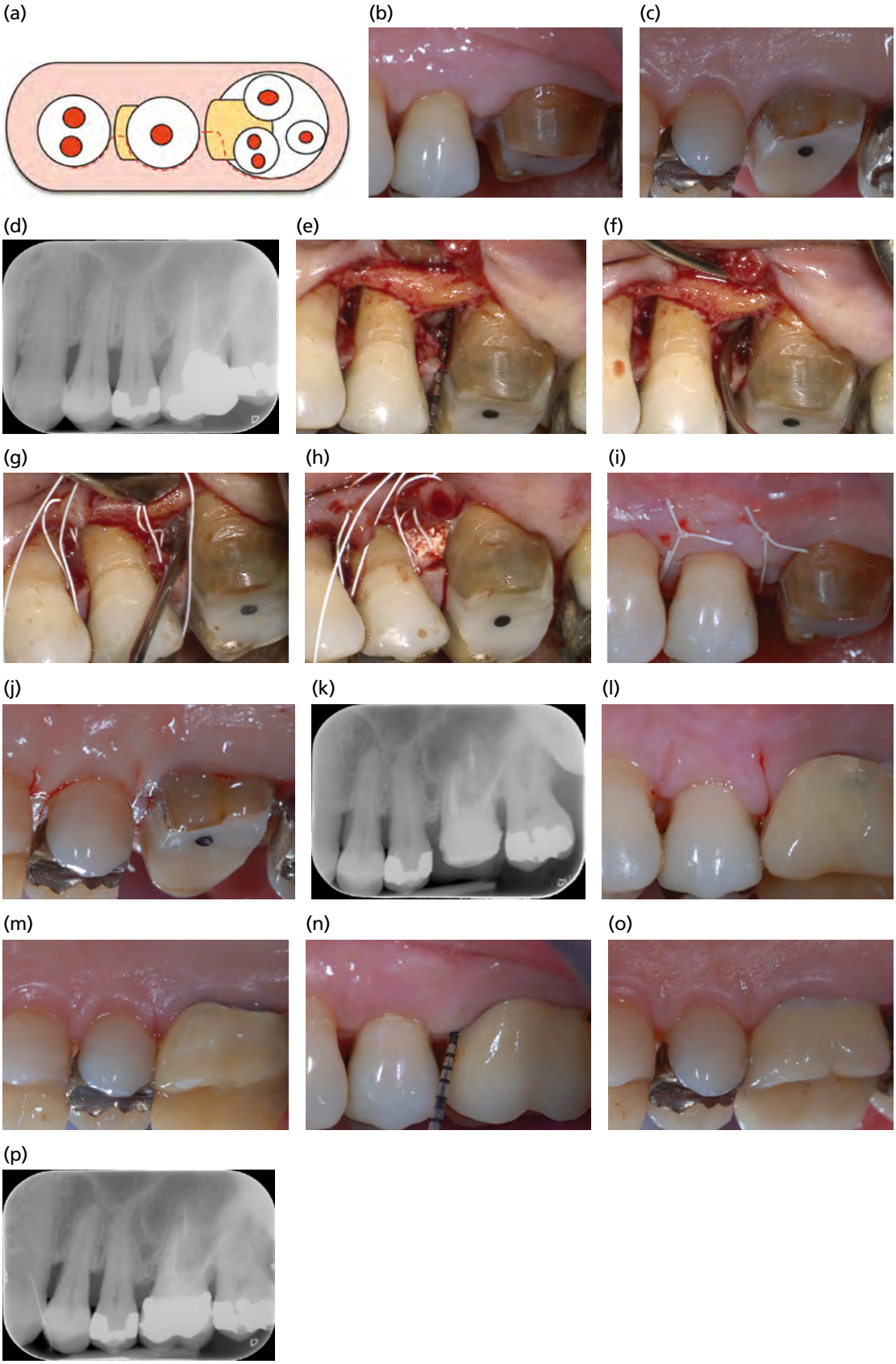
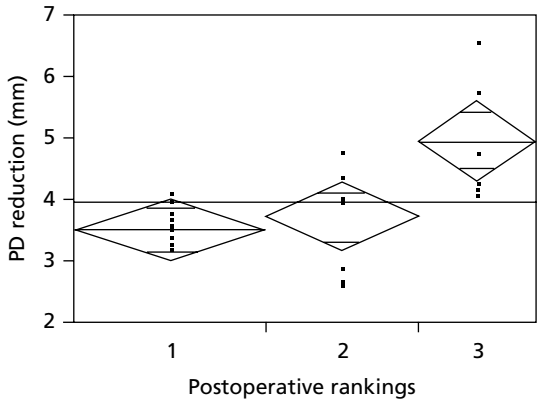


Fig. 38-37 Clinical illustration of the use of papilla preservation flap (PPF) and modifiedminimally invasive surgical technique (M-MIST) in a case presenting with a combined deep class II buccal furcation and intrabony defect involving the upper left first molar. In this case an intrabony defect was present on the second premolar. The schematic diagram (a) shows the extent of the incision involving the interdental space mesial to the premolar and the one between the bicuspid and the molar. In this case, the flap was elevated only on the buccal side. Preoperative images of the surgical area (b, c) and the radiograph (d) showing the intrabony defects mesial to the premolar and the molar. A 5 mm intrabony defect and a class II furcation are evident at the mesial side of the molar (e, f). Enamel matrix derivatives (g) and bovine bone mineral (h) were delivered into the defect area (e) and the flap was closed with internal mattress modified sutures (i, j). Postoperative radiograph showing the biomaterial in place (k). One week after surgery sutures were removed; primary intention closure of the wound was maintained (l, m). At 1 year, a 4 mm probing depth and no furcation involvement was detected (n, o). The 1-year radiograph shows the mineralization of the defects (p).



Rank	Number of studies	Mean
1	10	3.52
2	8	3.73
3	6	4.97

Source	DF	Sum of squares	Mean square	F ratio	Prob F
Post-op rank	2	8.45	4.22	7.21	0.004
Error	21	12.29	0.58		
C. Total	23	20.75			

Fig. 38-38 Regression analysis of intrabony defect studies examining the relationship between postoperative care protocol ranking and the reduction (in mm) in probing depth (PD). Group 3 is statistically different from groups 1 and 2. (Source: Murphy & Gunsolley 2003. Reproduced with permission from John Wiley & Sons.)

rinse b.i.d. or t.i.d. with chlorhexidine, not to perform mechanical oral hygiene, and not to chew in the treated area for 3–4 weeks. In this period, weekly professional control and prophylaxis are recommended. When bioresorbable membrane, BRG, or biologically active regenerative materials are used, the period of tight infection control is extended for 6–8 weeks. After this period, patients are re-instructed to resume mechanical oral hygiene gradually, including interdental cleaning, and to discontinue chlorhexidine. Patients are then enrolled in a monthly periodontal care program for 1 year. Probing or deep scaling in the treated area is generally avoided before the 1-year follow-up visit.

Postoperative period and local side effects

From the very beginning of the "guided tissue regeneration era", the frequent occurrence of complications, in particular barrier exposure, was apparent. Complications occurred in almost 100% of the cases in the prepapilla preservation techniques period (Becker *et al*. 1988; Cortellini *et al*. 1990, 1993a, b; Selvig *et al*. 1992; Falk *et al*. 1997; Trombelli *et al*. 1997; Murphy 1995a, b; Mayfield *et al*. 1998) but negative occurrences reportedly reduced to amounts ranging from 50% to 6% when PPF were adopted (Cortellini *et al*. 1995a, c, 1996b, 1999a, 2001; Tonetti *et al*. 1998, 2002, 2004a; Cortellini & Tonetti 2000a, 2005; Machtei 2001; Murphy & Gunsolley 2003). A consistent decrease of complications was observed when barriers were not incorporated into the surgical procedure. In particular, the adoption of EMDs largely reduced the prevalence of complications (Tonetti *et al*. 2002; Sanz *et al*. 2004; Esposito *et al*. 2009). Sanz *et al*. (2004) showed that all sites treated with membranes showed at least one surgical complication during healing, while a complication was observed in only 6% of sites treated with EMDs. This study indicates that some regenerative materials/procedures may be less technique-sensitive than others.

The development of MIS has greatly reduced the amount of complications and side effects in the postoperative period. Primary closure of the flap was reported in 100% of cases treated with MIST and was maintained in single sites in 95% of cases at 1 week (Cortellini & Tonetti 2007a, b) and in multiple sites in 100% of cases (Cortellini *et al*. 2008). Edema was noted in few cases (Cortellini and Tonetti 2007a, b; Cortellini *et al*. 2008). No postsurgical hematoma, suppuration, flap dehiscence, presence of granulation tissue, or other complications were reported in any of the treated sites (Cortellini & Tonetti 2007a, b; Cortellini *et al*. 2008). Root sensitivity was not a frequent occurrence: it was reported at 1 week by about 20% of the patients but this percentage rapidly decreased in the following weeks, with only one patient still reporting some root sensitivity at 6 weeks (Cortellini & Tonetti 2007b). Ribeiro *et al*. (2011a) reported that the extent of root hypersensitivity and edema was very discreet and no patients developed hematoma.

When applying M-MIST, Cortellini and Tonetti (2009b) reported primary closure obtained and maintained in 100% of cases. In a second controlled study (Cortellini & Tonetti 2011), one M-MIST/EMD/BMDX-treated site presented at suture removal (week 1) with a slight discontinuity of the interdental wound. At week 2, the gap appeared to have closed. No edema, hematoma or suppuration was noted in any of the treated sites in these studies (Cortellini & Tonetti 2009a, 2011).

Surgical and postsurgical morbidity

To date, little consideration has been given to critical elements that could contribute to the patient's assessment of the cost–benefit ratio of GTR procedures.

These include postoperative pain, discomfort, complications, and the perceived benefits from the treatment. A parallel group, randomized, multicenter, and controlled clinical trial designed to test the efficacy of GTR versus flap surgery alone assessed these patient issues (Cortellini *et al*. 2001). During the procedure, 30.4% of the test group and 28.6% of the controls reported moderate pain, and subjects in the test group estimated the hardship of the procedure as 24 ± 25 units on a visual analog scale (VAS from 0 to 100, with 0 = no hardship and 100 = unbearable hardship) and subjects in the control group 22 ± 23 VAS. Surgery with membranes required longer chair time than flap surgery alone (on average 20 minutes longer). Among the postoperative complications, edema was most prevalent at week 1 and most frequently associated with the GTR treatment, while postoperative pain was reported by fewer than 50% of both the test and control patients. Pain intensity was described as mild and lasted on average 14.1 ± 15.6 hours in the test patients and 24.7 ± 39.1 hours in the controls. Postoperative morbidity was limited to a minority of subjects: 35.7% of the test patients and 32.1% of the controls reported that the procedures interfered with daily activities for an average of 2.7 ± 2.3 days in the test group and 2.4 ± 1.3 days in the control group. These data indicate that GTR adds almost 30 minutes to a flap procedure and is followed by a greater prevalence of postsurgical edema, while no difference was observed between GTR and flap surgery alone in terms of postoperative pain, discomfort, and interference with daily activities.

No comparative study has reported the morbidity associated with the various regenerative approaches. Reports of multicenter trials on the application of EMDs or barrier membranes using the same methodology, however, show similar results for the two regenerative materials (Tonetti *et al*. 1998, 2004a; Cortellini *et al*. 2001).

Morbidity of the regenerative procedure was tested on a population treated with MIST and EMDs. Patients were questioned at the end of surgery and at week 1 about the intraoperative and postoperative period, respectively, and reported no pain (Cortellini & Tonetti 2007a). Three of the 13 patients reported very limited discomfort in the first 2 days of the first postoperative week. Seventy-seven percent of the patients described the first postoperative week as uneventful, reporting no feeling of having been surgically treated after the second postoperative day.

In a large case cohort of 40 patients treated with MIST and EMDs (Cortellini & Tonetti 2007b), none of the patients reported intraoperative pain or discomfort and 70% did not experience any postoperative pain. The subjects reporting pain described it as being very moderate (VAS 19 ± 10, with 0 = no pain and 100 = unbearable pain). In these patients, pain lasted for 26 ± 17 hours on average. Home consumption of analgesic tablets was 1 ± 2 on average. Twenty-three patients did not use any pain killer in addition to the first two compulsory tablets that were administered in the practice immediately after the surgery and 6 hours later. Seven of the 12 patients (17.5%) reporting pain also experienced some discomfort (VAS 28 ± 11, with 0 = no discomfort and 100 = unbearable discomfort) that lasted for 36 ± 17 hours on average. Only three patients reported some interference with daily activities (work and sport) for 1–3 days.

In a second case cohort study of MIST and EMDs on multiple adjacent intrabony defects (Cortellini *et al*. 2008), 14 of the 20 patients did not experience any postoperative pain. The six subjects reporting pain described it as being very mild (VAS 19 ± 9) and lasting for 21 ± 5 hours on average. Home consumption of painkillers was 0.9 ± 1.0. Nine patients did not use any analgesic in addition to the first two compulsory tablets. Ten patients experienced mild discomfort (VAS 21 ± 10) that lasted for 20 ± 9 hours on average. Only four patients reported some interference with daily activities (work and sport) for 1–3 days.

Ribeiro *et al*. (2011b) reported that the extent of discomfort/pain experienced during therapy with MIST and EMDs was very limited. In addition, the extent of discomfort during the first postoperative week was very discreet, and no patients developed high fever or reported any interference with daily activities. The quantity of analgesic medication taken by patients was minimal (fewer than one analgesic medication per patient).

In a case cohort study where 15 patients were treated with M-MIST and EMDs (Cortellini & Tonetti 2009b), none of the patients reported intraoperative or significant postoperative pain. Three of the patients reported very limited discomfort in the first 2 days after surgery. Fourteen described the first postoperative week as uneventful, reporting no feeling of having been surgically treated after the second postoperative day.

In a controlled study of the additional benefit from EMDs or EMD/BMDX with M-MIST compared with M-MIST alone (Cortellini & Tonetti 2011), none of the 45 patients reported having experienced intra- and postoperative pain. Slight discomfort was reported by three patients in the M-MIST group (average VAS 10.7 ± 2.1), by two patients in the M-MIST/EMD group (VAS 11.5 ± 0.7), and by four patients in the M-MIST/EMD/BMDX group (VAS 12.3 ± 3.1). Few patients needed pain control medications: three patients from the M-MIST group (average number of tablets 0.4 ± 0.7; maximum 2), four patients from the M-MIST/EMD group (average 0.3 ± 0.6; maximum 2), and four patients from the M-MIST/ EMD/BMDX group (average 0.5 ± 1; maximum 3).

Table 38-3 gives some of the surgical and postsurgical parameters used in four studies. Two studies concerned the application of traditional large PPF (MPPT and SPPF) with bioresorbable barriers (Cortellini *et al*. 2001) or EMDs (Tonetti *et al*. 2004b). The other two studies concerned the MIST (Cortellini *et al*. 2007b) and the M-MIST (Cortellini & Tonetti 2011) in

Table 38-3 Comparison between clinical studies of conventional versus those of minimally invasive surgery.

	Cortellini *et al*. (2001)	Tonetti *et al*. (2004b)	Cortellini *et al*. (2007b)	Cortellini & Tonetti (2011)
Regenerative approach	SPPF/MPPT + bioresorbable barrier	SPPF/MPPT+ EMD	MIST + EMD	M-MIST + EMD
Number of patients	56	83	40	15
Chair time (minutes)[a]	99 ± 46	80 ± 34	58 ± 11	54.2 ± 7.4
Interference with daily activity[b]	35.7%	29.5%	7.5%	0
Subjects with postoperative discomfort[b]	53.6%	47.5%	17.5%	13.3%
Subjects with postoperative pain[b]	46%	50%	30%	0
Pain intensity[c]	28.1 ± 2.5	28 ± 20	19 ± 10	–
Number of pain killers[d]	4.1 ± 2.5	4.3 ± 4.5	1.1 ± 2	0.3 ± 0.6

[a] Chair time measured from delivery of anesthesia to completion of the regenerative surgical procedures.
[b] Percentage of subjects reporting postoperative interference with daily activities, discomfort, and pain, as questioned at 1-week recall visit.
[c] Intensity of pain measured with a visual analog scale (VAS).
[d] Number of pain killers taken in addition to the two compulsory ones delivered at the end of surgery.
SPPF, simplified papilla preservation flap; MPPT, modified papilla preservation technique; MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique; EMD, enamel matrix derivative; bioresorbable barrier, polylactic and polyglycolic acid barrier.

combination with EMDs. This historical comparison clearly shows differences in most of the parameters between the four studies. Surgical chair time was the longest when large PPF and barriers were applied, shorter when large PPF were combined with EMDs, and by far the shortest when M-MIST and EMDs were used. The number of subjects reporting postoperative interference with daily activities, discomfort, and pain was similar in the two PPF studies, much reduced in the MIST study, and very limited or none in the M-MIST study; similarly, pain intensity and consumption of pain killers was very low in both studies. The reported outcomes indicate that postoperative discomfort and pain apparently are not influenced by the type of regenerative material, but are by the type of surgical approach: a more friendly, shorter chair time, MIS is associated with fewer postoperative problems. These considerations may prompt clinicians to adopt more patient-friendly approaches whenever possible.

Materials for regenerative surgery

In the area of materials and products, three different regenerative concepts have been explored: barrier membranes (GTR), grafts and wound-healing modifiers, plus many combinations of those (Cortellini & Tonetti 2015). A recent meta-analysis on intrabony defects (Nibali *et al*. 2020) concluded that both EMD and GTR were superior to OFD alone in improving CAL (1.27 mm; 0.79–1.74 mm and 1.43 mm; 0.76–2.22 respectively). Among biomaterials, the addition of DBBM improved the clinical outcomes of both GTR with resorbable barriers and EMD. PPFs enhanced the clinical outcomes. Another meta-analysis on furcations (Jepsen *et al*. 2020) concluded that furcation closure ranged between 0% and 60% (10 trials), and class I conversion from 29% to 100% (six trials). Regenerative techniques were superior to OFD for furcation improvement (closure/conversion, OR = 20.9; 90% CI = 5.81, 69.41), horizontal CAL gain (1.6 mm), vertical CAL gain (1.3 mm), and PPD reduction (1.3 mm). BRG resulted in the highest probability (61%) of being the best treatment for horizontal bone level gain. Non-resorbable membranes in combination with BRG ranked as the best treatment for vertical CAL gain (probability 75%) and PPD reduction (probability 56%).

The consensus panel of the XVI European Workshop on Periodontology recommended the use of either barrier membranes or EMD with or without the addition of bone-derived grafts to promote healing of residual deep pockets associated with a deep intrabony defect (Sanz *et al*. 2020). As for the regenerative treatment of residual deep pockets associated with class II mandibular and maxillary buccal furcation involvement the panel *recommended* the use of EMD alone or bone-derived graft with or without resorbable membranes

An detailed analysis of the different regenerative materials follows in the next section.

Barrier materials for regenerative surgery

In the first GTR attempts, a bacterial filter produced from cellulose acetate (Millipore®) was used as an occlusive membrane (Nyman *et al*. 1982; Gottlow *et al*. 1984; Magnusson *et al*. 1985). Although this type of membrane served its purpose, it was not ideal for clinical application.

Non-bioresorbable materials

Later studies have utilized membranes of e-PTFE specially designed for periodontal regeneration (Gore Tex Periodontal Material®). The basic molecule of this material consists of a carbon–carbon bond

with four attached fluorine atoms to form a polymer. It is inert and does not result in any tissue reaction when implanted in the body. This type of membrane persists after healing and must be removed in a second operation. Membranes of e-PTFE have been used successfully in animal experiments and in several clinical studies. From such studies it was found that for a barrier material to function optimally, it has to meet certain essential design criteria:

- Biocompatibility to assure good tissue acceptance. The material should not elicit an immune response, sensitization, or chronic inflammation that may interfere with healing and present a hazard to the patient. Biocompatibility, however, is a relative term since practically no materials are completely inert.
- Acts as a barrier to exclude undesirable cell types from entering the secluded space adjacent to the root surface. It is also considered to be an advantage that the material allows the passage of nutrients and gases.
- Tissue integration that allows the tissue to grow into the material without completely penetrating it. The goal of tissue integration is to prevent rapid epithelial downgrowth on the outer surface of the material or encapsulation of the material, and to provide stability to the overlying flap. The importance of tissue integration was demonstrated in a study in monkeys (Warrer *et al*. 1992) in which bioresorbable membranes of polylactic acid, a synthetic polymer, were used to treat circumferential periodontal defects. Due to the lack of tissue integration, the membranes in this study became surrounded by an epithelial layer and were often encapsulated and exfoliated.
- Capable of creating and maintaining a space adjacent to the root surface. This allows the blood clot to form at the interface between the flap and root surface (Haney *et al*. 1993; Sigurdsson *et al*. 1994; Cortellini *et al*. 1995c, d; Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al*. 2004). Some materials may be so soft and flexible that they collapse into the defect. Other materials are too stiff and may perforate the overlying tissue.
- Provide stability to the blood clot to maintain continuity with the root surface, thereby preventing the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993).

Bioresorbable materials

In recent years, natural or synthetic bioresorbable barrier materials for GTR have been introduced in order to avoid the second surgery necessary for removal of non-bioresorbable materials. Barrier materials of collagen from different species and from different anatomic sites have been tested in animals and in humans (Blumenthal 1988; Pitaru *et al*. 1988; Tanner *et al*. 1988; Paul *et al*. 1992; Blumenthal 1993; Wang *et al*. 1994; Camelo *et al*. 1998; Mellonig 2000). Often the collagen used is a cross-linked variety of porcine or bovine origin. When a collagen membrane is implanted in the human body, it is resorbed by the enzymatic activity of macrophages and polymorphonuclear leukocytes (Tatakis *et al*. 1999). Successful treatment with these barrier materials has been demonstrated, but the results of studies vary. Several complications, such as early degradation, epithelial down-growth along the material, and premature loss of the material, have been reported. The varying results are probably due to differences in the properties of the material and the handling of the material at the time of implantation. Although probably very minimal, there is a risk that infectious agents from animal products can be transmitted to humans, and autoimmunization has also been mentioned as a risk.

Barrier materials of polylactic acid or co-polymers of polylactic acid and polyglycolic acid were evaluated in animal and human studies and are now commonly used (Magnusson *et al*. 1988; Caffesse *et al*. 1994; Caton *et al*. 1994; Gottlow *et al*. 1994; Laurell *et al*. 1994; Hugoson *et al*. 1995; Polson *et al*. 1995a; Cortellini *et al*. 1996c, 2001; Hürzeler *et al*. 1997; Tonetti *et al*. 1998; Sculean *et al*. 1999a). These materials are biocompatible, but by definition they are not inert since some tissue reaction may be expected during degradation. The materials are degraded by hydrolysis and eliminated from the organism through the Krebs cycle as carbon dioxide and water (Tatakis *et al*. 1999).

The types of barrier materials that have been tested differ both in configuration and design. It appears that a number of bioresorbable materials meet to a varying extent the requirements of a good barrier listed above. Indeed, there are several studies (Hugoson *et al*. 1995; Cortellini *et al*. 1996b; Smith MacDonald *et al*. 1998; Tonetti *et al*. 1998; Cortellini & Tonetti 2000a, 2005) indicating that similar satisfactory results can be obtained with bioresorbable barrier materials of polylactic and polyglycolic acid as with non-bioresorbable materials.

Membranes for intrabony defects

Early evidence that GTR treatment of deep intrabony defects may produce clinical improvements in terms of CAL was presented in several case reports (Nyman *et al*. 1982; Gottlow *et al*. 1986; Becker *et al*. 1988; Schallhorn & McClain 1988; Cortellini *et al*. 1990). In recent years, a considerable number of clinical investigations have reported on intrabony defects treated with GTR (see Table 38-4). In these studies, the issue of evaluating the predictability of the clinical outcomes following application of GTR procedures was addressed. Table 38-4 gives the results for a total of 1283 intrabony defects treated with GTR. The weighted mean of the reported results indicates

Table 38-4 Clinical outcomes of guided tissue regeneration (GTR) treatment of deep intrabony defects.

Study	Membranes	Number	Gains in CAL ± SD (mm)	Residual PPD ± SD (mm)
Becker *et al*. (1988)	e-PTFE	9	4.5 ± 1.7	3.2 ± 1.0
Chung *et al*. (1990)	Collagen	10	0.6 ± 0.6	
Handelsman *et al*. (1991)	e-PTFE	9	4.0 ± 1.4	3.9 ± 1.4
Kersten *et al*. (1992)	e-PTFE	13	1.0 ± 1.1	5.1 ± 0.9
Proestakis *et al*. (1992)	e-PTFE	9	1.2 ± 1.3	3.5 ± 0.9
Quteish & Dolby (1992)	Collagen	26	3.0 ± 1.5	2.2 ± 0.4
Selvig *et al*. (1992)	e-PTFE	26	0.8 ± 1.3	5.4
Becker & Becker (1993)	e-PTFE	32	4.5	3.9 ± 0.3
Cortellini *et al*. (1993a)	e-PTFE	40	4.1 ± 2.5	2.0 ± 0.6
Falk *et al*. (1993)	Polylactic acid	25	4.5 ± 1.6	3.0 ± 1.1
Cortellini & Pini-Prato (1994)	Rubber dam	5	4.0 ± 0.7	2.4 ± 0.5
Laurell *et al*. (1994)	Polylactic acid	47	4.9 ± 2.4	3.0 ± 1.5
Al-Arrayed *et al*. (1995)	Collagen	19	3.9	2.5
Chen *et al*. (1995)	Collagen	10	2.0 ± 0.4	4.2 ± 0.4
Cortellini *et al*. (1995c)	e-PTFE	15	4.1 ± 1.9	2.7 ± 1.0
Cortellini *et al*. (1995c)	e-PTFE + titanium	15	5.3 ± 2.2	2.1 ± 0.5
Cortellini *et al*. (1995a)	e-PTFE + FFG	14	5.0 ± 2.1	2.6 ± 0.9
Cortellini *et al*. (1995a)	e-PTFE	14	3.7 ± 2.1	3.2 ± 1.8
Cortellini *et al*. (1995b)	e-PTFE + fibrin	11	4.5 ± 3.3	1.7
Cortellini *et al*. (1995b)	e-PTFE	11	3.3 ± 1.9	1.9
Mattson *et al*. (1995)	Collagen	13	2.5 ± 1.5	3.6 ± 0.6
Mattson *et al*. (1995)	Collagen	9	2.4 ± 2.1	4.0 ± 1.1
Mellado *et al*. (1995)	e-PTFE	11	2.0 ± 0.9	
Becker *et al*. (1996)	Polylactic acid	30	2.9 ± 2.0	3.6 ± 1.3
Cortellini *et al*. (1996c)	Polylactic acid	10	4.5 ± 0.9	3.1 ± 0.7
Cortellini *et al*. (1996b)	e-PTFE	12	5.2 ± 1.4	2.9 ± 0.9
Cortellini *et al*. (1996b)	Polylactic acid	12	4.6 ± 1.2	3.3 ± 0.9
Gouldin *et al*. (1996)	e-PTFE	25	2.2 ± 1.4	3.5 ± 1.3
Kim *et al*. (1996)	e-PTFE	19	4.0 ± 2.1	3.2 ± 1.1
Murphy (1996)	e-PTFE + ITM	12	4.7 ± 1.4	2.9 ± 0.8
Tonetti *et al*. (1996b)	e-PTFE	23	5.3 ± 1.7	2.7
Benqué *et al*. (1997)	Collagen	52	3.6 ± 2.2	3.9 ± 1.7
Caffesse *et al*. (1997)	Polylactic acid	6	2.3 ± 2.0	3.8 ± 1.2
Caffesse *et al*. (1997)	e-PTFE	6	3.0 ± 1.2	3.7 ± 1.2
Christgau *et al*. (1997)	e-PTFE	10	4.3 ± 1.2	3.6 ± 1.1
Christgau *et al*. (1997)	Polyglactin	10	4.9 ± 1.0	3.9 ± 1.1
Falk *et al*. (1997)	Polylactic acid	203	4.8 ± 1.5	3.4 ± 1.6
Kilic *et al*. (1997)	e-PTFE	10	3.7 ± 2.0	3.1 ± 1.4
Cortellini *et al*. (1998)	Polylactic acid	23	3.0 ± 1.7	3.0 ± 0.9
Eickholz *et al*. (1998)	Polylactic acid	14	3.4 ± 1.6	3.2 ± 0.7
Smith MacDonald *et al*. (1998)	e-PTFE	10	4.3 ± 2.1	3.7 ± 0.9
Smith MacDonald *et al*. (1998)	Polylactic acid	10	4.6 ± 1.7	3.4 ± 1.2
Parashis *et al*. (1998)	Polylactic acid	12	3.8 ± 1.8	3.5 ± 1.4

Table 38-4 (*Continued*)

Study	Membranes	Number	Gains in CAL ± SD (mm)	Residual PPD ± SD (mm)
Tonetti *et al*. (1998)	Polylactic acid	69	3.0 ± 1.6	4.3 ± 1.3
Cortellini *et al*. (1999a)	Polylactic acid	18	4.9 ± 1.8	3.6 ± 1.2
Pontoriero *et al*. (1999)	Diff. barriers	30	3.1 ± 1.8	3.3 ± 1.3
Sculean *et al*. (1999a)	Polylactic acid	52	3.4 ± 1.4	3.6 ± 1.3
Dorfer *et al*. (2000)	Polylactic acid	15	4.0 ± 1.2	2.7 ± 0.7
Dorfer *et al*. (2000)	Polidiossanon	15	3.4 ± 1.9	3.1 ± 1.1
Eickholz *et al*. (2000)	Polylactic acid	30	3.9 ± 1.2	2.6 ± 1.0
Karapataki *et al*. (2000)	Polylactic acid	10	4.7 ± 0.7	4.2 ± 1.4
Karapataki *et al*. (2000)	e-PTFE	9	3.6 ± 1.7	4.6 ± 1.4
Ratka-Kruger *et al*. (2000)	Polylactic acid	23	3.1 ± 2.3	4.7 ± 1.3
Zybutz *et al*. (2000)	Polylactic acid	15	2.4 ± 1.9	
Zybutz *et al*. (2000)	e-PTFE	14	2.4 ± 0.8	
Cortellini & Tonetti (2001)	Diff. barriers	26	5.4 ± 1.2	3.3 ± 0.6
Cortellini *et al*. 2001	Polylactic acid	55	3.5 ± 2.1	3.8 ± 1.5
Weighted mean		**1283**	**3.8 ± 1.7**	**3.4 ± 1.2**

CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; FGG, free gingival graft; ITM, interproximal tissue maintenance; PPD, probing pocket depth; SD, standard deviation.

a mean CAL gain of 3.8 ± 1.7 mm (95% CI 3.7–4.0 mm) (Cortellini & Tonetti 2000a). The reported CAL gains following GTR treatment were significantly larger than those obtained with conventional flap surgery. A review 40 studies on flap surgery with a weighted mean of 1172 defects reported CAL gains of 1.8 ± 1.4 mm (95% CI of 1.6–1.9 mm) (Lang 2000). A more recent review and meta-analysis of 27 trials on access flap surgery included 647 subjects and 734 defects (Graziani *et al*. 2011). Twelve months after flap surgery, tooth survival was 98% (IQ 96.77–100%), CAL gain was 1.65 mm (95% CI 1.37–1.94; P <0.0001), PPD reduction was 2.80 mm (CI 2.43–3.18; P <0.0001), and recession increase 1.26 mm (CI 0.94–1.49; P <0.0001).

Different types of non-bioresorbable (Fig. 38-39) and bioresorbable (Fig. 38-40) barrier materials were used in the clinical studies summarized in Table 38-4. Analysis of the results reported in some of the published studies (Proestakis *et al*. 1992; Cortellini *et al*. 1993a, 1995b, c, 1996b; Cortellini & Pini-Prato 1994; Laurell *et al*. 1994; Mattson *et al*. 1995; Mellado *et al*. 1995; Tonetti *et al*. 1996b) provides important information regarding the predictability of GTR in intrabony defects. CAL gains of 2–3 mm were observed in 29.2% of the defects, of 4–5 mm in 35.4% of the defects, and of ≥6 mm in 24.9% of the defects. Only in 10.5% of the treated defects was the gain <2 mm, while no change or attachment loss was observed in two cases.

In some of the investigations, changes in bone levels were also reported (Becker *et al*. 1988; Handelsman *et al*. 1991; Kersten *et al*. 1992; Cortellini *et al*. 1993a, b; Selvig *et al*. 1993). Bone gains ranged between 1.1 and 4.3 mm and correlated with the reported CAL gains. In a study by Tonetti *et al*. (1993b), 1 year after GTR the bone was found to be located 1.5 mm apically to the position of the attained CAL.

Another important parameter related to the outcome of regenerative procedures is the residual pocket depth. In the studies in Table 38-4, shallow pockets were consistently found at 1 year. The weighted mean residual pocket depth was 3.4 ± 1.2 mm (95% CI 2.3–3.5 mm).

The reported outcomes indicate that GTR procedures predictably result in clinical improvements in intrabony defects beyond those of flap surgery (see Fig. 38-6). This was further confirmed in 11 controlled randomized clinical trials in which GTR was compared with conventional flap surgery (Table 38-5). A total of 267 defects were treated with flap surgery and 317 with GTR. In nine of the 11 investigations, GTR resulted in a statistically significantly greater PAL gain when compared with flap surgery. Similar results were also observed for residual pocket depth.

Membranes for furcation involvement

The invasion of the furcation area of multirooted teeth by periodontitis represents a serious complication in periodontal therapy. The furcation area is often inaccessible to adequate instrumentation, and the roots frequently present concavities and furrows which make proper cleaning of the area impossible (see Chapter 40). As long as the pathologic process only extends a small distance (<5 mm; class I and II involvements) into the furcation area, further progress of the disease can usually be prevented by scaling and root planing, provided a proper oral hygiene program is established after treatment. In more advanced cases (5–6 mm; class II involvements), the initial cause-related treatment

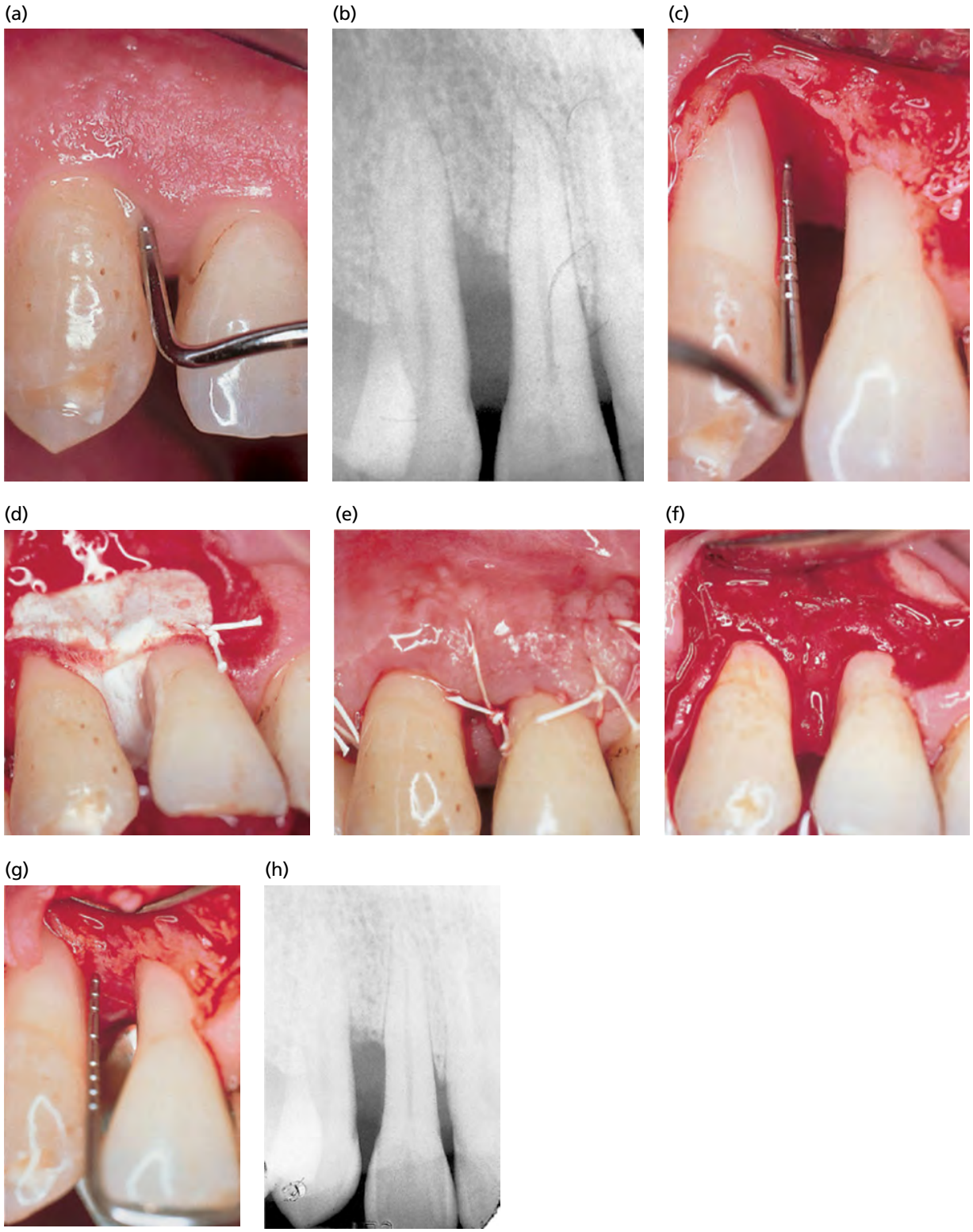


Fig. 38-39 Intrabony defect on the mesial aspect of a right maxillary canine treated with a non-bioresorbable barrier membrane. (a) Pocket depth was 9 mm and loss of clinical attachment was 10 mm. (b) Radiograph showing the presence of an interproximal intrabony defect. (c) After full-thickness flap elevation, defect debridement, and root planing, a 4-mm intrabony defect was evident. (d) An expanded polytetrafluoroethylene (e-PTFE) non-bioresorbable barrier membrane was tailored, positioned, and tightly sutured around the teeth adjacent to the defect. (e) Flap was repositioned and sutured to cover the membrane. Optimal preservation of the soft tissues was accomplished with an intrasulcular incision. (f) After removal of the membrane at 5 weeks, the defect appeared to be completely filled with newly formed tissue. (g) Treated site was surgically re-entered after 1 year. The intrabony defect was completely filled with bone. (h) One-year radiograph confirmed the complete resolution of the intrabony defect.

is frequently supplemented with surgery involving contouring of the interradicular bone (osteoplasty) or reduction of the tooth prominence at the furcation entrance by grinding (odontoplasty), in order to reduce the horizontal extension of the furcation involvement. In cases where the involvement extends even deeper into the furcation area (>5 mm; class II involvements), or a through-and-through defect (class

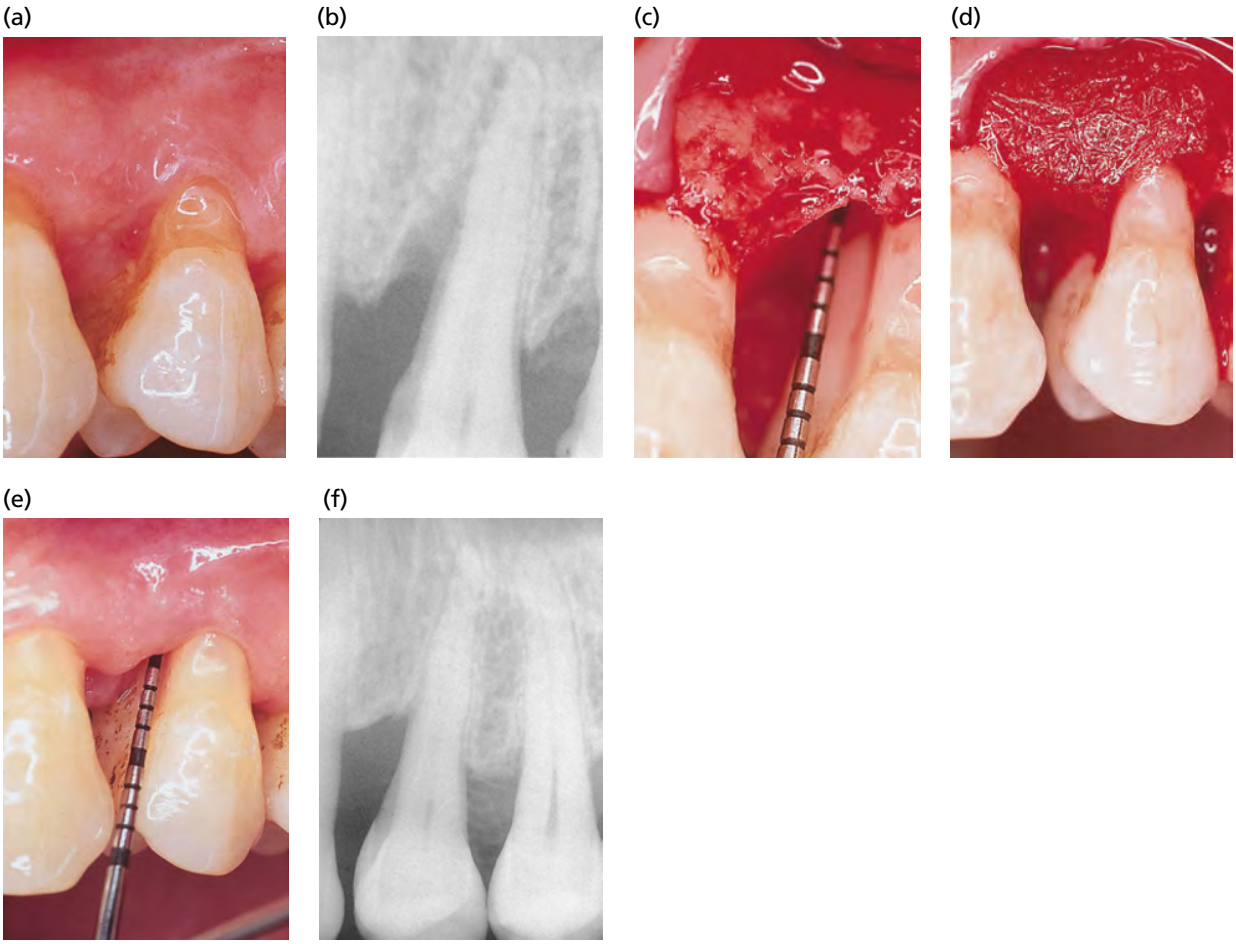


Fig. 38-40 Intrabony defect on the mesial aspect of a left maxillary premolar treated with a bioresorbable barrier membrane. (a) Clinical attachment loss was 12 mm. (b) Radiograph showing the presence of a deep interproximal intrabony defect approaching the apex of the tooth. (c) A 7-mm interproximal intrabony defect was measured after flap elevation, defect debridement, and root planing. (d) A bioresorbable barrier membrane was placed and sutured to cover the defect. (e) At 1 year, a 4-mm pocket depth and 5-mm clinical attachment length gain were recorded. (f) One-year radiograph showed that the intrabony defect was almost resolved.

III involvements) has developed, tunnel preparation or root resection has been advocated as the treatment of choice. However, both of these treatments run a risk of complications on a long-term basis. Following tunnel preparation, caries frequently develops in the furcation area and root-resected teeth often present complications of a non-periodontal nature, although controversial reports exist regarding the long-term results of these treatment modalities (Hamp *et al*. 1975; Langer *et al*. 1981; Erpenstein 1983; Bühler 1988; Little *et al*. 1995; Carnevale *et al*. 1998).

Considering the complexity of current techniques for the treatment of furcation problems, and in view of the long-term results and complications reported following treatment of advanced furcation involvements by traditional resective therapy, predictable regeneration of the periodontium at furcation-involved sites would represent considerable progress in periodontics.

Mandibular class II furcations

Pontoriero *et al*. (1988) reported a controlled randomized clinical trial in which significantly greater H-CAL gain (3.8 ± 1.2 mm) were obtained in 21 mandibular class II furcations treated with e-PTFE membranes compared with those in a control group treated with OFD alone (H-CAL gain of 2.0 ± 1.2 mm). Complete closure of the furcation was observed at 67% of the test sites and at only 10% of the control sites. Results from later studies, however, have not been as promising (Becker *et al*. 1988; Lekovic *et al*. 1989; Caffesse *et al*. 1990). Analysis of a series of studies published between 1988 and 1996 demonstrates a great variability in the clinical outcomes (Figs. 38-41, 38-42). Table 38-6 summarizes the outcomes of 21 clinical trials in which a total of 423 mandibular class II furcations were treated with different types of non-bioresorbable and bioresorbable barrier membranes. The weighted mean of the reported results showed an H-CAL gain of 2.3 ± 1.4 mm (95% CI 2.0–2.5 mm) in defects with a baseline horizontal PPD of 5.4 ± 1.3 mm. The reported number of complete furcation closures after GTR ranged from 0% to 67%. In three studies none of the treated furcations was closed (Becker *et al*. 1988; Yukna 1992; Polson *et al*. 1995b), in seven studies <50% were closed (Schallhorn & McClain 1988; Blumenthal 1993; Bouchard *et al*. 1993; Parashis & Mitsis 1993; Laurell *et al*. 1994; Mellonig *et al*. 1994;

Table 38-5 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with access flap procedures in deep intrabony defects.

Study	Membranes	Number	Gains in CAL ± SD (mm)		Residual PPD ± SD (mm)	
			GTR	Access flap	GTR	Access flap
Chung *et al*. (1990)	Collagen	10	0.6 ± 0.6	–0.7 ± 0.9	4.0 ± 1.1	
	Collagen	9	2.4 ± 2.1			
	Control	14				
Proestakis *et al*. (1992)	e-PTFE	9	1.2 ± 1.3		3.5 ± 0.9	
	Control	9		0.6 ± 1.0		3.7 ± 3.0
Quteish & Dolby (1992)	Collagen	26	3.0 ± 1.5		2.2 ± 0.4	
	Control	26		1.8 ± 0.9		3.4 ± 0.6
Al-Arrayed *et al*. (1995)	Collagen	19	3.9	2.7	2.5	3.5
	Control	14				
Cortellini *et al*. (1995c)	e-PTFE	15	4.1 ± 1.9		2.7 ± 1.0	
	e-PTFE + titanium	15			2.1 ± 0.5	
	Control	15	5.3 ± 2.2	2.5 ± 0.8		3.7 ± 1.3
Mattson *et al*. (1995)	Collagen	13	2.5 ± 1.5		3.6 ± 0.6	
	Control	9		0.4 ± 2.1		4.5 ± 1.8
Cortellini *et al*. (1996b)	e-PTFE	12	5.2 ± 1.4		2.9 ± 0.9	
	Polylactic acid	12		4.6 ± 1.2		3.3 ± 0.9
	Control	12		2.3 ± 0.8		4.2 ± 0.9
Tonetti *et al*. (1998)	Polylactic acid Control	69 67	3.0 ± 1.6	2.2 ± 1.5	4.3 ± 1.3	4.2 ± 1.4
Pontoriero *et al*. (1999)	Diff. barriers Control	30 30	3.1 ± 1.8	1.8 ± 1.5	3.3 ± 1.3	4.0 ± 0.8
Ratka-Kruger *et al*. (2000)	Polylactic acid Control	23 21	3.1 ± 2.3	3.3 ± 2.7	4.7 ± 1.4	4.9 ± 2.1
Cortellini *et al*. (2001)	Polylactic acid	55	3.5 ± 2.1		3.8 ± 1.5	
	Control	54		2.6 ± 1.8		4.7 ± 1.4
Weighted mean		**584**	**3.3 ± 1.8**	**2.1 ± 1.5**	**3.5 ± 1.1**	**4.1 ± 1.3**

CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; PPD, probing pocket depth; SD, standard deviation.

Hugoson *et al*. 1995), and in only one study were >50% of the treated furcations completely resolved (Pontoriero *et al*. 1988).

A subset analysis of the studies reported in Table 38-6 indicated that furcations treated with non-bioresorbable barrier membranes (287) showed a gain in H-CAL of 1.8 ± 1.4 mm (95% CI 1.5–2.1 mm) as compared with 2.3 ± 1.2 mm (95% CI 2–2.6 mm) in 174 defects treated with bioresorbable barrier membranes. Five controlled clinical trials compared treatment with non-bioresorbable e-PTFE membranes and treatment with different types of bioresorbable membranes (Table 38-7). In particular, one investigation reported significantly greater H-CAL gain in the non-bioresorbable group (Bouchard *et al*. 1993), while another trial (Hugoson *et al*. 1995) showed a significantly greater H-CAL gain in the bioresorbable group. The remaining three investigations failed to detect any significant differences between the outcomes of treatment with bioresorbable or non-bioresorbable membranes. Generally, the results indicate that the predictability of GTR in the treatment of mandibular class II furcations is questionable if the treatment objective is the complete resolution of the furcation involvement.

Significant gain in V-CAL and reduction in PPD was also reported by several investigators following treatment of mandibular class II furcation defects (Pontoriero *et al*. 1988; Lekovic *et al*. 1989, 1990; Blumenthal 1993; Machtei *et al*. 1993, 1994; Black *et al*. 1994; Laurell *et al*. 1994; Mellonig *et al*. 1994; Wang *et al*. 1994; Hugoson *et al*. 1995; Polson *et al*. 1995b). The reported mean values ranged from 0.1 mm to 3.5 mm for V-CAL gain and from 1 mm to 4 mm for PPD reduction.

The effect of using barrier membranes for the treatment of mandibular class II furcations was investigated in six controlled randomized clinical trials in which GTR procedures were directly compared to flap surgery (Table 38-8). Sixty-six furcations treated with flap surgery and 87 treated with GTR were included. Three of the four studies reporting H-CAL

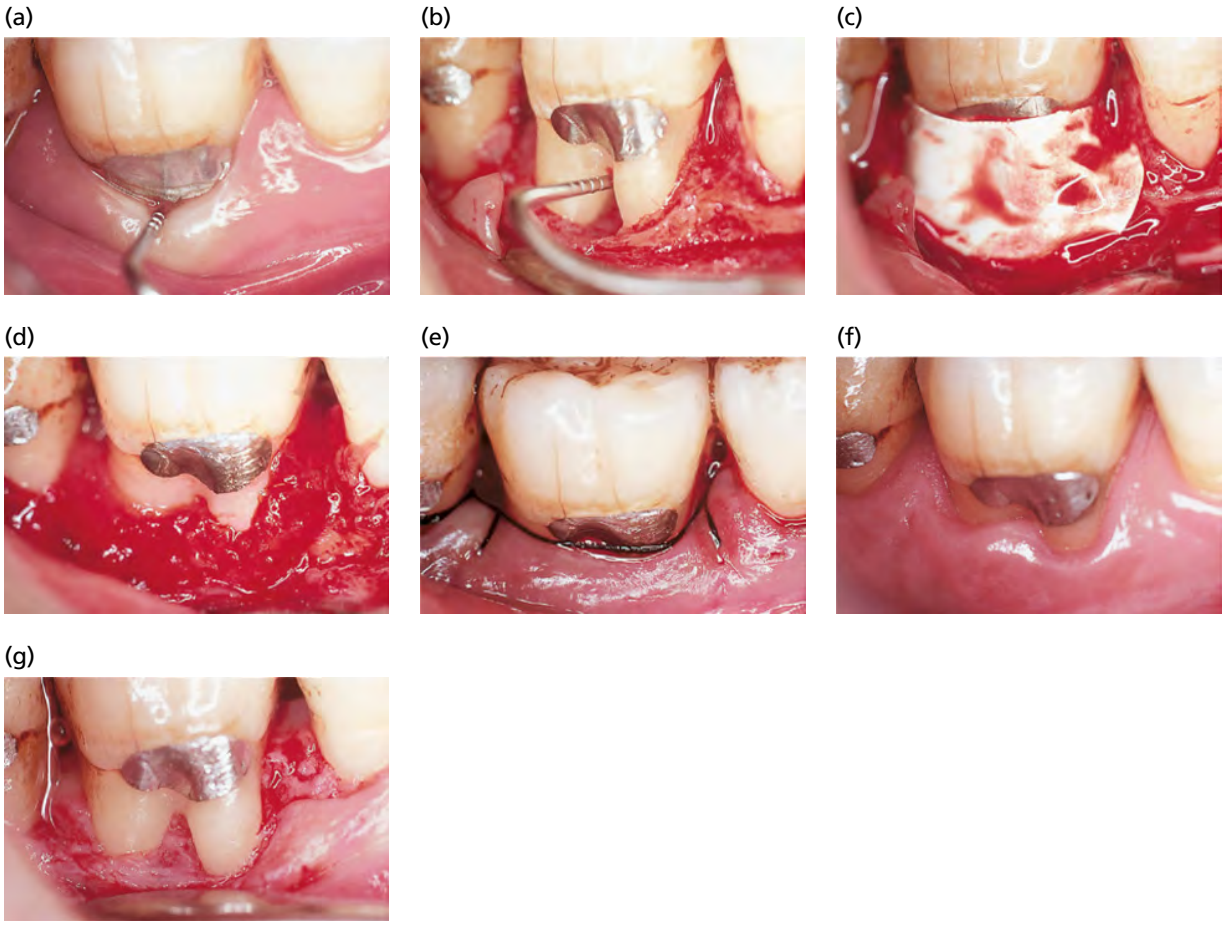


Fig. 38-41 (a) Right mandibular first molar presenting with a degree II furcation involvement. (b) Full-thickness buccal flaps were raised, the defect debrided, and the root carefully planed. (c) A non-bioresorbable barrier membrane was placed to cover the defect. (d) After membrane removal, newly formed tissue appeared to fill the furcation completely. (e) Regenerated tissue was covered with the flap. (f) Clinical appearance and surgery entry (g) after 1 year showed that the class II furcation was almost completely resolved.

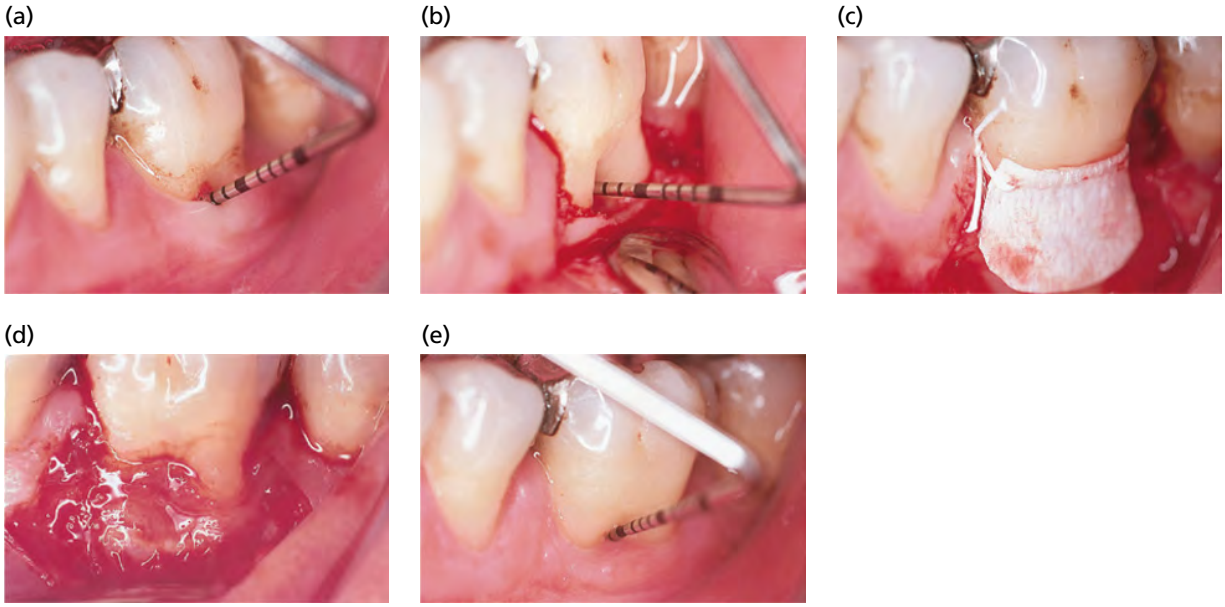


Fig. 38-42 (a) Left mandibular first molar presenting with a deep class II furcation involvement. (b) Horizontal loss of tooth support of 7 mm was probed. (c) An expanded polytetrafluoroethylene (e-PTFE barrier) membrane was trimmed and sutured to cover the furcation. (d) At membrane removal after 5 weeks, newly formed tissue filled the furcation completely. (e) At 1 year, a 3-mm gain of tooth support was measured, but a residual 4-mm class II furcation involvement was still present.

Table 38-6 Clinical outcomes and weighted mean of guided tissue regeneration (GTR) treatment of mandibular class II furcations.

Study		Treatment	Number	Defect depth (mm)	H-CAL gain (mm)	H-OPAL gain (mm)	No. of closed furcations
Pontoriero *et al*. (1988)	Controlled clinical trial	e-PTFE	21	4.4±1.2	3.8±1.2	NA	14 (67%)
Becker *et al*. (1988)	Case cohort	e-PTFE	6	8.3±2.3	NA	1.8±1.5	0
Schallhorn & McClain (1988)	Case cohort	e-PTFE	16	NA	NA	3.1±1.7	5 (31%)
Lekovic *et al*. (1989)	Controlled clinical trial	e-PTFE	6	NA	NA	0.2±0.5	NA
Lekovic *et al*. (1990)	Controlled clinical trial	e-PTFE	15	4.2±0.2	NA	0.1±0.1	NA
Caffesse *et al*. (1990)	Controlled clinical trial	e-PTFE	9	4.8±?	0.8±?	NA	NA
Anderegg *et al*. (1991)	Controlled clinical trial	e-PTFE	15	4.2±2.2	NA	1.0±0.8	NA
Yukna (1992)	Controlled clinical trial	e-PTFE	11	3.0±?	NA	1.0±?	0
		FDDMA	11	4.0±?	NA	2.0±?	0
Blumenthal (1993)	Controlled clinical trial	e-PTFE	12	4.4±0.9	1.8±1.0	1.7±0.5	4 (33%)
		Collagen	12	4.5±0.9	2.5±0.8	2.5±0.7	1 (8%)
Bouchard *et al*. (1993)	Controlled clinical trial	e-PTFE	12	NA	2.8±1.3	2.2±1.4	4 (33%)
		Conn. graft	12	NA	1.5±1.5	1.5±1.1	2 (17%)
Machtei *et al*. (1993)	Controlled clinical trial	e-PTFE	18	NA	2.3±1.7	NA	NA
Parashis & Mitsis (1993)	Controlled clinical trial	e-PTFE	9	5.7±0.7	4.7±1.5	NA	4 (44%)
Van Swol *et al*. (1993)	Controlled clinical trial	Collagen	28	5.1±1.4	2.3±1.0	1.7±?	NA
Wallace *et al*. (1994)	Controlled clinical trial	e-PTFE	7	NA	NA	2.3±?	NA
Black *et al*. (1994)	Controlled clinical trial	e-PTFE	13	4.3±2.0	0.8±2.2	NA	NA
		Collagen	13	4.4±1.5	1.5±2.0	NA	NA
Laurell *et al*. (1994)	Case cohort	Polylactic acid	19	NA	3.3±1.4	NA	9 (47%)
Machtei *et al*. (1994)	Controlled clinical trial	e-PTFE	30	7.7±1.8	2.6±1.7	NA	NA
Mellonig *et al*. (1994)	Controlled clinical trial	e-PTFE	11	8.4±1.2	NA	4.5±1.6	1 (9%)
Wang *et al*. (1994)	Controlled clinical trial	Collagen	12	6.0±2.7	2.0±0.4	2.5±?	NA
Hugoson *et al*. (1995)	Controlled clinical trial	e-PTFE	38	5.9±1.3	1.4±2.2	NA	4 (11%)
		Polylactic acid	38	5.6±1.4	2.2±2.0	NA	13 (34%)
Polson *et al*. (1995b)	Case cohort[a]	Polylactic acid	29	5.4±0.2	2.5±0.1	NA	0
Weighted mean			**423**	**5.4± 1.3**[b]	**2.3± 1.4**[c]	**1.9± 1**[d]	

[a] Mandibular and maxillary molars.
[b] *n* = mean (340) ± SD (302).
[c] *n* = mean (325) ± SD (316).
[d] *n* = mean (186) ± SD (177).
Conn graft, connective tissue graft; e-PTFE, expanded polytetrafluoroethylene; FDDMA, freeze dried dura mater allograft; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available.

Table 38-7 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with e-PTFE non-bioresorbable barrier membranes with different types of bioresorbable barrier membranes in mandibular class II furcations.

Study	Design and treatment (GTR C/GTR T)	*n* C/T	Defect depth (mm)		H-CAL gain (mm)		H-OPAL gain (mm)	
			GTR C	GTR T	GTR C	GTR T	GTR C	GTR T
Yukna (1992)	Intraindividual (e-PTFE/FDDMA)	11/11	3.0 ± ?	4.0 ± ?	NA	NA	1.0 ± ?	2.0 ± ?
Blumenthal (1993)	Intraindividual (e-PTFE/collagen)	12/12	4.4 ± 0.9	4.5 ± 0.9	1.8 ± 1.0	2.5 ± 0.8	1.7 ± 0.5	2.5 ± 0.7
Bouchard *et al*. (1993)	Intraindividual (e-PTFE/conn. graft)	12/12	NA	NA	2.8 ± 1.3[a]	1.5 ± 2.0	2.2 ± 1.4	1.5 ± 1.1
Black *et al*. (1994)	Intraindividual (e-PTFE/collagen)	13/13	4.3 ± 2.0	4.4 ± 1.5	0.8 ± 2.2	1.5 ± 2.0	NA	NA
Hugoson *et al*. (1995)	Intraindividual (e-PTFE/ polytetrafluoroethylene)	38/38	5.9 ± 1.3	5.6 ± 1.4	1.4 ± 2.2[a]	2.2 ± 2.0[a]	NA	NA
Weighted mean		**86/86**	**4.9 ± 1.4**[b]	**5 ± 1.3**[b]	**1.6 ± 1.9**[c]	**2 ± 1.7**[c]	**1.3 ± 1**[d]	**1.4 ± 0.9**[d]

[a] Statistically significant difference between treatments.
[b] *n* = mean (74) ± SD (63).
[c] *n* = mean (75) ± SD (75).
[d] *n* = mean (35) ± SD (124).
Conn graft, connective tissue graft; e-PTFE, expanded polytetrafluoroethylene; FDDMA, freeze dried dura mater allograft; GTR C, guided tissue regeneration control treatment; GTR T, guided tissue regeneration test treatment; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available; *n* C/T, number of defects in the control (C) and the test (T) treatment arms.

Table 38-8 Controlled clinical trials comparing clinical outcomes of guided tissue regeneration (GTR) procedures with access flap procedures in mandibular class II furcations.

	Design (GTR treatment)	*n* C/T	Defect depth (mm)		H-CAL gain (mm)		H-OPAL gain (mm)	
			Access flap	GTR	Access flap	GTR	Access flap	GTR
Pontoriero *et al*. (1988)	Intraindividual (e-PTFE)	21/21	4.0 ± 0.8	4.4 ± 1.2	2.0 ± 1.2	3.8 ± 1.2	NA	NA
Lekovic *et al*. (1989)	Intraindividual (e-PTFE)	6/6	NA	NA	NA	NA	–0.1 ± 0.3	0.2 ± 0.5
Caffesse *et al*. (1990)	Parallel (e-PTFE)	6/9	5.3 ± ?	4.8 ± ?	0.3 ± ?	0.8 ± ?	NA	NA
Van Swol *et al*. (1993)	Parallel (collagen)	10/28	5.7 ± 2.5	5.1 ± 1.4	0.7 ± 1.2[a]	2.3 ± 1[a]	0.8 ± ?	1.7 ± ?
Mellonig *et al*. (1994)	Intraindividual (e-PTFE)	6/6	7.5 ± 2.3	8.4 ± 1.2	NA	NA	1.1 ± 1.3[a]	4.5 ± 1.6[a]
Wang *et al*. (1994)	Intraindividual (collagen)	12/12	5.6 ± 2.7	6.0 ± 2.7	1.1 ± 0.6[a]	2.0 ± 0.4[a]	1.5 ± ?	2.5 ± ?
Weighted mean		**66/87**	**5.4 ± 1.8**[b]	**5.5 ± 1.5**[c]	**1.3 ± 1**[d]	**2.5 ± 1**[e]	**1 ± 1**[f]	**2.3 ± 1.2**[g]

[a] Statistically significant difference between treatments.
[b] *n* = mean (60) ± SD (54).
[c] *n* = mean (81) ± SD (72).
[d] *n* = mean (49) ± SD (43).
[e] *n* = mean (70) ± SD (61).
[f] *n* = mean (39) ± SD (17).
[g] *n* = mean (57) ± SD (17).
e-PTFE, expanded polytetrafluoroethylene; H-CAL, horizontal clinical attachment level; H-OPAL, horizontal open attachment level; NA, not available.

gains concluded that GTR resulted in statistically significantly greater H-CAL gains than flap surgery (Pontoriero *et al*. 1988; Van Swol *et al*. 1993; Wang *et al*. 1994). The weighted mean of the results of these studies for H-CAL gain in furcations treated with GTR was 2.5 ± 1 mm (95% CI 2.1–2.9 mm), and 1.3 ± 1 mm (95% CI 0.8–1.8 mm) for furcations treated with flap surgery. These results indicate an added benefit from GTR in the treatment of mandibular class II furcations.

Maxillary class II furcations

Results reported in three controlled studies (Metzeler *et al*. 1991; Mellonig *et al*. 1994; Pontoriero & Lindhe 1995a) comparing GTR treatment of maxillary class II furcations with non-bioresorbable e-PTFE membranes and with OFD indicated that GTR treatment of such defects is generally unpredictable. In a study including 17 pairs of class II furcations, Metzeler *et al*. (1991) measured CAL gains of 1.0 ± 0.9 mm in the GTR-treated sites versus 0.2 ± 0.6 mm in the control sites. Following re-entry, horizontal PAL gains (H-OPAL) of 0.9 ± 0.4 mm and 0.3 ± 0.6 mm were detected in the GTR- and flap-treated furcations, respectively. None of the furcations of the two groups was completely resolved. Similarly, Mellonig *et al*. (1994) treated eight pairs of maxillary class II furcations and reported H-OPAL gains of 1.0 mm (GTR sites) and 0.3 mm (flap-treated sites). Again, none of the treated furcations in the two groups was completely closed. On the other hand, in a study of 28 maxillary class II furcations, Pontoriero and Lindhe (1995a) found a

significant gain in CAL (1.5 mm) and horizontal bone (1.1 mm) in buccal class II furcations. Although these three investigations show a slight clinical improvement following treatment of class II maxillary furcations with GTR, the results are generally inconsistent.

Class III furcations

Four investigations of the treatment of mandibular class III furcations (Becker *et al*. 1988; Pontoriero *et al*. 1989; Cortellini *et al*. 1990; Pontoriero & Lindhe 1995b) indicate that the treatment of such defects with GTR is unpredictable. A controlled study by Pontoriero *et al*. (1989) showed that only eight of 21 "through-and-through" mandibular furcations treated with non-bioresorbable barrier membranes healed with complete closure of the defect. Another 10 defects were partially filled and three remained open. In the OFD-treated control group, 10 were partially filled and 11 remained open. Similar results were reported by Cortellini *et al*. (1990) who, in a case cohort of 15 class III mandibular furcations, found that 33% of the defects had healed completely, 33% were partially closed, and 33% were still through-and-through following treatment. Becker *et al*. (1988) did not observe complete closure of any of 11 treated class III mandibular furcations. Similarly, in a controlled clinical trial by Pontoriero and Lindhe (1995b) of 11 pairs of maxillary class III furcations randomly assigned to GTR or flap surgery, none of the furcation defects was closed.

Conclusion: Based on current evidence, it seems that mandibular class II furcations in the first or second molars, either buccal or lingual, with deep pockets at baseline and a gingival thickness of >1 mm, may benefit from GTR treatment.

Bone replacement grafts

Grafts for intrabony defects

BRGs comprise a heterogeneous group of materials of human (autologous or allogeneic), animal, or synthetic origin. Some consist of bone or exoskeletal minerals; others contain mainly bone matrix. There is evidence for periodontal regeneration for only a few of these materials. A randomized controlled clinical trial provided histologic support that the healing outcome following application of DFDBA in intrabony defects has a regenerative component in the apical to middle portion of the depth of the defect (Bowers *et al*. 1989a–c). Isolated evidence also supports the fact that allograft and bovine bone mineral may yield a regenerative outcome when used alone (i.e. without other regenerative materials such as barrier membranes or biologically active regenerative materials [BARGs]; see also Chapter 28) (Nevins *et al*. 2000).

BRGs were the first periodontal regenerative materials to be applied clinically. Today they are widely used in North America as DFDBAs and are frequently used in combination with other regenerative materials (GTR and/or BARG). Biologic principles supporting the use of *autologous and heterologous grafts* include osteoconductivity and osteoinductivity, but also their capacity for space provision and blood clot stabilization (Rosen *et al*. 2000; Trombelli & Farina 2008).

The clinical efficacy of allografts in terms of bone fill and CAL gain is supported by a meta-analysis of 27 controlled studies indicating that additional bone fill of 1 mm and additional CAL gain of 0.4 mm were observed (see Fig 38-8) (Reynolds *et al*. 2003). The total number of defects contributing to this meta-analysis however was relatively small (136 for CAL gain and 154 for bone fill). Furthermore, no large-scale multicenter trial has ever been performed and hence the applicability of these results to clinical practice settings remains to be established.

BRGs can be applied alone following elevation of a PPF for the treatment of intrabony defects. The graft is applied to overfill the defect to compensate for an expected degree of shedding of the graft in cases of imperfect containment of the graft by the closed flap. A study has suggested using BRGs in combination with an antibiotic powder to enhance control of the bacterial contamination of the surgical wound (Yukna & Sepe 1982). This study reported improved outcomes from mixing the graft with tetracycline powder. DFDBAs have been successfully used along with MIS (Harrel 1999).

Grafts for furcation involvement

A series of controlled clinical trials has evaluated the clinical performances of BRGs in the flap approach to the treatment of furcation defects. Reynolds *et al*. (2003) in their review found an overall PPD reduction ranging from 1.9 mm to 2.31 mm in class II furcations treated with BRGs, compared with 0–1.8 mm for those treated with OFD alone. For class III defects, BRGs produced a PPD change of 0.7–2.6 mm, as compared −1–2.6 mm in the controls. CAL changes were similar for mandibular class II and III furcations, ranging from 1.5 to 2.5 mm for grafted sites compared with 0–1.5 mm for the flap controls. The authors concluded that the results of these studies suggest that BRGs alone add relatively modest clinical benefit in the treatment of class II and III furcations, especially if complete closure of the furcation is the desired end point of treatment. More recently, Tsao *et al*. (2006b) tested a solvent-preserved, mineralized human cancellous bone allograft (MBA) with or without a collagen membrane in the treatment of 27 mandibular class II furcations. Their results indicated that solvent-preserved MBA, with or without a collagen membrane, can significantly improve bone fill in mandibular class II furcation defects.

Biologically active regenerative materials

Preclinical and clinical evidence for the use of BARGs has been reviewed (see also Chapter 28). The adoption of *biologic products/compounds* is based on their

ability to induce or accelerate the processes of matrix formation and cell differentiation (Bosshardt 2008). These products promote the healing process but lack mechanical properties to aid space provision and blood clot stabilization. Some of these, therefore, are loaded on solid, bioresorbable carriers to add some mechanical properties (Palmer & Cortellini 2008; Trombelli & Farina 2008). Currently, preparations based on growth factors or amelogenins are available for use in periodontal regeneration. Significant preclinical evidence supports the positive effect of both on periodontal wound healing and regeneration (Howell *et al*. 1997; Bosshardt 2008).

Growth factors for intrabony defects

Support for the clinical use of growth factors comes from two multicenter studies on recombinant human-derived growth factor (Nevins *et al*. 2005; Jayakumar *et al*. 2011) and two on fibroblast growth factor-2 (FGF-2) (Kitamura *et al*. 2008, 2011). Nevins *et al*. (2005) treated 180 defects comprising both intrabony and furcation defects with one of two concentrations of PDGF (0.3 mg/mL and 1.0 mg/mL) combined with the β-TCP delivery device or TCP alone. Results were assessed at 3 and 6 months and included both clinical and radiographic assessments. CAL gains at 6 months failed to demonstrate a significant benefit for either concentration of PDGF compared with the BRG alone. With regards to radiographic assessments, however, the lower tested concentration of PDGF resulted in significantly higher percentages of bone fill of the defect (57% versus 18%) and linear bone growth (2.6 mm versus 0.9 mm). The results of this study led to the approval of this material by the US Food and Drug Administration. The authors interpreted the dichotomy between the reported added benefit in terms of radiographic parameters and the lack of significant changes in CAL as the result of the biologic action of the growth factor formulation in shortening the healing time of the hard tissues.

In the Jayakumar *et al*. (2011) study, 54 patients were treated with rhPDGF-BB combined with the β-TCP delivery device or TCP alone. CAL gain, bone growth, and percent bone fill at 6 months were significantly greater in the test group as compared with the TCP control group.

The study of 74 patients by Kitamura *et al*. (2008) compared three different concentrations of a FGF-2 vehicle with 3% hydroxypropylcellulose (HPC) to HPC alone. No difference was reported in terms of CAL gain between the test and control groups. However, a significant difference in terms of bone gain was reported in favor of the 0.3% concentration of FGF-2 as compared with HPC alone. The other two concentrations (0.03% and 0.1%) did not show any advantage in terms of bone gain. A second randomized, double-blind, placebo-controlled clinical trial on 253 adult patients compared 0.2%, 0.3%, or 0.4% FGF-2 to vehicle alone in two- or three-walled vertical bone defects (Kitamura *et al*. 2011). Each dose of FGF-2 showed significant superiority over vehicle alone (P <0.01) for the percentage of bone fill at 36 weeks after administration. No significant differences were observed between the groups in CAL gain.

No clinical safety problems were reported in any of the four cited studies.

Drawing conclusions from the four studies, it is apparent that both the tested growth factors resulted into a measurable added benefit compared with controls in terms of bone gain, while three of the four studies did not reach a significant difference in terms of CAL gain. Both efficacy and effectiveness of rhPDGF-BB and FGF-2 have to be further explored for use in private settings.

A recent controlled study evaluated clinical and histologic wound healing/regeneration following surgical implantation of recombinant human growth/differentiation factor-5 (rhGDF-5) adsorbed onto a particulate β-TCP carrier (rhGDF-5/β-TCP) into periodontal defects in 28 patients (Stavropoulos *et al*. 2011). Control defects were treated with OFD alone. The authors reported greater PPD reduction, CAL gain, alveolar bone regeneration, and periodontal regeneration at sites that received rhGDF-5/β-TCP compared with control sites. However, these differences were not statistically significant. Block biopsies of the defect sites were collected at 6 months post-surgery. Histologically, bone regeneration height was almost three-fold greater for the rhGDF-5/β-TCP treatment compared with OFD alone (2.19 ± 1.59 mm versus 0.81 ± 1.02 mm; P = 0.08). Similarly, an almost twofold increase was observed for periodontal ligament (2.16 ± 1.43 mm versus 1.23 ± 1.07 mm; P = 0.26), cementum (2.16 ± 1.43 mm versus 1.23 ± 1.07 mm; P = 0.26), and bone regeneration area (0.74 ± 0.69 mm^2 versus 0.32 ± 0.47 mm^2; P = 0.14). Root resorption/ankylosis was not observed. Future studies with larger sample sizes need to be conducted to verify these findings.

Growth factors for furcation involvement

A human clinical trial (Camelo *et al*. 2003) was designed to evaluate the clinical and histologic response to rhPDGF-BB delivered in bone allograft for the treatment of advanced class II furcation defects. Three mandibular and one maxillary molar furcation defects were treated: two received 0.5 mg/mL and two 1.0 mg/mL of rhPDGF-BB, in all cases mixed with DFDBA. Both concentrations of rhPDGF-BB resulted in substantially improved horizontal (mean 3.5 mm) and vertical (mean 4.25 mm) probing depths and attachment levels (mean 3.75 mm). Histologic evaluation revealed periodontal regeneration, including new bone, cementum, and periodontal ligament coronal to the reference notch. This study documented the favorable tissue response to rhPDGF-BB treatment at

both the clinical and microscopic levels and demonstrated that periodontal regeneration can be achieved in advanced class II furcation defects using a combination of purified recombinant growth factor and bone allograft. These outcomes were confirmed by a second study of 15 sites presenting with class II furcations in which the PDGF was loaded on DFDBA (Nevins *et al*. 2003), and in another study of four class III furcations in which the growth factor was loaded on TCP (Mellonig *et al*. 2009).

Promising histologic and clinical outcomes can be envisioned from these pilot studies. However, larger controlled clinical trials are needed to assess the real potential of growth factors in the treatment of teeth with furcation involvement.

Enamel matrix derivatives for intrabony defects

EMDs have been in clinical use for over 10 years and their clinical efficacy is very well established. The benefit of use of EMD gel in the treatment of intrabony defects is supported by human histologic evidence, case report studies, meta-analysis of randomized controlled clinical trials, and a large multicenter trial (Heijl *et al*. 1997; Heden *et al*. 1999; Sculean *et al*. 1999b; Silvestri *et al*. 2000; Heden 2000; Tonetti *et al*. 2002; Giannobile & Somerman 2003; Heden & Wennström 2006) (Figs. 38-26, 45-27, 38-43). The prospective multicenter randomized controlled clinical trial (Tonetti *et al*. 2002) was designed to compare the clinical outcomes of PPF surgery with or without the application of EMDs in 172 patients with advanced chronic periodontitis in 12 centers in seven countries. All patients had at least one intrabony defect of 3 mm or deeper. Heavy smokers (>20 cigarettes/day) were excluded. The surgical procedures included access for root instrumentation using either the SPPF or the MPPT in order to obtain optimal tissue adaptation and primary closure. After debridement, roots were conditioned for 2 minutes with a gel containing 24% EDTA. EMDs were applied to the test subjects and omitted in the controls. A total of 166 patients were available for the 1-year follow-up. On average, the test defects gained 3.1 ± 1.5 mm of CAL, while the control defects yielded a significantly lower CAL gain of 2.5 ± 1.5 mm. Pocket reduction was also significantly higher in the test group (3.9 ± 1.7 mm) compared with the controls (3.3 ± 1.7 mm). A multivariate analysis indicated that the treatment, the clinical centers, cigarette smoking, baseline PPD, and defect corticalization significantly influenced CAL gain. A frequency distribution analysis of the studied outcomes indicated that EMDs increased the predictability of clinically significant results (CAL gain >4 mm) and decreased the probability of obtaining negligible or no gain in CAL (CAL gain <2 mm). The results of this trial indicated that regenerative periodontal surgery with EMDs offers an additional benefit in terms of CAL gain, PPD reduction, and predictability of outcomes over PPF alone.

A secondary analysis of the multicenter trial has shown that, in intrabony defects, the added benefit of EMDs was greater in three-wall defects than in one-wall defects (Tonetti *et al*. 2002). Furthermore, another secondary analysis of the trial, but this time assessing the effect of the radiographic angle of the defect angle on the outcome (Tsitoura *et al*. 2004), uncovered a negative association between this angle and the CAL

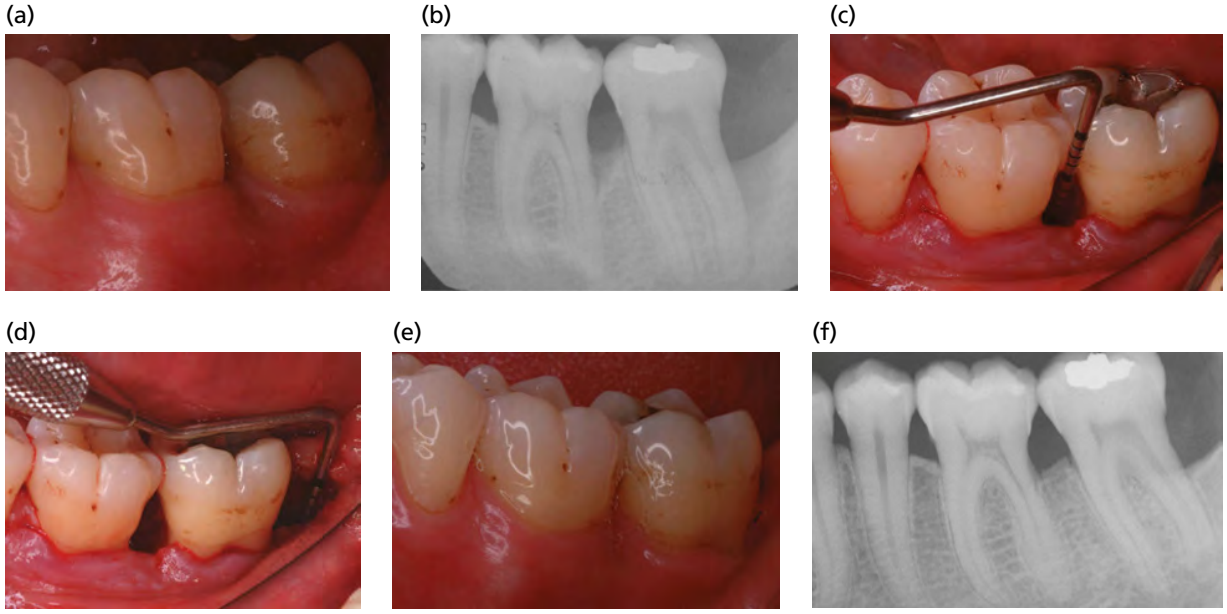


Fig. 38-43 Clinical case illustrating the use of enamel matrix derivatives (EMDs) to regenerate defects located on two adjacent teeth. At re-evaluation, deep pockets associated with deep intrabony defects were evident on the distal aspect of the first and second molars (a, b). Defects were accessed with the modified papilla preservation technique (MPPT) on the distal aspect of the first molar and with the use of a crestal incision in the retromolar area (c, d). Deep defects were exposed following debridement and root instrumentation (c, d). Following application of EMDs in gel form, primary closure was obtained with multilayered sutures. At 1-year follow-up, shallow probing depths associated with the elimination of the defects were observed (e, f).

gain observed at 1 year. These data have questioned the suitability of the gel formulation of EMDs for the treatment of defects with a non-supporting anatomy (wide defects with missing bony walls) and spurred considerable research interest in the incorporation of EMDs into a variety of BRGs in order to enhance wound stability and space maintenance. At this stage, however, no systematic evidence is available to support the use of such combinations.

More recently, EMDs have been successfully used in combination with minimally invasive techniques from MIS (Harrel *et al*. 2005), to MIST (Cortellini & Tonetti 2007a, b; Cortellini *et al*. 2008; Ribeiro *et al*. 2011a), and to M-MIST (Cortellini & Tonetti 2009a, 2011). This product is very well suited to sites where flap reflection is minimal since its positioning does not require any flap extension and the improved stability provided by MIS to the wound seems to favor the expression of its activity (Cortellini *et al*. 2008; Cortellini & Tonetti 2009a).

Clinically, the rate of wound healing following application of EMDs seems to be enhanced. A study looking at soft tissue density in the surgical site by using underexposed radiographs (Tonetti *et al*. 2004b) found that the rate of increase in density following application of EMDs may be faster than in the access flap control. Such modulation has been interpreted as the outcome of the local release of growth and differentiation factors by the cells involved in local wound healing. Given their hydrophobic nature, enamel matrix proteins for clinical use are mixed in a gel carrier at low pH. Following an increase in pH in the periodontal wound and rapid elimination of the gel, enamel matrix proteins (consisting mainly of EMDs) are deposited in the wound environment and the root surface. While the mechanism(s) of action of EMDs are not fully understood, significant evidence suggests that periodontal ligament cells exposed to EMDs switch their phenotype by increasing expression of a host of growth and differentiation factor-related genes (Brett *et al*. 2002; Parkar & Tonetti 2004), including transforming growth factor-beta (Lyngstadaas *et al*. 2001). A recent review (Bosshardt 2008) concluded that: (1) EMDs increase the cell proliferation of periodontal ligament and gingival fibroblasts and cells of osteoblast and chondrocyte lineage; (2) EMDs have biologic effects on cells of the osteoblast lineage, including up-regulation of markers of bone formation; (3) specific small amelogenin polypeptides (5 kDa) have osteoinductive properties when tested in an ectopic bone-forming model; and (4) the evidence does not demonstrate an inductive role for EMDs on cementogenesis.

Enamel matrix derivatives for furcation involvement

Treatment of mandibular class II furcations with EMDs was attempted by Jepsen *et al*. (2004). A randomized intraindividual study of 45 patients was designed to compare EMDs and bioresorbable barriers. Both treatment modalities led to a significant clinical improvement. The authors reported a median reduction of open furcation depth of 2.8 mm in the EMD-treated sites compared with a reduction of 1.8 mm in the barrier-treated sites. Complete furcation closure was recorded in eight of 45 EMD-treated sites and three of 45 barrier-treated sites. Differences between test and control sites were not statistically significant. Chitsazi *et al*. (2007) reported an H-CAL gain that was significantly greater in EMD-treated mandibular class II furcations than in OFD controls ($P = 0.002$).

Another randomized study (Casarin *et al*. 2008) compared the use of EMDs with open flap alone in 15 patients with contralateral proximal maxillary class II furcations. At 6 months, the V-CAL gains in the control and test groups were 0.39 ± 1.00 mm and 0.54 ± 0.95 mm, respectively, while the H-CAL gains were 1.21 ± 2.28 mm and 1.36 ± 1.26 mm, respectively ($P = 0.05$). The vertical bone level and horizontal bone level gains of the control group were 1.04 ± 1.12 mm and 1.00 1.79 mm, respectively, and of the test group were 0.82 ± 1.82 mm and 1.17 ± 1.38 mm, respectively ($P = 0.05$). However, a statistically significant greater number of reduced/closed furcations was observed in the test group ($P = 0.05$). The authors concluded that the use of EMDs in proximal furcations does not promote a superior reduction in PPD or a gain in clinical and osseous attachment levels but can result in a higher rate of conversion of class II to class I furcations.

Controversial outcomes have been so far observed in the treatment of class II either maxillary or mandibular furcations with EMDs. Their use seems, however, to provide an added benefit compared with flap treatment alone.

Combination therapy

Combination therapy for intrabony defects

Biologic principles supporting *combination therapy* relate to the possibility of obtaining an additive effect from combining different regenerative principles, including osteoconductivity and osteoinductivity, capacity for space provision and blood clot stabilization, and ability to induce or accelerate the processes of matrix formation and cell differentiation that are inherent in barriers, grafts, and bioactive substances.

Compromised results after GTR may be observed in cases where the gingival flap, eventually supported by a membrane, collapses/falls (partially or totally) into the defect and/or towards the root surface, thereby reducing the space available for blood clot formation and growth of new tissues capable of forming periodontal ligament and bone in particular. Reduced amounts of regenerated bone due to membrane collapse were noted in early studies of GTR. In the study of Gottlow *et al*. (1984), it was observed that collapse of the membrane towards the root surface

resulted in new cementum formation on the entire exposed root surface, whereas bone regeneration was minimal. Although the authors reported that the degree of coronal regrowth of bone was unrelated to the amount of new cementum formation, they did not comment on what effect membrane collapse might have had. Experimental studies, however, recognized the negative effect of membrane collapse on periodontal regeneration generally and on bone formation in particular (Caton *et al*. 1992; Haney *et al*. 1993; Sigurdsson *et al*. 1994; Sallum *et al*. 1998). Haney *et al*. (1993) observed a highly significant correlation between the space provided by the membrane and the amount of regenerated alveolar bone in a supra-alveolar defect model in dogs. This finding corroborates that of Cortellini *et al*. (1995c) who reported that clinical application of self-supporting (reinforced with titanium) e-PTFE membranes, which could be positioned more coronally than ordinary e-PTFE membranes, yielded a statistically significant increase in PAL gain in intrabony defects. A particular risk for gingival flap/membrane collapse exists in cases where the configuration of the defect is incapable of supporting/preserving the membrane at the position where it was originally placed.

As already discussed, membrane materials must possess certain characteristics in order to be efficient. Among these, the membrane needs to be capable of keeping its shape and integral features, thereby maintaining the space created adjacent to the root surface. The e-PTFE membranes reinforced with titanium are the closest to meeting these requirements, but they have the disadvantage that they are non-bioresorbable. At present there are no bioresorbable membranes available that fulfil this requirement sufficiently, which means that the placement of a bioresorbable membrane on, for instance, a wide one-wall defect involves the risk of membrane collapse. The collapse may be prevented by implantation of a biomaterial into the defect to support the membrane so that it maintains its original position (Figs. 38-24, 38-44). While biologic products can enforce the healing process, they also lack mechanical properties to aid space provision and blood clot stabilization. A potential solution, therefore, could be to load the biologic products onto solid, bioresorbable carriers to provide the necessary mechanical properties (Palmer & Cortellini 2008; Trombelli & Farina 2008). However, the biomaterial to be used for this purpose must not interfere with the process of periodontal regeneration and ideally it should also promote bone regeneration.

As previously described, periodontal regeneration has been attempted with a variety of grafting materials, among which DFDBAs apparently facilitate regeneration in humans (Ouhayoun 1996). In three controlled clinical trials, the treatment of a total of 45 pairs of intrabony defects with DFDBA grafting and GTR was compared with GTR treatment alone (Table 38-9). The weighted mean of the results of the reported investigations showed similar gain in CAL in the GTR group (2.1 ± 1.1 mm; 95% CI 1.6–2.6 mm) and in the GTR + DFDBA group (2.3 ± 1.4 mm; 95% CI 1.7–2.9 mm). The differences between the two treatments did not reach statistical significance, thus indicating no added effect of combining DFDBAs with barrier materials in the treatment of intrabony defects. Guillemin *et al*. (1993) compared the effect of DFDBAs alone with a combination of barrier materials plus DFDBAs in 15 pairs of intrabony defects. Both treatments resulted in significant CAL gain and bone fill at 6 months, but no difference was found between the treatments. Reynolds *et al*. (2003), in their systematic review, highlighted that clinical improvements from graft/barrier combinations were often obtained in large non-space maintaining defects. They concluded that the combination of graft and barriers can provide a significant gain in CAL and PPD reduction and a non-significant increase in bone fill when compared with graft alone.

Promising clinical results with a PAL gain of 1.0–5.5 mm were obtained in human case reports in which the GTR technique was combined with grafting of Bio-Oss®, an anorganic bovine bone xenograft, for the treatment of intrabony periodontal defects (Lundgren & Slotte 1999; Mellonig 2000; Paolantonio *et al*. 2001). The combined use of Bio-Oss® and GTR treatment resulted in greater PPD reduction, PAL gain, and defect fill compared to implantation of Bio-Oss® alone in case series (Camelo *et al*. 1998) and to flap surgery alone in a split-mouth study (Camargo *et al*. 2000).

In a randomized controlled clinical study including 60 patients (Stavropoulos *et al*. 2003), Bio-Oss® alone or impregnated with gentamicin was used as an adjunct to GTR in the treatment of one-wall or two-wall intrabony defects, and the outcomes were compared with those obtained following GTR or flap surgery alone. Treatment with a membrane alone (Fig. 38-45) resulted in a mean PAL gain of 2.9 mm, while it was 3.8 mm and 2.5 mm, respectively, when Bio-Oss® grafts with or without gentamicin were placed in the defects prior to membrane coverage (Fig. 38-46). The control defects treated with flap surgery demonstrated a PAL gain of only 1.5 mm. The clinical improvements in defects treated with GTR alone or in combination with Bio-Oss® grafting were significantly better than those obtained with flap surgery, whereas the differences between the groups treated with membranes were not statistically significant. A prospective multicenter randomized controlled clinical trial (Tonetti *et al*. 2004b) was designed to compare the clinical outcomes of PPF surgery with or without the application of a GTR/bone replacement material. One hundred and twenty-four patients with advanced chronic periodontitis were treated in 10 centers in seven countries. All patients had at least one intrabony defect of at least 3 mm. One year after treatment, the test defects gained 3.3 ± 1.7 mm of CAL, while the control defects yielded a significantly lower

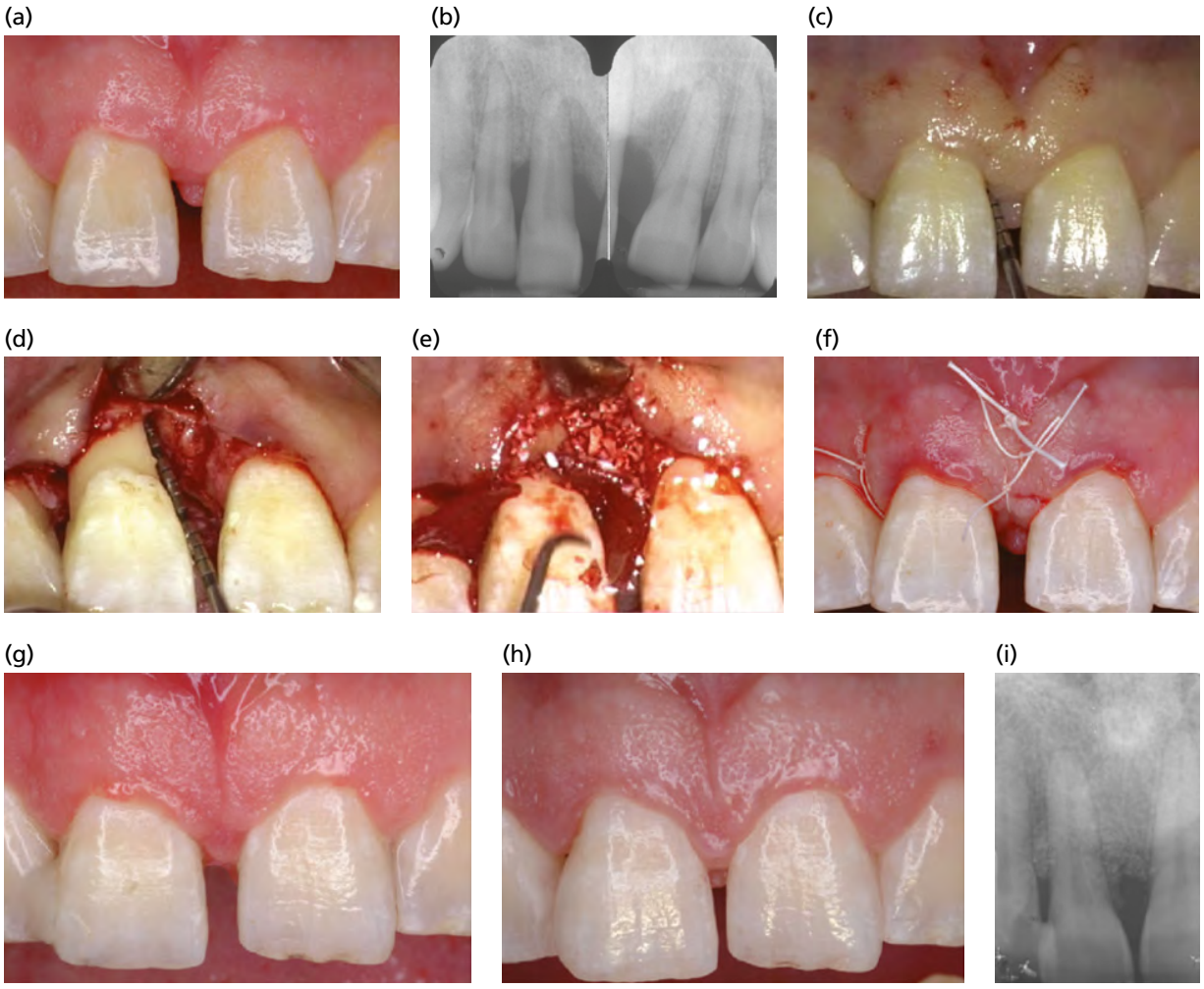


Fig. 38-44 Clinical case illustrating the application of a bone replacement graft (BRG) to support a bioresorbable membrane in a defect with poor space maintaining anatomy. Following control of periodontitis and risk factors, the upper right central incisor presented with a 12-mm deep pocket associated with a defect extending close to the apex of the tooth (a–c). The defect was accessed with the modified papilla preservation flap to reveal an 8-mm intrabony component (d). A BRG was placed under a bioresorbable collagen membrane (e). Primary closure was achieved with a multilayered suture technique (f). Excellent early healing was observed already at the 2-week follow-up (g). At 1 year, periodontal regeneration resulted in shallow probing depths and good resolution of the intrabony defect (h, i). Radio-opaque BRG particles were visible within the newly formed mineralized tissue.

Table 38-9 Controlled clinical trials evaluating the combined effects of decalcified freeze-dried bone allografts (DFDBAs) and barrier membranes in deep intrabony defects.

Study	Design (GTR treatment)	Number[a]	Gains in CAL (mm)		*P* value	Residual PPD (mm)		*P* value
			GTR	GTR + DFDBA		GTR	GTR + DFDBA	
Chen *et al*. (1995)	Intraindividual (collagen)	8	2.0 ± 0.4	2.3 ± 0.5	>0.05, NS	4.2 ± 0.4	4.2 ± 0.5	>0.05, NS
Mellado *et al*. (1995)	Intra-individual (e-PTFE)	11	2.0 ± 0.9	2.0 ± 1.4	0.86, NS	NA	NA	NA
Gouldin *et al*. (1996)	Intra-individual (e-PTFE)	26	2.2 ± 1.4	2.4 ± 1.6	NS	3.7 ± 1.6	3.7 ± 1.8	NS
Weighted mean		**45**	**2.1 ± 1.1**	**2.3 ± 1.4**		**3.8 ± 1.3**[b]	**3.8 ± 1.5**[b]	

[a] Defects per treatment arm.
[b] *n* = mean (34) ± SD (34).
CAL, clinical attachment level; e-PTFE, expanded polytetrafluoroethylene; GTR, guided tissue regeneration; NA, not available; NS, not significant.

CAL gain of 2.5 ± 1.5 mm. Pocket reduction was also significantly higher in the test group (3.7 ± 1.8 mm) when compared with the controls (3.2 ± 1.5 mm). A multivariate analysis indicated that the treatment, the clinical centers, baseline PPD and baseline full-mouth bleeding score (FMBS) significantly influenced CAL gains. The OR for achieving above-median CAL gains were significantly improved

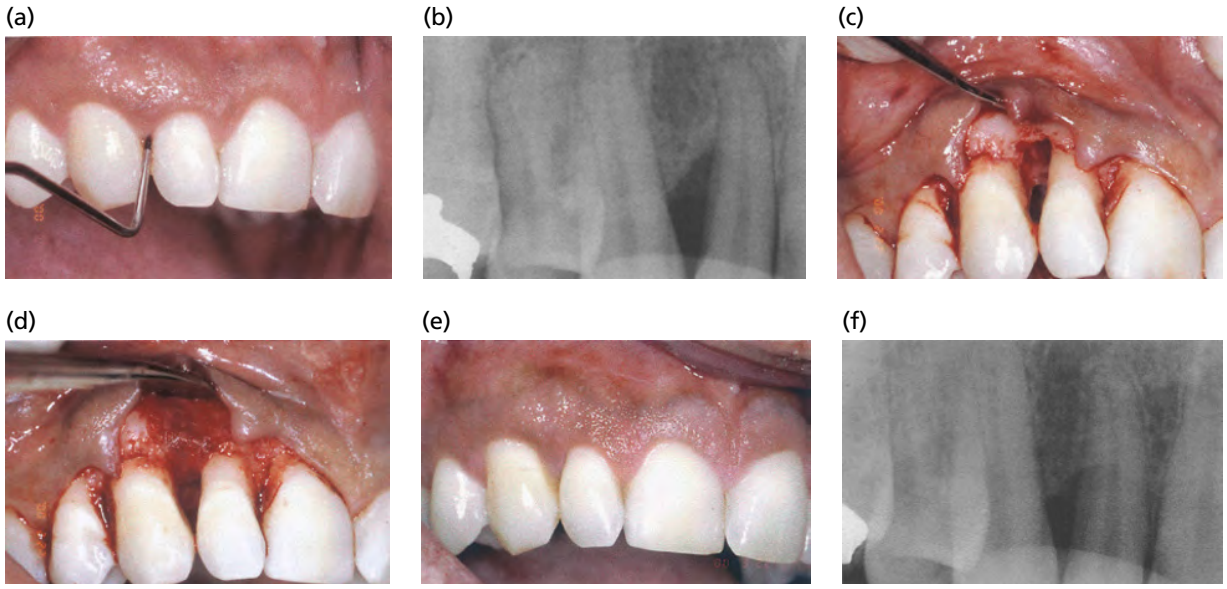


Fig. 38-45 Right lateral maxillary incisor with an 8-mm deep pocket associated with an intrabony defect on the distal aspect (a), as seen on the radiograph (b). Full-thickness buccal and palatal flaps were raised and the defect was debrided (c). A bioresorbable membrane was placed over the defect (d). The level of the interdental gingiva was maintained after 1 year (e) and the intrabony defect (f) had resolved.

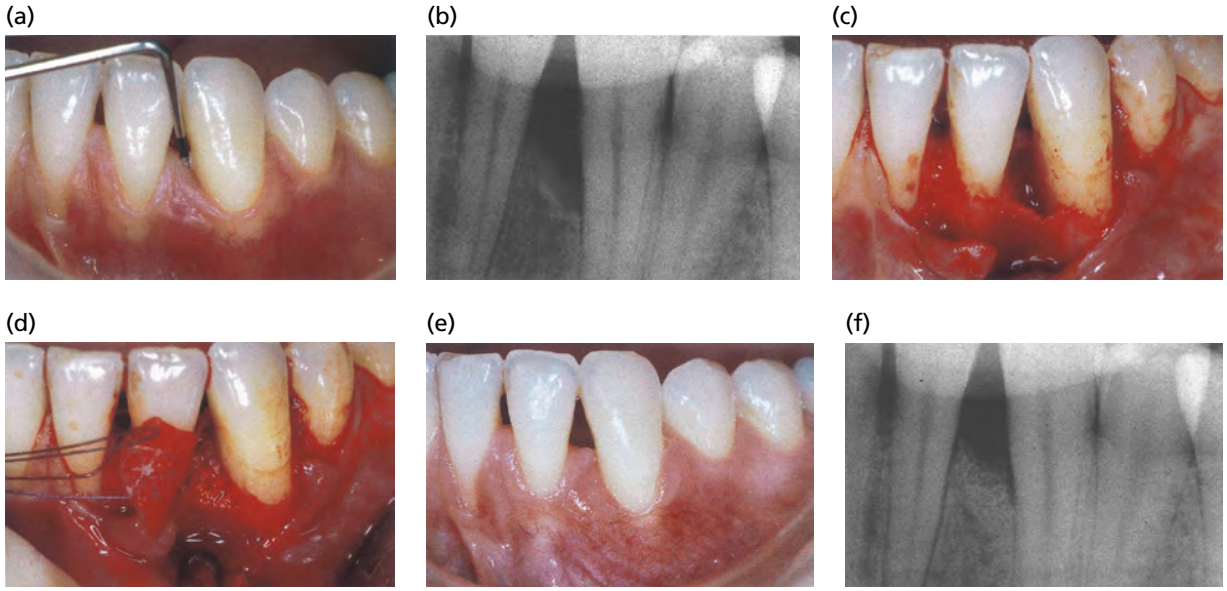


Fig. 38-46 Left mandibular canine with an 8-mm deep pocket (a) associated with an intrabony defect on its mesial aspect (b). The defect was debrided after flap elevation (c) and Bio-Oss® particles were placed in the defect (d) prior to placement of a bioresorbable membrane. After 1 year (e), no gingival recession had occurred and the intrabony defect had almost resolved (f).

by the test procedure (OR 2.6, 95% CI 1.2–5.4) and by starting with deeper PPD (OR 1.7, 1.3–2.2), but were decreased by receiving treatment at the worst-performing clinical center (OR 0.9, 0.76–0.99). The results of this trial indicated that regenerative periodontal surgery with a GTR/bone replacement material offers an additional benefit in terms of CAL gain, PPD reduction, and predictability of outcomes with respect to PPF alone.

In a controlled study (Pietruska 2001), similar clinical improvements were obtained when Bio-Oss® combined with GTR was compared with the use of enamel matrix protein (Emdogain®).

Camelo *et al*. (1998) and Mellonig (2000) presented histologic data indicating that the use of Bio-Oss® under a membrane may result in partial regeneration of the periodontal apparatus, but in all the cases most of the defect was still occupied by deproteinized bone particles. Bone was not observed near the root, and the connective tissue fibers of the "new" periodontal ligament were mostly oriented parallel to the root surface. These results corroborate findings reported by Paolantonio *et al*. (2001), who observed only limited bone formation in the vicinity of the pre-existing bone in a biopsy, taken from a site treated 8 months earlier with Bio-Oss® and a collagen membrane.

Most of the space in the defect was occupied by Bio-Oss® particles embedded in connective tissue. However, in a case report where intrabony defects were treated with Bio-Oss® combined with intraoral autogenous bone and GTR, new attachment formation had occurred consistently, but a major portion of the regenerated osseous tissue consisted of deproteinized bone particles (Camelo *et al*. 2001).

Combination therapy including use of EMDs plus barrier membranes and/or grafting materials have been tested. A systematic review (Trombelli & Farina 2008) concluded that there is evidence to support the use of EMDs either alone or in combination with grafts to effectively treat intraosseous defects and the additional use of a graft seems to enhance the clinical outcome with EMDs alone. The combined use of rhPDGF-BB and P-15 with a graft biomaterial has shown beneficial effects in intraosseous defects; contrasting results were reported for PRP and graft combinations. A systematic review by Tu *et al*. (2010) concluded that there was little evidence to support the additional benefits of EMDs in conjunction with other regenerative materials when compared with EMDs alone. When different types of bone grafts and barrier membranes were used, EMDs with bovine bone grafts showed greatest treatment effects.

More recently, combination therapy has been successfully used in sites treated with minimally invasive surgeries. Cortellini and Tonetti (2011) proposed a combination of EMDs and Bio-Oss® with the M-MIST, and Trombelli *et al*. (2010) a combination of a bioresorbable barrier and a graft with the single flap approach.

Combination therapy for furcation involvement

Schallhorn and McClain (1988) reported on improved clinical results in intrabony defects and class II furcations, following a combination therapy including barrier membranes plus DFDBA and citric acid root conditioning. The authors reported a complete furcation closure in 75% of the treated sites (McClain & Schallhorn 1993).

In one study, barrier membranes alone were compared to combination therapy with hydroxyapatite. The difference in clinical outcomes between the two treatments was not statistically significant, but the combination therapy resulted in a greater extent of furcation fill (Lekovic *et al*. 1990).

In three studies on mandibular class II furcations, GTR treatment alone was compared with GTR treatment combined with DFDBA. In one of these investigations, a statistically significant improvement was found in terms of H-OPAL in the group of furcations treated with the combination therapy (Anderegg *et al*. 1991). In a second investigation, a non-bioresorbable barrier with and without DFDBA was tested in six patients with 17 mandibular class II buccal molar furcal invasions (Wallace *et al*. 1994). Ten teeth were randomly selected as test sites (e-PTFE + DFDBA) and seven as controls (e-PTFE alone). After 6 months, all sites were re-entered and both soft tissue and open surgical measurements were recorded. The addition of DFDBA to the GTR procedure did not significantly improve any of the mean soft tissue and open surgical measurements between the control and test groups. Both treatment procedures resulted in significant decreases in PPD, distance from the cementoenamel junction to the bottom of the defect (CEJ–BD), and horizontal bone fill and a significant increase in recession. In a third study, a bioresorbable barrier with and without DFDBA was tested in 14 subjects with paired class II mandibular molar furcation defects (Luepke *et al*. 1997). When the bioresorbable barrier alone was compared with the bioresorbable barrier in combination with DFDBA, PPD reduction was significantly (P <0.01) in favor of the combination therapy. Vertical bone gain was significant greater with the combination treatment (P <0.02). The authors concluded that the combination therapy of bioresorbable barrier plus DFDBA is superior to the control therapy of bioresorbable barrier alone.

Lekovic *et al*. (2003) tested a combination of PRP, bovine porous bone mineral (BPBM), and GTR in 52 class II furcations (26 treated with the test material and 26 with OFD, which served as controls). The experimental group presented with significantly greater pocket reduction (4.07 ± 0.33 mm for experimental and 2.49 ± 0.38 mm for control sites), CAL gain (3.29 ± 0.42 mm for experimental and 1.68 ± 0.31 mm for control sites), vertical defect fill (2.56 ± 0.36 mm for experimental and −0.19 ± 0.02 for control sites), and horizontal defect fill (2.28 ± 0.33 mm for experimental and 0.08 ± 0.02 mm for control sites) than the control group. The authors concluded that the PRP/BPBM/GTR combined technique is an effective modality of regenerative treatment for mandibular grade II furcation defects. However, further studies are necessary to elucidate the role played by each component of the combined therapy in achieving these results.

Houser *et al*. (2001) compared the use of Bio-Oss® in combination with a bioresorbable collagen barrier (BioGide®) to OFD surgery in human mandibular class II furcation defects. A total of 31 furcations (18 test, 13 control) in 21 patients were treated. There was a statistically significant improvement in most clinical parameters for the experimental group, with minimal improvement noted for the flap control group. Vertical PPD reduction of 2.0 mm and horizontal PPD reduction of 2.2 mm were reported for the experimental group, while 0.3 mm and 0.2 mm reductions, respectively, were reported for the control group. Hard tissue measurements showed 2.0 mm of vertical furcation bone fill for the test group and 0.5 mm for the control group. The test group had 3.0 mm of horizontal furcation bone fill and the control group had 0.9 mm. The test group had a defect resolution of 82.7% compared with 42.5% in the flap control group. There was a statistically significant difference between the two groups in all soft and hard tissue

measurements with the exception of attachment level, recession, and alveolar crest resorption. The authors concluded that the combination of Bio-Oss® and Bio-Gide® is effective in the treatment of mandibular class II furcations.

Belal *et al*. (2005) treated 50 furcations in 20 patients with five different approaches (bioresorbable membrane or a connective tissue graft with or without bioresorbable hydroxylapatite, and flap alone as a control therapy). All experimental groups showed statistically significant improvement in the clinical parameters and bone density as compared with the control group. However, no statistically significant differences were observed between any of the experimental groups. Percentages of complete furcation closure ranged from 20% to 40% in the experimental groups, but was 0% in the flap control group.

Root surface biomodification

The effect of combining citric acid root biomodification with GTR treatment was evaluated in two randomized controlled clinical trials in intrabony defects. The first investigation (Handelsman *et al*. 1991) demonstrated significant CAL gain in both the test (e-PTFE membranes + citric acid; 3.5 ± 1.6 mm) and control sites (e-PTFE membranes alone; 4.0 ± 1.4 mm). Less favorable results following these two treatment modalities were reported by Kersten *et al*. (1992) who found CAL gains of 1.0 ± 1.1 mm in the test group and of 0.7 ± 1.5 mm in the control group. Both studies, however, failed to demonstrate any added effect of the use of citric acid in combination with non-bioresorbable barrier membranes.

Root surface biomodification with tetracycline alone and in combination with GTR was evaluated in two controlled studies on class II furcations (Machtei *et al*. 1993; Parashis & Mitsis 1993). Both investigations failed to show significant differences between sites treated with non-bioresorbable barrier membranes alone or in combination with tetracycline root surface biomodification. Similarly, the use of other surface-active chemicals like EDTA also failed to provide a significant added effect to GTR treatment in humans (Lindhe & Cortellini 1996).

The suggested role of root surface biomodification for improving periodontal regeneration has been assessed in a systematic review (Mariotti 2003). The results of that exhaustive review of the evidence indicated that there was no evidence for a measurable improvement following root conditioning with agents like citric acid, tetracycline–HCl, phosphoric acid, fibronectin, or EDTA.

Clinical potential and limits for regeneration

From the very beginning of modern periodontal regeneration it was apparent that periodontal tissues could express a surprising regenerative potential under favorable circumstances. Sparse case reports demonstrated that very deep defects reaching the apical third of the root could be filled with new bone and new clinical attachment (Pini Prato *et al*. 1988; Becker *et al*. 1988; Cortellini *et al*. 1990). Larger studies suggested that in deeper defects, greater clinical improvement is generally obtained (Tonetti *et al*. 1993a, 1996a; Garrett *et al*. 1998; Slotte *et al*. 2007). These observations raised a question about the "potential" for regeneration: is the potential greater in deeper defects? Cortellini *et al*. (1998) addressed this question in a controlled study and reported similar attachment gain in defects presenting with an intrabony component of ≤3 mm (76% defect resolution) and defects of ≥4 mm (77% defect resolution), indicating that the potential for regeneration is similar in both shallow and deep intrabony components. The conclusions of this study are indirectly supported by the results of large controlled clinical trials performed with the application of different successful regenerative approaches (Cortellini *et al*. 1995c, 1996b, 2001; Tonetti *et al*. 1998, 2002, 2004b). Unpublished subanalyses of these experimental populations, in which the treated defects were clustered according to defect depth, showed that CAL gain is obtained in all defects from shallow to deep, but deeper defects gain more attachment in millimeters than shallow ones. In other words, regeneration seems to express its potential as much as the "container" allows it, independent of the "regenerative approach" chosen, within the panel of the well tested, sound regenerative approaches. A recent controlled study has challenged the limits of the periodontium to repair or regenerate (Cortellini *et al*. 2011). The aim of this randomized, long-term clinical trial was to compare clinical and patient-based outcomes following periodontal regeneration or extraction and replacement of hopeless teeth with attachment loss to or beyond the apex. Twenty-five hopeless teeth were treated with a regenerative strategy. Most of the treated teeth had a periodontal lesion exceeding the apex of the tooth and involving three to four sides of the root (Fig. 38-47). Twenty-three of the 25 regenerated teeth obtained extensive clinical improvements. The average CAL gain was 7.7 ± 2.8 mm, the radiographic bone gain 8.5 ± 3.1 mm, and the PPD reduction 8.8 ± 3 mm. Most of the regenerated teeth showed a decrease in tooth mobility. Only two teeth showing unsatisfactory outcomes were extracted at 1 year. The 23 successfully regenerated teeth (92%) were in good health and function at the 5-year follow-up visit and 84% did not develop biologic complications during the recall period. The authors concluded that regenerative therapy can be successfully applied even to hopeless teeth and has the potential to change their prognosis. However, it should be underlined that the reported outcomes were obtained in a carefully selected patient population, and by applying "state of the art" regenerative therapy by very experienced clinicians, within a high-quality program of periodontal and dental therapy

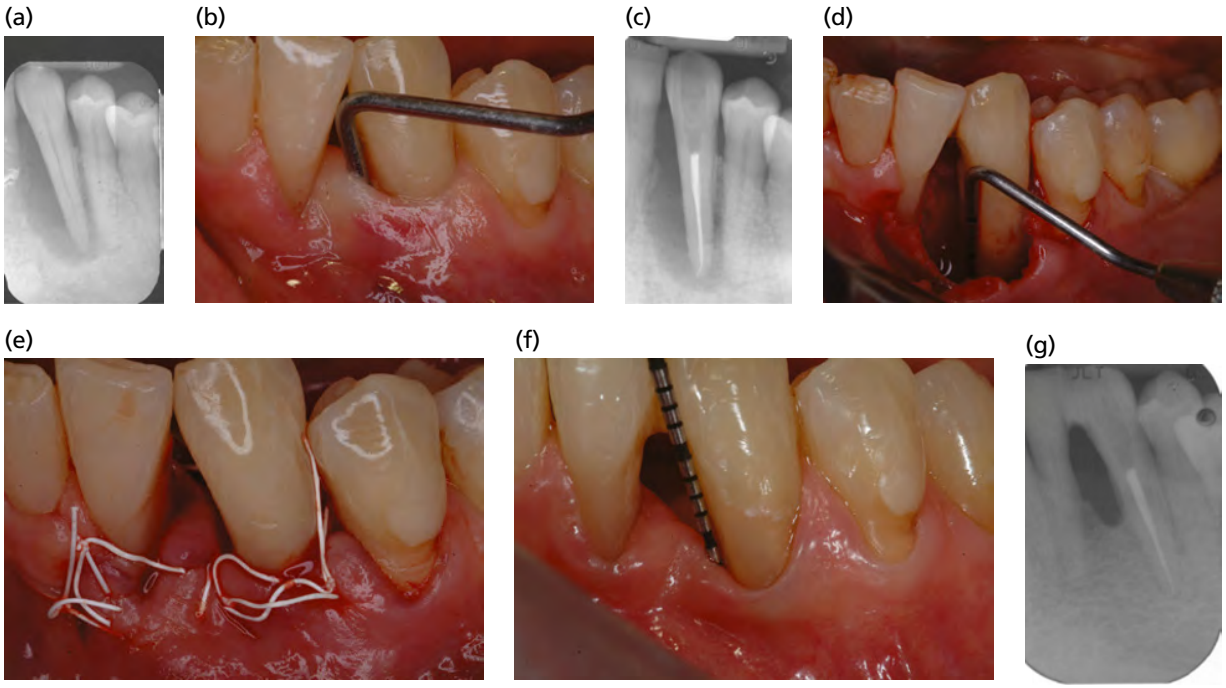


Fig. 38-47 Treatment of a very severe periodontal defect with periodontal regeneration. Baseline radiograph showed a very severe defect extending far beyond the apex of the tooth (a). A pocket deeper than 15 mm was evident at the mesial aspect of the lower left cuspid (b). The tooth was root canal treated (c). The area was accessed with a large flap: bone destruction almost all around is evident (d). The gingival flap was repositioned and sutured with a multilayer technique (e). At 1 year, a 4-mm pocket was probed (f). The radiograph showed the resolution of the periodontal defect (g).

and a strict periodontal supportive care program. In other words, it is apparent from the cited studies that to succeed in extreme conditions, a sound strategy has to be adopted.

A 10-year follow-up of the aforementioned RCT was recently published (Cortellini *et al*. 2020b). Three subjects in the test group exited the study due to extraction of the experimental tooth (two at year 1 for inadequate improvement following regeneration, and one at year 8 due to trauma on the experimental tooth). Four subjects (two in the test and two in the control groups) were lost to follow up after 6 and 7 years: three were unavailable to continue participation and one subject died for study unrelated reasons. The 10-year survival of regenerated teeth was 88% while the 10-year survival of implant or tooth retained fixed partial dentures to replace the extracted teeth was 100%. There was no statistically significant difference comparing test and control treatments ($P = 0.08$, Mantel–Cox log rank test). The 95% confidence interval for the complication free survival time was 6.7–9.1 years for the regeneration group and 7.3–9.1 years for the extraction and tooth replacement group. The difference was statistically not significant ($P = 0.788$, Mantel–Cox log rank test). Periodontal regeneration was more cost-effective than replacement. Sustained improvements in patient reported outcomes and quality of life measures were observed for both groups. The authors concluded that periodontal regeneration is the treatment of choice for compromised teeth with deep vertical intrabony defects.

Clinical strategies

Periodontal regeneration in intrabony defects has been successfully attempted with a variety of different approaches. As discussed, meta-analyses of randomized controlled clinical trials as well as human and animal histologic findings support the potential of barrier membranes (Nyman *et al*. 1982; Gottlow *et al*. 1986), DFDBAs (Bowers *et al*. 1989a–c), combinations of barrier membranes and grafts (Camelo *et al*. 1998; Mellonig 2000), and the use of EMDs (Mellonig 1999; Yukna & Mellonig 2000) or growth factors (Howell *et al*. 1997) to induce periodontal regeneration. Controlled clinical trials report that these approaches provide added benefits in terms of CAL gain as compared with OFD alone (Needleman *et al*. 2002; Trombelli *et al*. 2002; Giannobile & Somerman 2003; Murphy & Gunsolley 2003; Esposito *et al*. 2009; Needleman *et al*. 2006; Darby & Morris 2013). Comparisons between some of the regenerative approaches failed to demonstrate a clear superiority of any of the tested materials (Giannobile & Somerman 2003; Murphy & Gunsolley 2003; Reynolds *et al*. 2003).

The existing evidence, therefore, does not support any particular single regenerative approach. In addition, all the cited studies have shown a substantial degree of variability in terms of CAL gain, reporting failures or unsatisfactory outcomes in part of the treated population.

Research conducted mostly in the past decade has clearly established that the variability observed in outcomes of periodontal regenerative procedures is

dependent on a variety of patient-, defect-, and surgical-associated factors. This is not unexpected since each individual patient presents with unique characteristics as well as each defect presenting with very different and unique anatomies. The outcomes of the randomized studies indicates clearly that none of the regenerative approaches can solve all the different patient/defect presentations. It is therefore mandatory to build up a clinical decision tree that allows clinicians to apply the regenerative strategy most appropriate to each individual case.

While relevant patient factors include cigarette smoking, residual periodontal infection, and oral hygiene, factors associated with the morphology of the defect are consistently found to be of relevance to the final outcome (Tonetti *et al*. 1998; Cortellini *et al*. 2001). Interestingly, however, the number of residual bony walls defining the defect seems to impact the outcomes of different periodontal regenerative materials in a divergent way. Non-bioresorbable (e-PTFE and titanium-reinforced e-PTFE) barrier membranes and bioresorbable barriers supported by a graft do not seem to be affected by the number of residual bony walls of the defect (Tonetti *et al*. 1993a, 1996a, 2004b), while EMDs result in better outcomes in three-wall defects (Tonetti *et al*. 2002). Furthermore, healing following application of bioresorbable barriers and non-bioresorbable e-PTFE barriers as well as EMDs is associated with the radiographic width of the intrabony defect (Tonetti *et al*. 1993a; Falk *et al*. 1997; Tsitoura *et al*. 2004). No such association has been found for the use of a xenogenic BRGs and bioresorbable barrier combination (Tonetti *et al*. 2004b).

Among the technical/surgical factors, membrane exposure and contamination have been associated with poorer outcomes (Selvig *et al*. 1992; Nowzari & Slots 1994; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b). Similar problems were also encountered with bone grafting (Sanders *et al*. 1983). Poorer outcomes were also observed when the regenerated tissue was not properly protected with the flap on removal of non-bioresorbable barrier membranes (Tonetti *et al*. 1993a; Cortellini *et al*. 1995c).

A controlled clinical trial demonstrated that the combination of a PPF and titanium-reinforced e-PTFE membrane resulted in greater CAL gain as compared with a conventional flap approach with an e-PTFE membrane (Cortellini *et al*. 1995c). This evidence, also partly supported by a systematic review (Murphy & Gunsolley 2003), strongly suggests that optimization of the surgical approach and control of surgical variables, particularly in relation to flap design and management and selection of the regenerative material, could improve outcomes. In the context of periodontal regeneration, several flap designs aimed specifically at the full preservation of the soft tissues during access to the defect have been described (Cortellini *et al*. 1995c, d, 1996c, 1999a; Murphy 1996; Cortellini & Tonetti 2007a, 2009b). Experimental testing of these regenerative flaps showed great improvements in achieving primary closure during the surgical session, with optimal interdental closure being obtained in virtually all cases (Cortellini *et al*. 1995c, d, 1999a, 2001; Tonetti *et al*. 2004b). During the subsequent healing, however, dehiscence of the interdental tissue and membrane exposure was observed in up to a third of the cases. The ability to accomplish and maintain primary closure of the tissues over a GTR membrane was further improved by the use of a microsurgical approach that resulted in maintenance of primary wound closure in 92.3% of the treated sites for the whole healing period (Cortellini & Tonetti 2001, 2005, 2007a, b, 2009b, 2011).

This body of evidence has been utilized together with a degree of clinical experience to develop an "evidence-based regenerative strategy" to guide clinicians through a decision-making process aimed at the optimization of the clinical outcomes of periodontal regeneration in intrabony defects (Cortellini & Tonetti 2000a, 2005). Key steps of this process are the careful evaluation of the patient and of the defect, access to the defect with a PPF, choice of the most appropriate regenerative technology/material, and ability to seal the regenerating wound from the contaminated oral environment with optimal suturing techniques.

The performance of this clinical strategy has been assessed in a 40-patient consecutive case series (Cortellini & Tonetti 2005). Following completion of initial, cause-related periodontal therapy, subjects presented FMPSs of 10.2 ± 2.7% and full-mouth bleeding scores at baseline of 7.9 ± 2.8%. At the intrabony defects, CAL was 10.2 ± 2.4 mm and PPD 8.9 ± 1.8 mm. The radiographic defect angle was 29 ± 5.9°. CEJ–BD was 11.2 ± 2.7 mm and the intrabony component of the defects (INFRA) was 6.6 ± 1.7 mm. In this population, the SPPF could be used in 37.5% of sites, while the MPPT was selected in 45% of cases. The remaining sites, presenting with defects adjacent to edentulous areas, were accessed with a crestal incision.

Based on defect anatomy, non-bioresorbable titanium-reinforced e-PTFE barrier membranes were used in 30% of cases. In these cases, defect angles ranged from 27° to 42° (average 32.4 ± 4.3°), and eight of the 11 selected defects had a one-wall intrabony subcomponent of 1–3 mm (the average one-wall component of the 12 sites was 1.4 ± 1.2 mm). Ten of the 11 defects treated with bioresorbable membranes supported with a BRG presented a one-wall subcomponent of 1–5 mm (the average one-wall component of the 11 sites was 1.8 ± 1.3 mm); defect angles in this group ranged from 21° to 45° (average 31.4 ± 7°). Bioresorbable barriers alone were used in seven sites presenting with a prevalent two- and three-wall morphology and narrow defect angles, ranging from 20° to 28° (average 24.1 ± 3.7°). EMDs were applied to ten defects with a prevalent three-wall component. The defect angle in this group ranged from 19° to 31° (average 26.5 ± 4.3°).

Primary closure was obtained at completion of the surgical procedure for all treated sites. At the

1-week follow-up, when sutures were removed, two sites, both accessed with a SPPF, presented with a small interdental wound dehiscence: one had been treated with a bioresorbable membrane and BRG, the other with EMDs. At week 2, two additional small wound dehiscences were detected: one accessed with MPPT and treated with a bioresorbable membrane and BRG, the other accessed with SPPF and treated with a bioresorbable barrier alone. All the other sites (90%) remained closed during the entire early healing phase.

The 40 patients presented at the 1-year follow-up visit with excellent levels of plaque control and low levels of BoP. The 1-year CAL gain was 6 ± 1.8 mm (range 4–11 mm). No sites gained <4 mm of CAL; 77.5% gained ≥5 mm and 40% >6 mm. Residual PPDs were 2.7 ± 0.6 mm, with an average reduction of 6.1 ± 1.9 mm. Only four sites showed a residual PPD of 4 mm; all the other sites had a 1-year PPD of ≤3 mm. A minimal increase of 0.1 ± 0.7 mm in gingival recession between baseline and 1 year was recorded.

This study indicated that, whenever the treatment choice was made according to the protocol (i.e. based on: width of the interdental space to select the papilla preservation surgery; morphology of the defect to select the regenerative material; and choice of the material and local anatomy to select the suturing approach), all four approaches gave excellent results with CAL gains equal to 88–95% resolution of the original depth of the intrabony component of the defect (Cortellini & Tonetti 2005).

The CAL gain of 6 ± 1.8 mm at 1 year was obtained in defects with an intrabony component of 6.6 ± 1.7 mm. The percentage CAL gain therefore was 92.1 ± 12%. This indicates that a large part of the intrabony component of the defects was resolved. Using the Ellegaard criteria (Ellegaard & Loe 1971), resolution of the intrabony component of the defect was either satisfactory or complete in all treated cases. In particular, 40.5% of defects had CAL gains equal to or greater than the baseline depth of the intrabony component, while the defect with the worst response showed a 71.4% CAL gain. Historical comparison with clinical experiments using bone grafting or GTR clearly indicates that the results of this trial approach were in the top percentiles in terms of CAL gains and defect resolution (Cortellini & Tonetti 2000a; Rosen *et al*. 2000).

A novel, more comprehensive clinical strategy has been developed to further improve the clinical capacity to ensure appropriate therapy for each patient/defect. This approach takes into proper account the relevance of the patient characteristics, as described earlier in this chapter, and is based on the need to satisfy the three major contributors to periodontal regeneration: (1) space for the formation of the blood clot at the interface between the flap and root surface (Haney *et al*. 1993, Sigurdsson *et al*. 1994, Cortellini *et al*. 1995b, c; Tonetti *et al*. 1996a; Wikesjo *et al*. 2003; Kim *et al*. 2004); (2) stability of the blood clot to maintain a continuity with the root surface and thereby avoid the formation of a long junctional epithelium (Linghorne & O'Connel 1950; Hiatt *et al*. 1968; Wikesjo & Nilveus 1990; Haney *et al*. 1993); and (3) soft tissue protection of the treated area to avoid bacterial contamination (Selvig *et al*. 1992; Nowzari *et al*. 1995; De Sanctis *et al*. 1996a, b; Sanz *et al*. 2004; Polimeni *et al*. 2006). *Space* and *blood clot stability* are self-provided in the so-called "containing defects", particularly the narrow three-wall defects (Goldman & Cohen 1958; Schallhorn *et al*. 1970; Selvig *et al*. 1993; Cortellini & Tonetti 1999; Tsitoura *et al*. 2004; Linares *et al*. 2006). The "non-containing defects", the large one- or two-wall defects, require an intervention to supplement the deficient anatomy (Tonetti *et al*. 1993a, 1996a, 2002, 2004a, b; Falk *et al*. 1997). The intervention can be based on the use of biomaterials such as "exoskeleton"-like barriers or "endoskeleton"-like grafts that are able to support the soft tissues and to stabilize the blood clot, or a combination of the two approaches. In other words, the anatomic deficiencies of the defects have to be supplemented by the additional use of biomaterials. The same goal could be obtained by adopting different surgical strategies in which tissues are minimally elevated to increase their stability (the MIST and the M-MIST approaches) (Cortellini & Tonetti 2007a, b, 2009a, b). Blood clot stability is also clearly influenced by tooth hypermobility: splinting teeth with class II or III mobility is mandatory to avoid the disruption of the blood clot in the early healing phase (Cortellini *et al*. 2001; Trejo & Weltman 2004).

Protection of the regenerating area has to be provided with the adoption of specifically designed surgical approaches. The different surgical approaches differ in terms of flap design and suturing technique. In addition to their ability to provide protection to the regenerating area, they could differently contribute to improving one or more of the many aspects potentially relevant to the wound healing process. The traditional PPF (Cortellini *et al*. 1995a, 1999a) were designed as wide and very mobile flaps in order to allow for perfect visibility of the defect area, for easy placement of biomaterials, and for the coronal positioning of the buccal flap to cover barriers and biomaterials. In other words, PPF do not have the mechanical characteristics to improve wound stability or the capacity to independently create space for regeneration. The MIST (Cortellini & Tonetti 2007a, b), in contrast, was designed to reduce flap extension and mobility as much as possible to increase the capacity for primary wound closure and blood clot stability. This potential was illustrated in two studies that demonstrated the reduced impact of the number of residual bony walls and of the defect width on the outcomes obtained with EMDs under a MIST (Cortellini *et al*. 2008; Cortellini & Tonetti 2009a), and recently confirmed in a comparative study demonstrating similar outcomes between MIST alone and MIST plus EMDs (Ribeiro *et al*. 2011a).

A further development of the surgical approach was the M-MIST (Cortellini & Tonetti 2009b, 2011). This advanced flap design further enhanced the potential of the flap to provide space and stability for regeneration by leaving the interdental papillary soft tissues attached to the root surface of the crest-associated tooth and by avoiding any palatal flap elevation. The interdental soft tissues are the stable "ceiling" of a "room" into which blood flows and forms a clot. In addition, the hanging papilla prevents the collapse of the soft tissues, thereby maintaining space for regeneration: the anatomic bone deficiencies are potentially supplemented by the peculiar novel flap design that provides additional "soft tissue walls" in place of the missing bony walls and thus improves stability. The walls of the "room" are the residual bony walls, the root surface, and the buccal/lingual soft tissues. The minimal flap extension and elevation also reduces greatly the damage to the vascular system. It is clear that such a flap is not designed to allow the positioning of a barrier, but biologicals or grafts can easily be used with it.

Clinical flowcharts

Clinical flowcharts have been developed that take into account also the scientific contributions on surgical and postsurgical events, like chair time, side effects, and postoperative pain.

The step-by-step clinical approach to the treatment of intrabony defects includes two presurgical flow charts dealing with patient and local factors and four surgical flow charts (surgical nodes). The development of the surgical nodes was driven by the wish to treat any given defect with the procedure judged fastest, easiest, least burdened by side effects, and best tolerated by the patients. Lastly, postoperative care is suggested.

The step-by-step approach starts with control of patient-associated characteristics (see Fig. 38-10): low levels of plaque and residual infection, high levels of compliance, and absence of adverse conditions like smoking, stress, and uncontrolled diabetes or other systemic diseases have to be well established.

A few conditions, like endodontic condition, local contamination, and mobility of the involved tooth, must be controlled before surgery (Fig. 38-48). Endodontic diagnosis and eventual treatment should be performed well in advance of the regenerative approach (Cortellini & Tonetti 2001). Vital teeth should preferably be kept vital, with the only exception being a tooth whose apex is involved with the periodontal lesion (Cortellini *et al*. 2011). Non-vital teeth must be properly treated with root canal therapy. Existing root canal therapies should be carefully evaluated: improper treatments should be corrected. Local contamination of the defect-associated pocket should be as low as possible (Heitz-Mayfield *et al*. 2006). The presence of BoP (i.e. bacteria) should be controlled with additional gentle root planing and then the additional use of local antimicrobials (Tunkel *et al*. 2002; Hanes & Purvis 2003) a few weeks before regeneration (Cortellini *et al*. 2011). Teeth with mobility of class II or III should be splinted before or immediately after the surgical procedure (Cortellini *et al*. 2001; Trejo & Weltman 2004). Tooth hypermobility should be re-evaluated during the early healing phase: any detected increase in mobility should be taken care of.

The surgical access to the intrabony defects is selected from three different approaches: the SPPF (Cortellini *et al*. 1999a), the MPPT (Cortellini *et al*. 1995d), and the crestal incision (Cortellini & Tonetti 2000a) (Fig. 38-49). The SPPF is chosen whenever the width of the interdental space is 2 mm or less, as measured at the level of the supracrestal portion of the papilla. The MPPT is used at sites with an interdental width of >2 mm; the crestal incision is applied next to an edentulous area.

The next surgical step (Fig. 38-50) concerns the selection of the flap design. Whenever a defect involves one or two sides of a root and can be cleaned

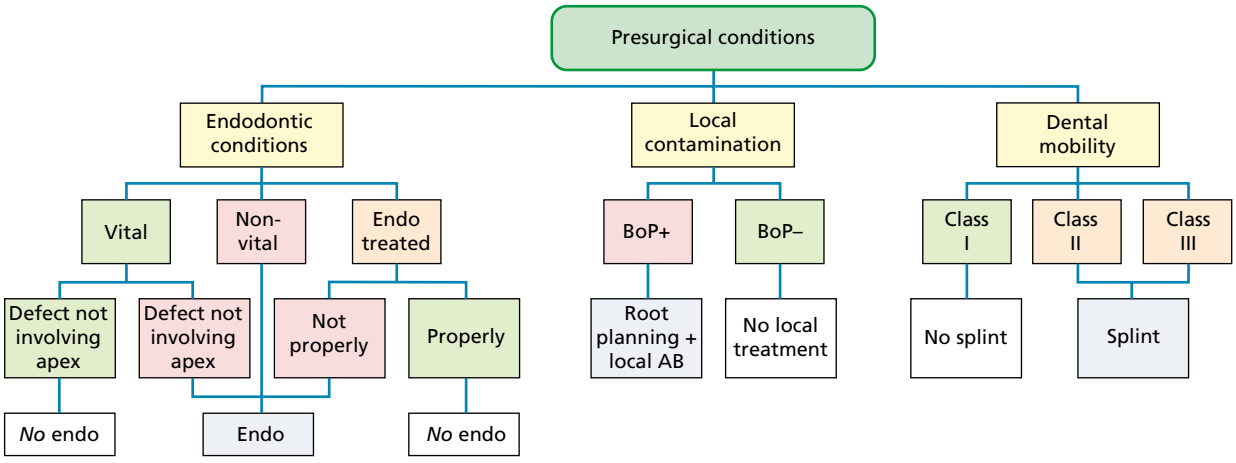


Fig. 38-48 Decision-making algorithm highlighting the clinical conditions to be checked before periodontal regeneration. These relate mainly to the endodontic status, presence of local contamination, and dental hypermobility of the tooth to be treated with periodontal regeneration. BoP, bleeding on probing; AB, antibiotic.

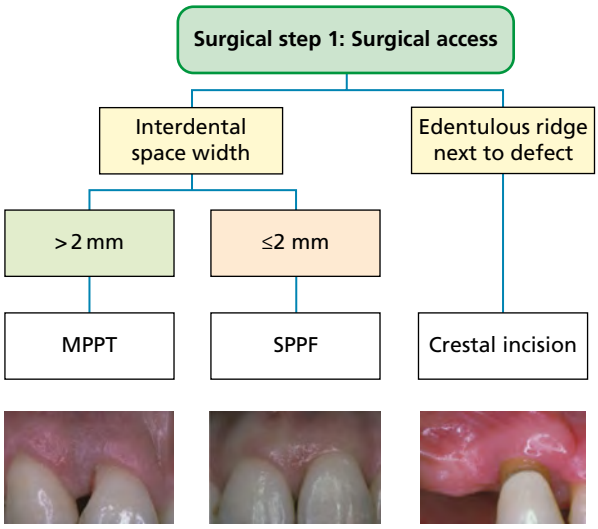


Fig. 38-49 Decision-making algorithm for obtaining access to an intrabony defect: the simplified papilla preservation flap (SPPF) is used for narrow interdental spaces (2 mm or narrower), while the modified papilla preservation technique (MPPT) is used to access defects associated with wider interdental spaces (3 mm or wider). Crestal incision is applied at a tooth neighboring an edentulous ridge.

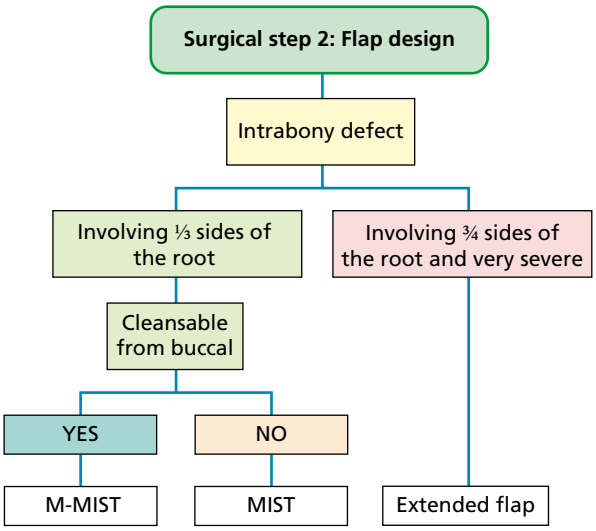


Fig. 38-50 Decision-making algorithm for choice of flap design. The type of surgical access from very small to very ample is chosen according to the severity and extension of the periodontal defect. MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique.

through a tiny buccal window, an M-MIST is applied (Cortellini & Tonetti 2009b, 2011). In some instances, the M-MIST can be applied to both the interdental spaces neighboring the defect-associated tooth, allowing for instrumentation of a defect involving up to three sides of a root. If the defect cannot be cleaned through the buccal window, the interdental papilla is elevated by applying a MIST approach (Cortellini & Tonetti 2007a; Cortellini *et al*. 2008). A large flap, extended to the neighboring teeth and including also an eventual periosteal incision and/or vertical releasing incisions, is chosen in the presence of a very severe and deep defect, involving three or four sides of the root, which requires ample visibility for instrumentation and the use of either endo- or exo-skeletons (Cortellini *et al*. 1995d, 1999a).

Step 1 and step 2 might follow a different path when the pocket is associated with a 2-wall intrabony with a missing buccal bony wall and without a consistent lingual/palatal involvement. In this instance, EPP might be the flap design of choice.

Selection of the regenerative material is based on the defect anatomy and on the flap design chosen to expose the defect (Fig. 38-51). If an M-MIST approach is applied, EMDs or no regenerative materials are the elective choices (Cortellini & Tonetti 2009b, 2011). If a MIST is applied, EMDs can be used alone in containing defects or in combination with a filler in non-containing defects (Cortellini & Tonetti 2007a; Cortellini *et al*. 2008; Ribeiro *et al*. 2011a). If a large flap is elevated, the area should be stabilized by applying barriers or fillers, or a combination of barriers and fillers, or a combination of EMDs/growth factors and fillers. EMDs alone

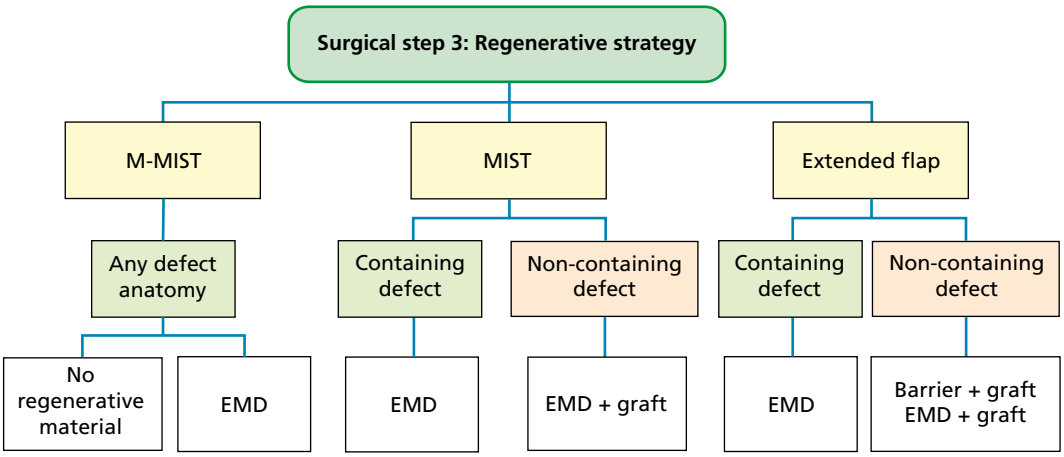


Fig. 38-51 Decision-making algorithm for choice of currently available technologies for application of regeneration in the treatment of intrabony defects. The clinical decision is based on two main parameters: (1) type of surgical access performed; (2) morphology of the periodontal defect. MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique; EMD, enamel matrix derivative.

are preferred in defects with a prevalent three-wall morphology or in well-supported two-wall defects.

The suturing approach is selected according to the type of regenerative strategy applied (Fig. 38-52). It will consist of a single internal modified mattress suture when an M-MIST or an MIST approach is chosen and EMDs alone are applied (Cortellini & Tonetti 2007a, 2009a, 2011; Cortellini *et al*. 2008). When a large flap with a periosteal incision is used in association with a barrier or a graft or a combination of these, the suturing approach will consist of two internal mattress sutures applied at the defect-associated interdental area to achieve primary closure of the papilla in the absence of any tension (Cortellini *et al*. 1995b, c, 1999a; Cortellini & Tonetti 2000a, 2005).

The surgical procedure is preferably performed with the aid of magnification such as loupes or an operating microscope (Cortellini & Tonetti 2001, 2005; Wachtel *et al*. 2003). Microsurgical instruments and materials should be utilized to complement the normal periodontal set.

Postsurgical and early home-care protocols are derived from the experiences gained from running many controlled clinical trials (Cortellini *et al*. 1995c, 1996b, 2001; Tonetti *et al*. 1998, 2002, 2004b). An empirical protocol for the control of bacterial contamination consisting of doxycycline (100 mg b.i.d. for 1 week), 0.12% chlorhexidine mouth rinsing t.i.d., and weekly prophylaxis is prescribed. Sutures are removed after 1 week. Patients are requested to avoid normal brushing, flossing, and chewing in the treated area for periods of 6–10 weeks. A postsurgical soft toothbrush soaked in chlorhexidine is adopted from week 1 to gently wipe the treated area. Nonbioresorbable membranes are removed after 6 weeks. Patients can resume full oral hygiene and chewing function in the treated area 2–4 weeks after membrane removal or when bioresorbable membranes are fully resorbed. Patients treated with EMDs can resume full oral hygiene after a period of 4–5 weeks. At the end of the "early healing phase", patients are placed in a 3-month recall system. A general suggestion to avoid any invasive clinical maneuver, like hard subgingival instrumentation, restorative dentistry, orthodontics, and additional surgery, for a period of about 9 months is also part of the strategy to optimize the clinical outcomes of periodontal regeneration.

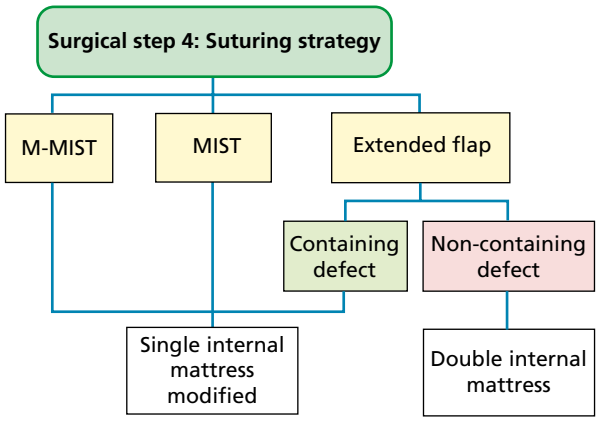


Fig. 38-52 Decision-making algorithm for the choice of suturing technique. MIST, minimally invasive surgical technique; M-MIST, modified minimally invasive surgical technique.

Conclusion

Periodontal regeneration has demonstrated significant clinical improvements in intrabony defects far beyond those achieved with debridement alone, with many different regenerative materials, including barrier membranes, grafts, active biologic compounds, and combinations of these. Different surgical approaches have been proposed and tested in combination with the various regenerative materials, but none has demonstrated a clear superiority over the others. Moreover, all of the proposed regenerative approaches have shown a high degree of clinical variability in terms of CAL gain: none has demonstrated the capacity to solve all the different and unique patient/defect presentations. Therefore, to treat a given defect, the regenerative strategy has to be chosen from a panel of options. The adoption of a clinical strategy for optimal application of materials and surgical approach could increase the efficacy of periodontal regeneration and give a clear advantage in terms of improved clinical outcomes. Periodontal regeneration expresses its potential in defects of any depth, from very shallow to very deep, and in extreme conditions can change the prognosis of teeth from hopeless to maintainable units.

Clinical outcomes obtained with periodontal regeneration can be maintained on a long-term basis, provided good oral hygiene and infection control within a stringent recall program are enforced. Current data indicate that, in patients participating in a supportive periodontal care program, 96% of teeth with severe intrabony defects and treated with a periodontal regenerative procedure could be retained for a period of up to 15 years.

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Chapter 39

Mucogingival Therapy: Periodontal Plastic Surgery

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Introduction

Mucogingival therapy is a general term used to describe periodontal treatments involving surgical procedures for the correction of defects in the morphology, position, and/or amount of soft tissue and underlying bone support at teeth and implants (American Academy of Periodontology 2001).

The term *mucogingival surgery* was introduced by Friedman (1957) and was defined as "surgical procedures designed to preserve gingiva, remove aberrant frenulum or muscle attachments, and increase the depth of the vestibule". The term "mucogingival surgery" at this time was used to describe all surgical procedures that involved both the gingiva and the alveolar mucosa. Consequently, not only were techniques designed to enhance the width of the gingiva and to correct particular soft tissue defects regarded as mucogingival procedures, but also pocket elimination approaches were too. In 1993, Miller proposed the term *periodontal plastic surgery*, considering that mucogingival surgery had moved beyond the traditional treatment of problems associated with gingival augmentation and root coverage procedures to also include correction of alveolar ridge deformities and soft tissue esthetics.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

Embracing this concept, the American Academy of Periodontology defined periodontal plastic surgery as "surgical procedures performed to prevent or correct anatomic, developmental, traumatic or disease-induced defects of the gingiva, alveolar mucosa or bone" (Proceedings of the 1996 World Workshop in Periodontics 1996). In 2014, the 10th European Workshop in Periodontology redefined periodontal plastic surgery procedures as the surgical interventions aimed at modifying the position of the gingival margin and/or the amount and characteristics of marginal soft tissues, at teeth and dental implants (Tonetti & Jepsen 2014)

Among treatment procedures that may fall within this definition are various soft and hard tissue procedures aimed at:

- Gingival augmentation
- Root coverage
- Correction of mucosal defects at implants
- Crown lengthening
- Gingival preservation at ectopic tooth eruption
- Removal of aberrant frenulum.

The focus of this chapter, however, will be restricted to treatment procedures for corrections of soft tissue defects in relation to the tooth, while alveolar ridge augmentation procedures will be covered in Chapter 41 and treatment of the marginal soft tissues around dental implants in Chapter 45.

Mucogingival conditions

The 1999 AAP Workshop for the Classification of Periodontal Diseases and Conditions defined a number of mucogingival deformities and conditions around teeth (1. Gingival/soft tissue recession; 2. Lack of keratinized gingiva; 3. Decreased vestibular depth; 4. Aberrant frenum/muscle position; 5. Gingival excess and 6. Abnormal color). This 1999 classification was modified in the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions with additional information for more accurate case definitions, such as periodontal phenotype, recession severity, dimension of the residual gingiva, presence/absence of caries and non-carious cervical lesions, aesthetic concern of the patient, and presence of dentin hypersensitivity. The resulting list of mucogingival deformities and conditions around teeth is depicted in Table 39-1 (Cortellini & Bissada 2018).

Normal mucogingival conditions have been defined as any variation of individual anatomy and morphology where there is absence of pathosis (i.e. gingival recession, gingivitis, periodontitis). However, there will be conditions without obvious pathology in which the deviation from what is considered "normal" in the oral cavity lies outside of the range of individual variability. At the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. two main case definitions of mucogingival conditions were defined (Jepsen *et al*. 2018):

Table 39-1 Mucogingival deformities and conditions around teeth. (Source: Cortellini & Bissada 2018. Reproduced with permission from John Wiley & Sons.)

1. Periodontal phenotype
   a. Thin scalloped
   b. Thick scalloped
   c. Thick flat
2. Gingival/soft tissue recession
   a. Facial or lingual surfaces
   b. Interproximal (papillary)
   c. Severity of recession (Cairo RT1, 2, 3)
   d. Gingival thickness
   e. Gingival width
   f. Presence of NCCL/cervical caries
   g. Patient aesthetic concern (Smile Esthetic Index)
   h. Presence of hypersensitivity
3. Lack of keratinized gingiva
4. Decreased vestibular depth
5. Aberrant frenum/muscle position
6. Gingival excess
   a. Pseudo-pocket
   b. Inconsistent gingival margin
   c. Excessive gingival display
   d. Gingival enlargement
7. Abnormal color

1. *Mucogingival condition without gingival recessions*. This case definition in the absence of gingival recession describes different conditions in relation to the gingival phenotype (gingival thickness [GT] and keratinized tissue [KT] width), either at the entire dentition, or at individual sites. Relevant features contributing to the description of this condition might be tooth position, aberrant frenum, or vestibular depth.
2. *Mucogingival condition with gingival recessions*. A case with gingival recession presents with an apical shift of the gingival margin apical to the cemento enamel junction (CEJ) resulting in exposure of the root surface. Relevant features contributing to the description of this condition are: (1) the interdental clinical attachment level, (2) the gingival phenotype (GT and KT width), (3) root surface condition (presence/absence of non-carious cervical lesion [NCCL] or caries), (4) detection of the CEJ, (5) tooth position, (6) aberrant frenum, and (7) number of adjacent recessions.

Some of these "mucogingival conditions and deformities" listed previously are not necessarily associated with the development of pathosis and in many individual cases they are associated with periodontal health. Therefore, the need for professional intervention must be assessed individually

Mucogingival condition without gingival recession

The term periodontal phenotype has been used in several dental disciplines (periodontal, orthodontic, restorative dentistry, etc.) to describe a series of anatomical characteristics including: (1) the gingival phenotype defined by the GT and the KT width; (2) the bone morphotype (BM) defined by the thickness of the labial bone plate; and (3) the tooth dimension.

A systematic review using these characteristics has classified the "phenotypes" in three categories (Zweers 2014):

- *Thin scalloped phenotype* in which there is an association with a slender triangular crown, subtle cervical convexity, interproximal contacts close to the incisal edge and a narrow zone of keratinized tissue, clear thin delicate gingiva, and a relatively thin alveolar bone.
- *Thick flat phenotype* associated with more square-shaped tooth crowns, pronounced cervical convexity, large interproximal contact located more apically, a broad zone of KT, thick, fibrotic gingiva, and a comparatively thick alveolar bone.
- *Thick scalloped phenotype* associated with a thick fibrotic gingiva, slender teeth, narrow zone of keratinized tissue, and a pronounced gingival scalloping.

The strongest association within the different parameters used to identify the different phenotypes has been found among GT, KTW, and BM.

GT is assessed by:

- *Transgingival probing* using fine endodontic files with stops and assessed by a gauge. Although this technique may have an accuracy to the nearest 0.5 mm it requires local anesthetic, thus increasing the patient discomfort.
- *Ultrasonic measurement*. Although it has also shown high accuracy in research environments (within 0.5–0.6 mm range) there are currently no validated devices for clinical use (Eger *et al*. 1996).
- *Probe visibility* after its placement in the buccal gingival sulcus. This method has shown a high reproducibility (De Rouck *et al*. 2009) mainly with the use of colour coded probes that will become visible through the gingiva when the thickness is ≤1 mm. Using this method GT has been defined as thin (≤1.0 mm) or thick (>1 mm).

KT width is easily measured with a periodontal probe positioned between the gingival margin and the mucogingival junction.

Bone thickness (BM) can be assessed through cone beam computed tomography, although the high radiation dosages needed preclude this diagnostic method for routine assessment of the patient's phenotype.

At the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions the term "periodontal phenotype" was adopted instead of "biotype" (Jepsen *et al*. 2018) since the phenotype indicates a dimension that may change through time being determined not only by the gingival phenotype (gingival thickness, keratinized tissue width), and bone morphotype (thickness of the buccal bone plate), but also by the tooth position and therapeutic interventions.

Gingival dimensions and periodontal health

For many years the prevailing concept was that a narrow zone of gingiva (Fig. 39-1) was insufficient (1) to protect the periodontium from injury caused by friction forces encountered during mastication and (2) to dissipate the pull on the gingival margin created by the muscles of the adjacent alveolar mucosa (Friedman 1957; Ochsenbein 1960). Moreover, it was believed that an "inadequate" zone of gingiva would (1) facilitate subgingival plaque formation because of the improper pocket closure resulting from the movability of the marginal tissue (Friedman 1962) and (2) favor attachment loss and soft tissue recession because of less tissue resistance to apical spread of plaque-associated gingival lesions (Stern 1976; Ruben 1979). It was also considered that a narrow gingiva in combination with a shallow vestibular fornix might (1) favor the accumulation of food particles during mastication and (2) impede proper oral hygiene measures (Gottsegen 1954; Rosenberg 1960; Corn 1962; Carranza & Carraro 1970).

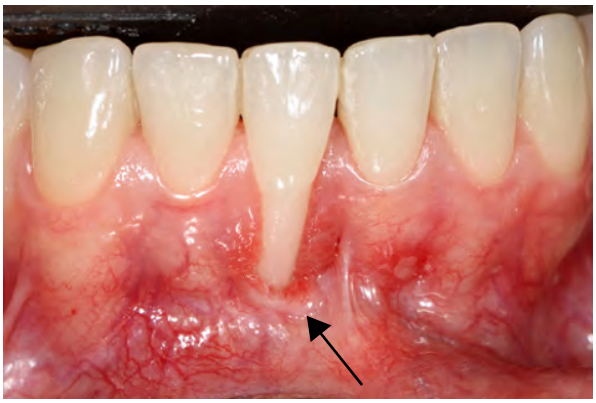

Fig. 39-1 Mandibular front tooth region. The gingiva on the buccal aspect of tooth 41 (arrow) has a narrow width and shows more pronounced signs of inflammation than adjacent gingival units with a wider zone of gingiva.

The opinions expressed concerning what could be regarded as being an "adequate" or "sufficient" dimension of the gingiva varied. While some authors suggested that ≥1 mm of gingiva may be sufficient (Bowers 1963), others claimed that the apicocoronal height of keratinized tissue ought to exceed 3 mm (Corn 1962). A third category of authors had a more biologic approach to the question and stated that an adequate amount of gingiva is any dimension that (1) is compatible with gingival health or (2) prevents retraction of the gingival margin during movements of the alveolar mucosa (Friedman 1962; De Trey & Bernimoulin 1980).

One of the first studies in which attempts were made to evaluate the significance of the gingival zone for the maintenance of periodontal health was carried out by Lang and Löe (1972) on dental students who had their teeth professionally cleaned once a day for 6 weeks. All buccal and lingual sites were examined for plaque, gingival conditions, and apicocoronal height of the gingiva. The results showed that despite the fact that the tooth surfaces were free from plaque, all sites with <2 mm of gingiva exhibited persisting clinical signs of inflammation. Based on this observation, the authors suggested that 2 mm of gingiva is an adequate width for maintaining gingival health. Subsequent clinical trials (Grevers 1977; Miyasato *et al*. 1977), however, failed to substantiate this concept of a required minimum dimension of gingiva. In fact, these clinical trials demonstrated that it is possible to maintain clinically healthy marginal tissues even in areas with <1 mm of gingiva.

The question whether a firmly attached portion of gingiva is critical for the protection of the periodontium was addressed by Wennström and Lindhe (1983a, b) utilizing the Beagle dog model. In these studies, dentogingival units with different clinical characteristics were experimentally established: (1) units with only a narrow and mobile zone of keratinized tissue and (2) units with a wide, firmly attached gingiva (Fig. 39-2).

With mechanical plaque-control measures performed daily, the gingival units could be maintained free from clinical as well as histologic signs of inflammation irrespective of the presence or absence of an attached portion of gingiva. When bacterial plaque was allowed to accumulate (for 40 days), clinical signs of inflammation (redness and swelling) developed that were more pronounced in tooth regions with mobile gingiva (Fig. 39-3b) than in areas with a wide and firmly attached gingival zone (Fig. 39-3a).

However, histologic analysis revealed that the size of the inflammatory cell infiltrate and its extension in an apical direction (an assessment which indirectly may be used as an estimate of the apical migration of the bacterial plaque) were similar in the two categories of dentogingival units. The finding that the clinical signs of gingival inflammation did not correspond with the size of the inflammatory cell infiltrate illustrates the difficulties inherent in the interpretation of data from clinical examinations made in areas with varying gingival widths. This should be kept in mind when interpreting the data from the human study by Lang and Löe (1972) showing that clinically visible signs of inflammation, such as redness and swelling, were more frequent in areas with <2 mm of gingiva than in areas with a wider zone of gingiva.

The necessity for and effectiveness of gingival augmentation in maintaining periodontal attachment was examined by Dorfman *et al*. (1980). Ninety-two patients with bilateral facial tooth surfaces exhibiting minimal keratinized tissue (i.e. <2 mm) had a free gingival graft placed on one side, while the contralateral side served as the untreated control. Prior to and after surgery the patients were subjected to scaling and root planing and instruction in oral hygiene measures. Not surprisingly, the investigators found a significant increase (approximately 4 mm) in the width of keratinized tissue at the grafted sites. This increased width of gingiva, as well as the clinical attachment level, was maintained throughout the 2 years of follow-up. In the control sites, the gingival width was <2 mm and did not vary significantly

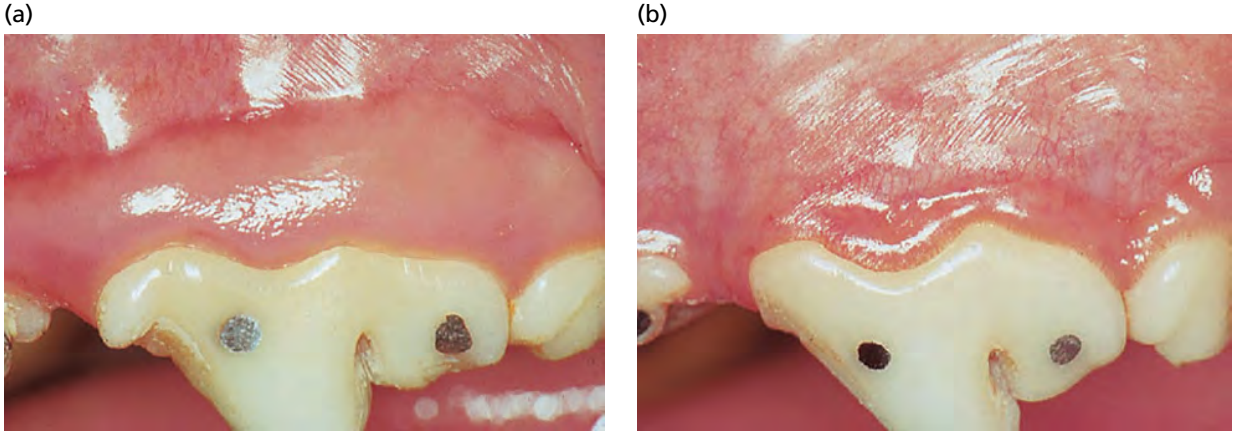

Fig. 39-2 Two teeth in a dog with varying dimensions of the marginal gingiva. (a) Buccal tooth site with a wide zone of attached gingiva. (b) Site with an unattached, narrow band of gingiva.

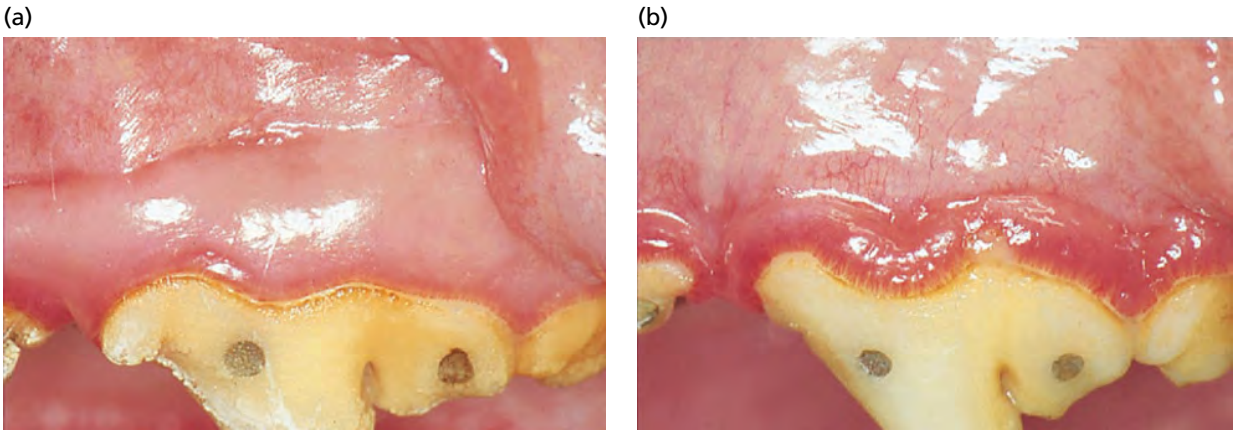

Fig. 39-3 Same teeth as in Fig. 39.2 after 40 days of plaque accumulation. The clinical signs of inflammation are more pronounced at the site with the narrow band of gingiva (b) than at the site with the wide zone of attached gingiva (a).

during the observation period. However, the attachment level was also maintained unchanged in the non-grafted areas. Thus, the resistance to continuous attachment loss was not linked to the height (width) of the gingiva, a conclusion that was further substantiated by subsequent 4- and 6-year follow-up reports of this patient material (Dorfman *et al*. 1982; Kennedy *et al*. 1985).

Further support for the conclusion that a minimal zone of gingiva may not compromise periodontal health is available from a number of other longitudinal clinical studies (e.g. De Trey & Bernimoulin 1980; Hangorsky & Bissada 1980; Lindhe & Nyman 1980; Schoo & van der Velden 1985; Kisch *et al*. 1986; Wennström 1987; Freedman *et al*. 1999). Hence, Hangorsky and Bissada (1980), who evaluated the long-term clinical effect of free soft tissue grafts, concluded that while the free gingival graft is an effective method to widen the zone of the gingiva, there is no indication that this increase has direct influence upon periodontal health.

Conclusion: Gingival health can be maintained independent of its dimensions. Furthermore, there is evidence from both experimental and clinical studies that, in the presence of plaque, areas with a narrow zone of gingiva possess a similar degree of "resistance" to continuous attachment loss as areas with a wide zone of gingiva. Hence, the traditional dogma of the need for an "adequate" width (in millimeters) of gingiva, or an attached portion of gingiva, for prevention of attachment loss is not scientifically supported.

Gingival augmentation

The introduction of surgical procedures for gingival augmentation was based on the assumption that the presence of a wide band of keratinized and attached gingiva around the tooth was critical for maintaining gingival health and preventing attachment loss and soft tissue recession (Nabers 1954; Ochsenbein 1960; Friedman & Levine 1964; Hall 1981; Matter 1982).

Indications for gingival augmentation

Scientific data obtained from well-controlled clinical and experimental studies have unequivocally demonstrated that the apicocoronal width of gingiva and the presence of an attached portion of gingiva are not of decisive importance for the maintenance of gingival health and the height of the periodontal tissues. Consequently, the presence of a narrow zone of gingiva *per se* cannot justify surgical intervention (Lang & Karing 1994; Proceedings of the 1996 World Workshop in Periodontics 1996). However, gingival augmentation should be considered in situations where, for example, the patient experiences discomfort during toothbrushing and/or chewing due to interference from a lining mucosa at teeth or implants. Furthermore, when orthodontic tooth movement is planned and the final positioning of the tooth can be expected to result in an alveolar bone dehiscence, an increase of the *thickness* of the covering soft tissue may reduce the risk for development of soft tissue recession. An increase of the *thickness* of the gingiva may also be considered when subgingival restorations are placed in areas with a thin marginal tissue.

Gingival augmentation procedures

Gingival augmentation operations comprise a number of surgical techniques, the majority of which have been developed mainly on an empiric basis. The earliest of these techniques were the "vestibular extension operations", which were designed mainly with the objective of extending the vestibular depth (Bohannan 1962a, b). In recent years, however, pedicle or free soft tissue grafts have become the most commonly used techniques in the management of "insufficient" gingival dimensions, because of higher predictability of the healing result.

Vestibular/gingival extension procedures

The "denudation techniques" included the removal of all soft tissue within an area extending from the

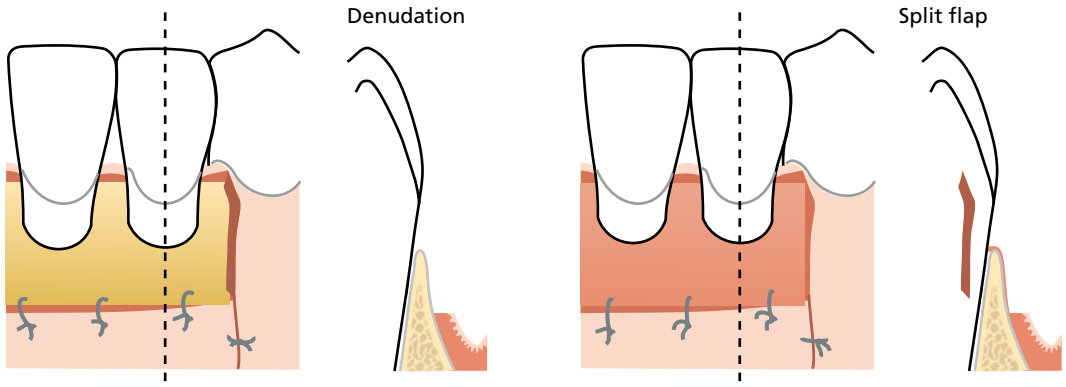

Fig. 39-4 Use of vestibular extension operations for increasing the width of the gingiva involves the production of a wound extending from the gingival margin to a level some millimeters apical to the mucogingival junction. With the "denudation" technique, all soft tissue is removed, leaving the alveolar bone exposed. With the "split flap" procedure, only the superficial portion of the oral mucosa is removed, leaving the bone covered with connective tissue. (Sources: Staffileno *et al*. 1963, 1966; Wilderman 1963; Pfeifer 1965. Reproduced with permission from John Wiley & Sons.)

gingival margin to a level apical to the mucogingival junction, leaving the alveolar bone completely exposed (Ochsenbein 1960; Corn 1962; Wilderman 1964) (Fig. 39-4). Healing following this type of treatment resulted often in an increased height of the gingival zone, although in some cases only a very limited effect was observed. However, the exposure of alveolar bone produced severe bone resorption with permanent loss of bone height (Wilderman *et al*. 1961; Costich & Ramfjord 1968). In addition, the recession of marginal gingiva in the surgical area often exceeded the gain of gingiva obtained in the apical portion of the wound (Carranza & Carraro 1963; Carraro *et al*. 1964). Due to these complications and severe postoperative pain for the patient, the use of the "denudation technique" can hardly be justified.

With the "periosteal retention" procedure or "split-flap" procedure (Fig. 39-4), only the superficial portion of the oral mucosa within the wound area was removed, leaving the bone covered by periosteum (Staffileno *et al*. 1962, 1966; Wilderman 1963; Pfeifer 1965). Although the preservation of the periosteum implies that less severe bone resorption will occur than following the "denudation technique", loss of crestal bone height was also observed following this type of operation unless a relatively thick layer of connective tissue was retained on the bone surface (Costich & Ramfjord 1968). If a thick layer was not secured, the periosteal connective tissue tended to undergo necrosis and the subsequent healing closely resembled that following the "denudation technique" described above.

These vestibular/gingival extension procedures were based on the assumption that it is the frictional forces during mastication that determine the presence of a keratinized tissue adjacent to the teeth (Orban 1957; Pfeifer 1963). Therefore, it was believed that by the displacement of muscle attachments and the extension of vestibular depth, the regenerating tissue in the surgical area would be subjected to physical impacts and adapt to the same functional requirements as those met by "normal" gingiva (Ivancie 1957; Bradley *et al*. 1959; Pfeifer 1963). Later studies, however, showed that the characteristic features of the gingiva are determined by inherent factors in the tissue rather than being the result of functional adaptation and that the differentiation (keratinization) of the gingival epithelium is controlled by morphogenetic stimuli from the underlying connective tissue (see Chapter 4).

Grafting procedures

The gingival and palatal soft tissues will maintain their original characteristics after transplantation to areas of the alveolar mucosa (see Chapter 4). Hence, the use of transplants offers the potential to predict the postsurgical result. The type of transplants used can be divided into (1) pedicle grafts, which maintain their connection to the donor site after placement at the recipient site (Fig. 39-5), and (2) free grafts that are completely deprived of their connection with the donor area (Fig. 39-6). For gingival augmentation, free grafts from the palate have been used most commonly (Haggerty 1966; Nabers 1966; Sullivan & Atkins 1968a; Hawley & Staffileno 1970; Edel 1974). As an alternative to the use of a mucosal graft from the palate, various allogenic graft materials, for example acellular freeze-dried dermal matrix (ADM) (Wei *et al*. 2000; Harris 2001) and human fibroblast-derived dermal substitute (McGuire & Nunn 2005) may be used, but the increase in the width of keratinized tissue following the use of these grafts may not be as predictable as with the use of autogenous grafts. Based on a systematic review of soft tissue augmentation techniques, Thoma *et al*. (2009) concluded that: (1) there is evidence for an increased width of keratinized tissue and attached gingiva following apically repositioned flap/vestibuloplasty; (2) the addition of an autogenous tissue graft significantly increases the width of attached gingiva; and (3) the use of allogenic grafts produces dimensional increases in keratinized tissue similar to those produced with autogenous tissue. More recently, collagen matrixes of porcine

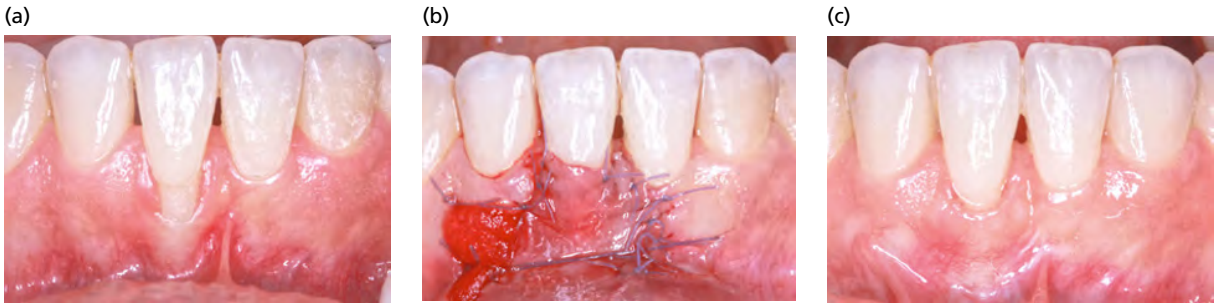

Fig. 39-5 Pedicle graft procedure for gingival augmentation. (a) Lower central incisor with facial soft tissue recession associated with high attachment of a frenulum. (b) Frenulum is released, and a split flap of keratinized tissue is dissected from the area of the neighboring tooth, mobilized laterally and secured in position at the recipient site. (c) Healing result 1-year post-treatment shows the establishment of a broad zone of keratinized tissue without interfering frenulum.

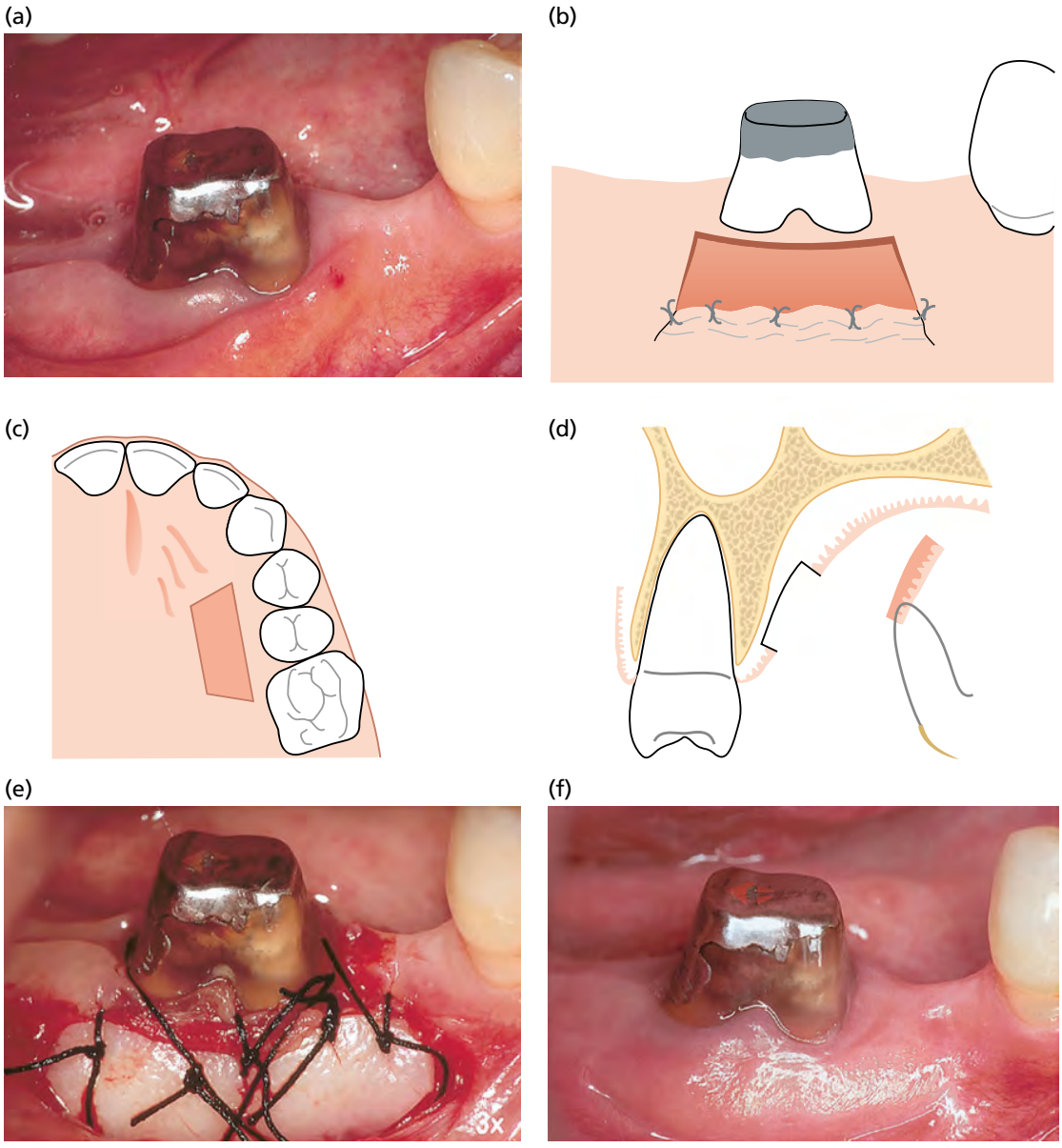

Fig. 39-6 Grafting procedure for gingival augmentation. (a) Lower molar at which the patient experiences discomfort during toothbrushing due to interfering lining mucosa and high attachment of a frenulum. The decision was made to displace the attachment of the frenulum apically and augment the gingival zone through the placement of a free graft. (b) Partial-thickness flap is dissected to prepare a recipient bed. The flap is displaced apically and sutured. (c, d) Graft with a thickness of 1.5–2 mm and of sufficient size and contour (a foil template of the recipient site may be used) is dissected from the palatal mucosa in the region of the premolars. (e) Graft is immediately transferred to the prepared recipient bed and anchored by sutures to secure a close adaptation of the graft to the recipient bed. (f) Following healing, a broad zone of keratinized tissue has been established. (Source: Courtesy of Professor Giampaolo Pini Prato.)

origin have shown to be as effective and predictable as the free autogenous connective tissue grafts (CTGs) in increasing the band of keratinized tissue at teeth and implants, but with significantly lower patient morbidity (Sanz *et al*. 2009; Nevins *et al*. 2011; Lorenzo *et al*. 2012). With the use of the alternative graft materials the preparation of the recipient site is similar to that using an autogenous graft.

Technique

1. The surgical procedure is initiated with the preparation of the recipient site (Fig. 39-6a, b). A periosteal bed free from muscle attachment and of sufficient size is prepared by sharp dissection. The partial-thickness flap is displaced apically and sutured.
2. In order to ensure that a graft of sufficient size and proper contour is removed from the donor area, the palatal mucosa in the region of the premolars is usually the region of choice. It is recommended to use a foil template of the recipient site, which is transferred to the donor site where it is outlined by a shallow incision (Fig. 39-6c). A graft with a thickness of approximately 1.5–2 mm is then dissected from the donor area (Fig. 39-6d).
3. The graft is immediately transferred to the prepared recipient bed and sutured (Fig. 39-6e). In order to immobilize the graft at the recipient site, the sutures must be placed in the periosteum or the adjacent attached gingiva. After suturing, pressure is exerted against the graft for 5 minutes in order to eliminate blood and exudate from between the graft and the recipient bed. The palatal wound may be protected with a palatal stent.
4. The sutures are removed after 1–2 weeks.

For a description of the pedicle graft procedure, see Root coverage procedures, later.

Healing following gingival augmentation procedures

Vestibular/gingival extension procedures

Since the specificity of the gingiva is determined by some inherent factor in the tissues, the postoperative results of vestibular extension procedures depend on the degree to which the various tissues contribute to the formation of granulation tissue in the wound area (Karring *et al*. 1975). Following the "denudation" or "split-flap technique", the wound area is filled with granulation tissue derived from the periodontal ligament, the tissue of the bone marrow spaces, the retained periosteal connective tissue, and the surrounding gingiva and lining mucosa (Fig. 39-7). The degree of bone resorption induced by the surgical trauma influences the relative amount of granulation tissue that grows into the wound from these various tissue sources. The resorption of crestal bone exposes varying amounts of the periodontal ligament tissue in the marginal area, allowing granulation tissue from the periodontal ligament to fill out the coronal portion of the wound. The greater the bone loss, the greater is the portion of the wound that becomes filled with granulation tissue from the periodontal ligament. This particular tissue possesses the capability to induce keratinization of the covering epithelium. This means that the widening of the keratinized tissue following "denudation" and "split flap" operations

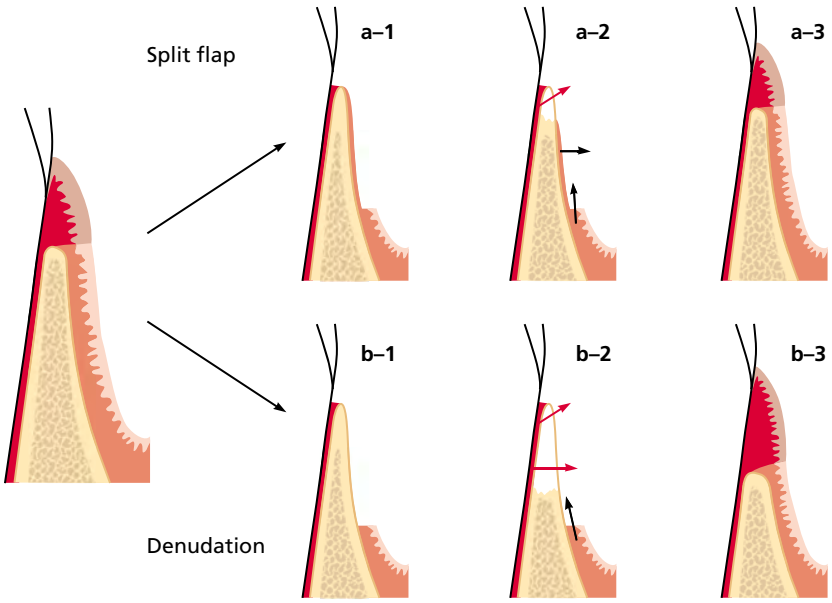

Fig. 39-7 The different stages of healing following the "split flap" (a) and "denudation" (b) techniques. Cells from the oral mucosa, bone, and periodontal ligament (arrows) participate in granulation tissue formation. Due to the difference in the degree of bone resorption (a-2, b-2), a larger area of the coronal portion of the wound is filled with granulation tissue from the periodontal ligament following "denudation" than following the "split flap" technique. Since granulation tissue from the periodontal ligament possesses the ability to induce a keratinized epithelium, "denudation" usually results in a wider zone of keratinized tissue than is the case following the "split flap" technique (a-3, b-3).

is achieved at the expense of a reduced bone height. The "denudation technique" usually results in more bone loss than the "split-flap technique". Therefore, a greater amount of granulation tissue with the capability of inducing a keratinized epithelium develops in the marginal area following the "denudation technique" than following the "split-flap technique". This is in accordance with the clinical observation that the "denudation technique" usually is superior to the "split-flap technique" in terms of increasing the width of keratinized tissue (Bohannan 1962a, b).

It can be concluded that the success or failure in extending the width of keratinized tissue by the "denudation" or "split-flap" techniques rests with the origin of the granulation tissue, which is related to the extent of bone loss induced by the surgical trauma. This in turn means that the result with respect to increasing the gingival width by methods involving periosteal exposure or denudation of the alveolar bone is unpredictable. The use of such methods is therefore not justified in periodontal therapy. The procedures discussed merely represent examples of how lack of knowledge about basic biologic principles may lead to the development of inappropriate therapeutic methods.

Grafting procedures

Healing of free soft tissue grafts placed entirely on a connective tissue recipient bed were studied in monkeys by Oliver *et al*. (1968) and Nobuto *et al*. (1988). According to these authors, healing can be divided into three phases (Fig. 39-8):

1. *Initial phase (from 0 to 3 days)*. During these first days of healing, a thin layer of exudate is present between the graft and the recipient bed. During this period the grafted tissue survives with an avascular "plasmatic circulation" from the recipient bed. Therefore, it is essential for the survival of the graft that a close contact is established to the underlying recipient bed at the time of operation. A thick layer of exudate or a blood clot may hamper the "plasmatic circulation" and result in rejection of the graft. The epithelium of the free graft degenerates early in the initial healing phase, and subsequently is desquamated. In placing a graft over a recession, part of the recipient bed will be the avascular root surface. Since the graft is dependent on the nature of its bed for diffusion of plasma and subsequent revascularization, the utilization of free grafts in the treatment of gingival

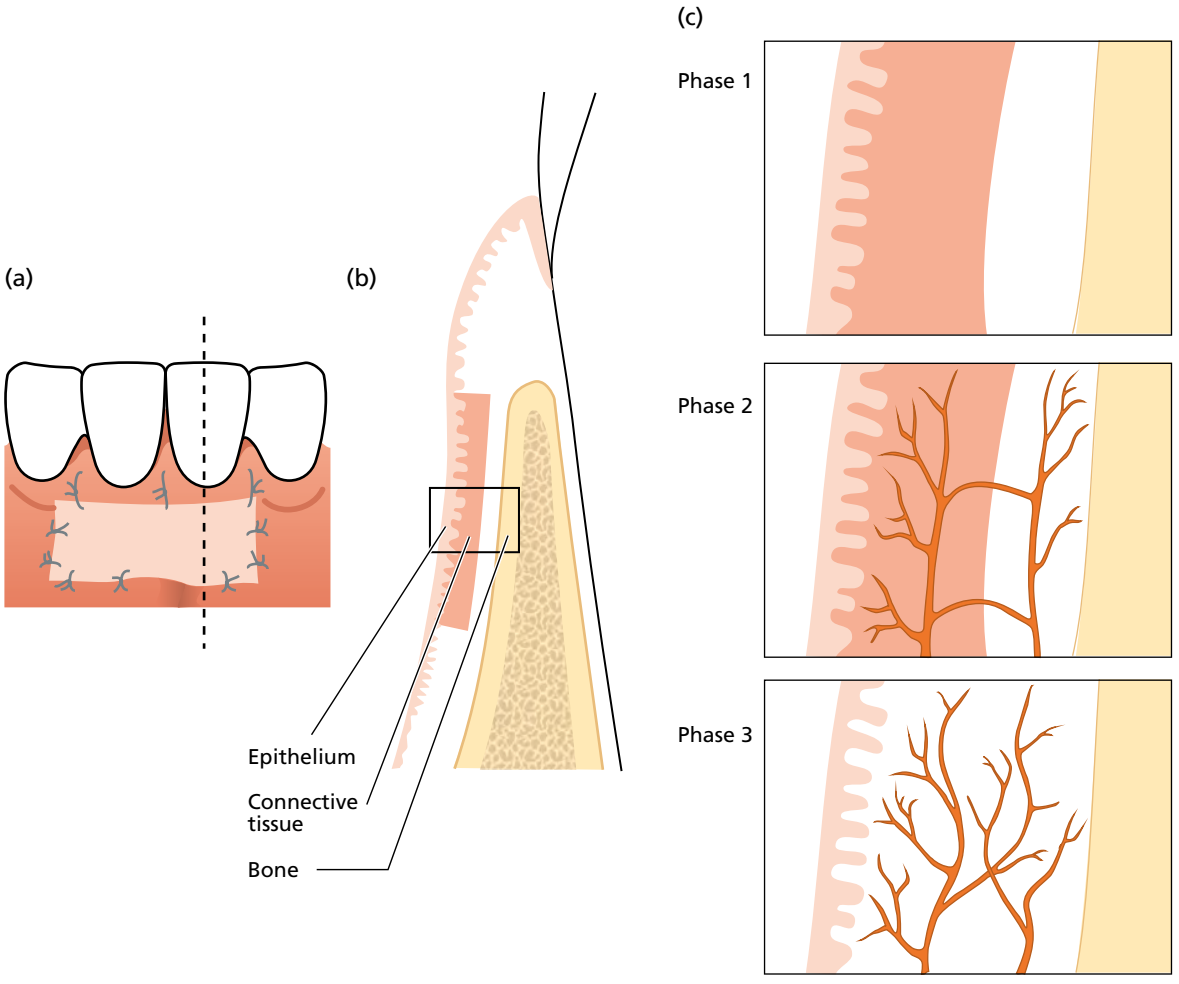

Fig. 39-8 Healing of a free gingival graft placed entirely on a connective tissue recipient bed (a). (b) Cross-section through the area. The framed areas (c) illustrate the three phases into which the healing process can be divided.

recessions involves a great risk of failure. The area of the graft over the avascular root surface must receive nutrients from the connective tissue bed that surrounds the recession. Thus, the amount of tissue that can be maintained over the root surface is limited by the size of the avascular area.

2. *Revascularization phase (from 2 to 11 days)*. After 4–5 days of healing, anastomoses are established between the blood vessels of the recipient bed and those in the grafted tissue. Thus, the circulation of blood is re-established in the pre-existing blood vessels of the graft. The subsequent time period is characterized by capillary proliferation, which gradually results in a dense network of blood vessels in the graft. At the same time, a fibrous union is established between the graft and the underlying connective tissue bed. The re-epithelialization of the graft occurs mainly by proliferation of epithelium from the adjacent tissues. If a free graft is placed over the denuded root surface, apical migration of epithelium along the tooth-facing surface of the graft may take place at this stage of healing.
3. *Tissue maturation phase (from 11 to 42 days)*. During this period, the number of blood vessels in the transplant is gradually reduced, and after approximately 14 days the vascular system of the graft appears normal. Also, the epithelium gradually matures with the formation of a keratin layer during this stage of healing.

The establishment and maintenance of a "plasmatic circulation" between the recipient bed and the graft during the initial phase of healing is critical in this kind of therapy. Therefore, in order to ensure ideal conditions for healing, blood between the graft and the recipient site must be removed by exerting pressure against the graft following suturing.

Mucogingival condition with gingival recessions

Gingival recession is defined as the apical shift of the gingival margin with respect to the CEJ. It is associated with attachment loss and with exposure of the root surface to the oral environment (Cortellini & Bissada 2018).

Gingival recessions are a common feature in populations with high standards of oral hygiene (e.g. Sangnes & Gjermo 1976; Murtomaa *et al*. 1987; Löe *et al*. 1992; Serino *et al*. 1994), as well as in populations with poor oral hygiene (e.g. Baelum *et al*. 1986; Yoneyama *et al*. 1988; Löe *et al*. 1992; Susin *et al*. 2004). In populations maintaining high standards of oral hygiene, loss of attachment and marginal tissue recession are predominantly found at buccal tooth surfaces (Löe *et al*. 1992; Serino *et al*. 1994) and are frequently associated with the presence of a "wedge-shaped defect in the crevicular area of one or several teeth" (Sangnes & Gjermo 1976) (Fig. 39-9). In contrast, all tooth surfaces are usually affected by soft tissue recession in periodontally untreated populations, although the prevalence and severity are more pronounced at single-rooted teeth than at molars (Löe *et al*. 1978; Miller *et al*. 1987; Yoneyama *et al*. 1988; Löe *et al*. 1992).

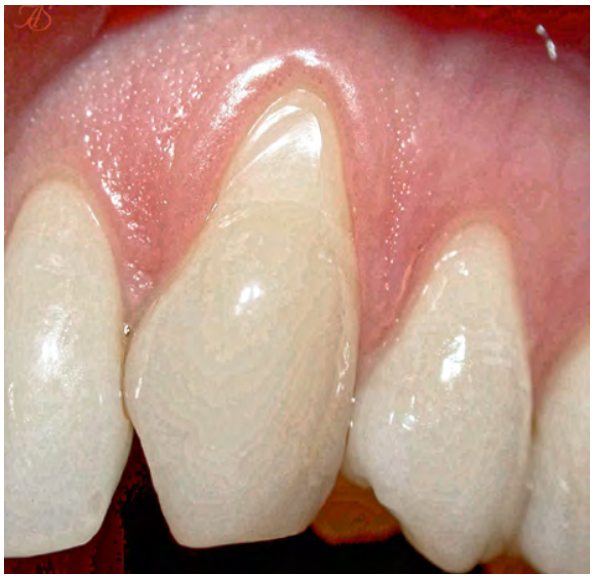

Fig. 39-9 Maxillary cuspid with gingival buccal buccal recessions illustrating the presence of a "wedge-shaped defect in the buccal tooth surface".

Although the etiology of localized gingival recessions remains unclear, several predisposing factors have been suggested.

Periodontal phenotype and attached gingiva

A thin periodontal phenotype, absence of attached gingiva, and reduced thickness of the alveolar bone due to abnormal tooth position in the arch have been considered risk factors for the development of gingival recession (Kim & Nieva 2015) (Fig. 39-10).

Cross-sectional studies have shown that a correlation exists between the presence of recession defects and the height (width) of the gingiva (e.g. Stoner & Mazdyasna 1980; Tenenbaum 1982), which has often been interpreted as evidence that a narrow zone of

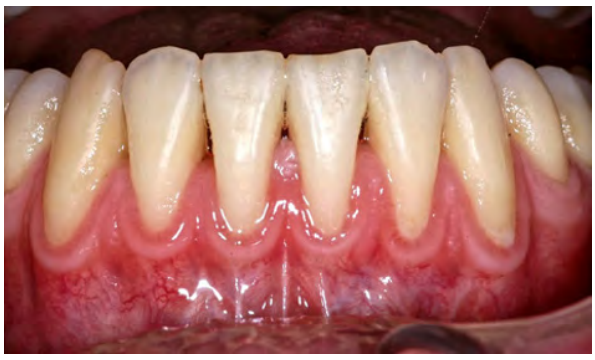

Fig. 39-10 Mandibular tooth segment with multiple buccal recessions illustrating the association proposed between a thin phenotype and attachment loss

gingiva is a contributing factor in the development of soft tissue recessions (Fig. 39-9). It should be realized, however, that this data was derived from cross-sectional studies, which can neither prove nor disprove a cause–effect relationship. In fact, data obtained from prospective, longitudinal studies of patients showing areas with only a minimal zone of gingiva favor the conclusion that a certain quantity of gingiva is not essential for the prevention of soft tissue recessions. Lindhe and Nyman (1980) examined the alterations of the position of the gingival margin following periodontal surgery in 43 patients with advanced periodontal breakdown. Following active treatment, all patients were recalled once every 3–6 months for maintenance care. The position of the soft tissue margin in relation to the CEJ was assessed on the facial aspect of all teeth after initial healing and after 10–11 years of maintenance. The results showed that both in areas with and without visible keratinized tissue after healing, a small coronal regrowth (≈1 mm) of the soft tissue margin had occurred during the period of maintenance. In other words, no recession was observed in this group of patients maintained on a careful prophylaxis program.

Dorfman *et al*. (1982) reported a 4-year follow-up study including 22 patients with bilateral tooth areas exhibiting gingival recession and lack of firmly attached marginal soft tissue. In conjunction with scaling and root planing, a free gingival graft was placed on one side, while the contralateral control side was treated by scaling and root planing only. All patients were recalled for prophylaxis once every 3–6 months during a 4-year period. The data obtained from the examinations of the non-grafted control areas revealed that no further recession of the soft tissue margin or loss of probing attachment had occurred despite the lack of attached marginal tissue. In fact, there was a slight gain of probing attachment. The authors concluded that recession sites without attached gingiva might not experience further attachment loss and recession if the inflammation is controlled. In a subsequent report, Kennedy *et al*. (1985) presented data on 10 patients who had not participated in the maintenance program for a period of 5 years. In these patients, plaque and clinical signs of inflammation as well as some further recessions were noted at the 5-year examination as compared with the data obtained after termination of active treatment. However, except for the clinical signs of inflammation, which were more pronounced in non-grafted sites, no differences were observed between control sites with <1 mm or complete lack of attached gingiva and grafted sites.

The lack of relationship between the height of the gingiva and the development of soft tissue recession is further validated by results from longitudinal clinical studies (Schoo & van der Velden 1985; Kisch *et al*. 1986; Wennström 1987; Freedman *et al*. 1999). The prospective study by Wennström (1987) reported observations made at 26 buccal sites surgically deprived of all keratinized tissue. A baseline examination carried out 6 months after treatment revealed that these sites had regained a zone of gingiva which was, however, not attached or had only a minimal (<1 mm) portion attached to the underlying hard tissues (Figs. 39-11a, 39-12a). Adjacent teeth with a broad zone of attached gingiva were also included in the examinations. In most sites, the position of the soft tissue margin was maintained unchanged over 5 years (Figs. 39-11b, 39-12b).

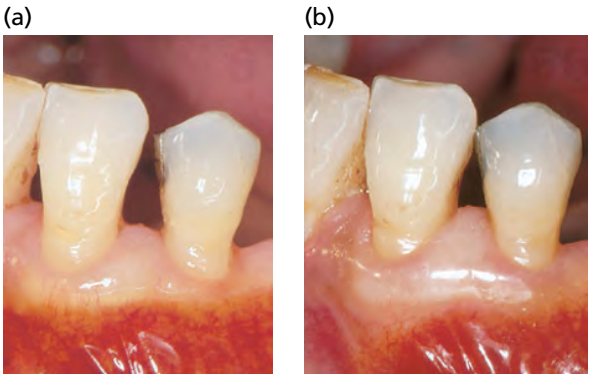

Fig. 39-11 (a) A canine and a first premolar in the mandibular jaw with <1 mm of attached portion of gingiva 6 months after surgical treatment. (b) Note the increase of the width of the gingiva at the facial aspect of the teeth and the more coronally positioned gingival margin 5 years later.

In conclusion, evidence from prospective longitudinal studies shows that the gingival height is not a critical factor for the prevention of marginal tissue recession, but that the development of a recession will result in loss of gingival height.

Recessions associated with mechanical factors, predominantly toothbrushing trauma

Traumatizing toothbrushing and tooth malposition are the factors that have been most frequently associated with marginal tissue recession (Sangnes 1976; Vekalahti 1989; Checchi *et al*. 1999; Daprile *et al*. 2007). Tissue trauma caused by vigorous or "improper" toothbrushing is considered a predominant causative

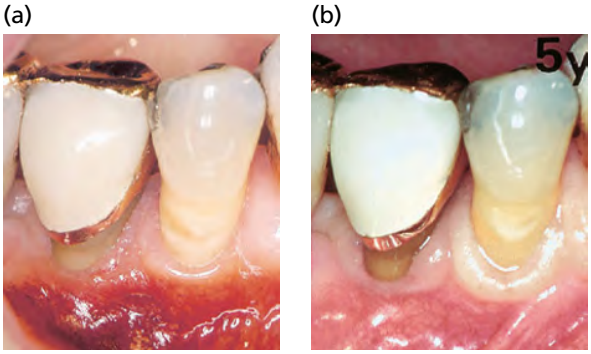

Fig. 39-12 (a) Mandibular canine and first premolar tooth region showing a very narrow zone of gingiva 6 months after surgical therapy. (b) No major change in the position of the soft tissue margin has occurred during a 5-year period despite the lack of attached gingiva.

factor for the development of recessions, particularly in young individuals. These recessions are often found at sites with clinically healthy gingiva and where the exposed root has a wedge-shaped defect, the surface of which is clean, smooth, and polished (Fig. 39-13).

Studies have reported that duration of toothbrushing, brushing force, frequency of changing the toothbrush, brush (bristle) hardness (Khocht *et al*. 1993), and tooth-brushing technique may be contributing factors. However, a a systematic review was not able to fully validate these hypotheses (Rajapakse *et al*. 2007). Among the 18 examined studies, one concluded that the toothbrushing significantly reduced recessions on facial tooth surfaces over 18 months, two concluded that there appeared to be no relationship between toothbrushing frequency and gingival recession, whereas eight studies reported a positive association between toothbrushing frequency and recession.

Recessions associated with localized plaque-induced inflammatory lesions

Other local factors that have been associated with marginal tissue recession are the presence of: (1) alveolar bone dehiscences (Bernimoulin & Curilovic 1977; Löst 1984), (2) high muscle attachment and frenum pull (Trott & Love 1966), (3) plaque and calculus (van Palenstein Helderman *et al*. 1998; Susin *et al*. 2004), and (4) iatrogenic factors related to restorative and periodontal treatment procedures (Lindhe & Nyman 1980; Valderhaug 1980).

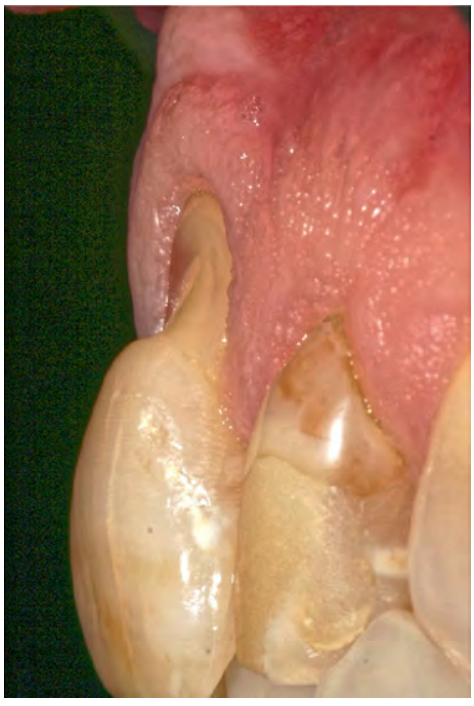

Fig. 39-13 Recessions associated with toothbrushing trauma. The marginal gingiva is clinically healthy, and an abrasion wedge-shaped defect can be noted in the exposed root.

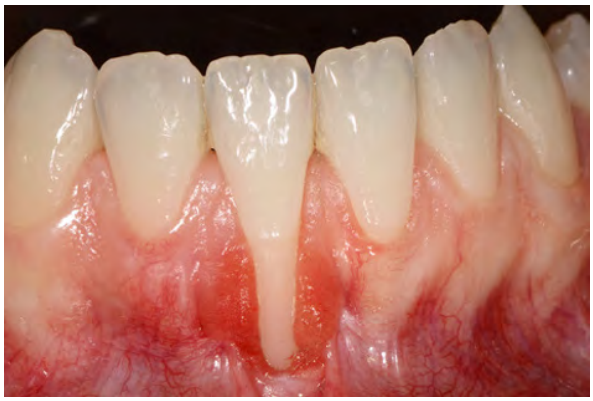

Fig. 39-14 Recession associated with a localized plaque-induced inflammatory lesion.

Such recessions may be found at teeth that are prominently positioned, where the alveolar bone is thin or absent (bone dehiscence), and where in addition the gingival tissue is thin (delicate) (Fig. 39-14). An inflammatory lesion that develops in response to subgingival plaque occupies the connective tissue adjacent to the dentogingival epithelium. Measurements made by Waerhaug (1952) suggest that the distance between the periphery of microbial plaque on the tooth surface and the lateral and apical extension of the inflammatory cell infiltrate seldom exceeds 1–2 mm. Thus, if the free gingiva is voluminous, the infiltrate will occupy only a small portion of the connective tissue. In a thin and delicate gingiva, on the other hand, the entire connective tissue portion may be engaged. Proliferation of epithelial cells from the oral as well as the dentogingival epithelium into the thin and degraded connective tissue may bring about a subsidence of the epithelial surface, which clinically becomes manifest as recession of the tissue margin (Baker & Seymour 1976).

Recessions associated with cervical restorative margins

A systematic review (Kim & Nieva 2015) reported clinical observations suggesting that sites with minimal or no gingiva associated with intrasulcular restorative margins were more prone to gingival recession and inflammation. However, these conclusions were based mainly on clinical observations (low level of evidence).

The placement of restoration margins subgingivally may not only create a direct operative trauma to the tissues (Donaldson 1974), but may also facilitate subgingival plaque accumulation, with resultant inflammatory alterations in the adjacent gingiva and recession of the soft tissue margin (Parma-Benfenati *et al*. 1985; Lang 1995; Günay *et al*. 2000). Over a 10-year period, Valderhaug (1980) evaluated longitudinally the soft tissue alterations taking place at facial sites of 286 teeth with subgingivally or supragingivally placed crown margins in 82 patients. The re-examination performed 1 year after insertion of the

restorations revealed that the gingivae at teeth with subgingival restoration margins were more commonly inflamed than at those with supragingivally placed borders. Of the 150 teeth which had the facial crown margin located subgingivally at the time of cementation, 40% already showed supragingival exposure of the crown margin after 1 year, and at the 10-year examination as many as 71% had become supragingivally positioned due to recession of the soft tissue margin. Compared with teeth with supragingivally placed crown margins, the amount of recession and clinical attachment loss was greater at sites with subgingivally placed restoration margins.

Stetler and Bissada (1987) evaluated the periodontal conditions at teeth with subgingivally placed restoration margins and showed that in subgingivally placed restorations with plaque accumulation, if the adjacent gingiva was thin, there was a potential risk for the development of soft tissue recession. Accordingly, if recession is to be prevented, either the plaque-control standard has to be improved or the *thickness* of the gingival margin has to be increased.

Recessions associated with orthodontic treatments

Results from clinical and experimental research have documented that most forms of orthodontic therapy are innocuous to the periodontium (see Chapter 47). The clinician may observe, however, that some patients respond to frontal movements of incisors and lateral movements of posterior teeth by gingival recession and loss of attachment (Maynard & Ochsenbein 1975; Coatoam *et al*. 1981; Foushee *et al*. 1985) (Fig. 39-12). In fact, a systematic review (Kim & Nieva 2015) has reported that the direction of the orthodontic tooth movement and the bucco-lingual thickness of the gingiva may contribute to marginal gingival recession during orthodontic treatment. The reported prevalence of gingival recessions at the end of orthodontic treatment ranges between 5% and 12%, although authors have reported an increase of the prevalence up to 47% in long-term observation (5 years) (Renkema et al 2015). Based on these clinical observations it has been suggested that a grafting procedure to increase the gingival dimensions should precede the initiation of orthodontic therapy in such areas (Boyd 1978; Hall 1981; Maynard 1987).

As discussed previously, the presence of an alveolar bone dehiscence is a prerequisite for the development of a marginal tissue recession, since this dehiscence may establish an environment that is conducive for loss of gingival tissue. With respect to orthodontic therapy, this would imply that as long as a tooth is moved exclusively within the alveolar bone, soft tissue recession will not develop (Wennström *et al*. 1987). On the other hand, predisposing alveolar bone dehiscences may be induced by uncontrolled facial expansion of a tooth through the cortical plate, thereby rendering the tooth liable to the development of soft tissue recession. In this context it is interesting to note that experimental studies have shown that labial bone will reform in the area of a dehiscence when the tooth is retracted towards a proper positioning of the root within the alveolar process (Engelking & Zachrisson 1982; Karring *et al*. 1982) (Fig. 39-15). It is therefore likely that the reduction in recession seen at a previously prominently positioned tooth that has

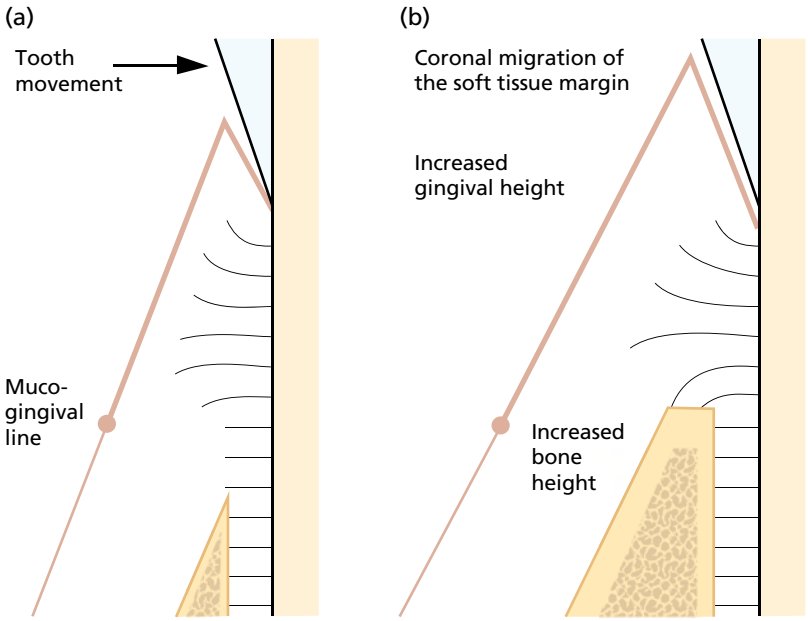

Fig. 39-15 (a) Alterations occurring in the marginal periodontal tissues following lingual movement of a tooth prominently positioned in the arch and having a bone dehiscence. (b) An increase in bone height and gingival height will be seen as well as a coronal migration of the soft tissue margin following lingual positioning of the tooth. (Sources: Engelking & Zachrisson 1982; Karring et al. 1982. Reproduced with permission from John Wiley & Sons.)

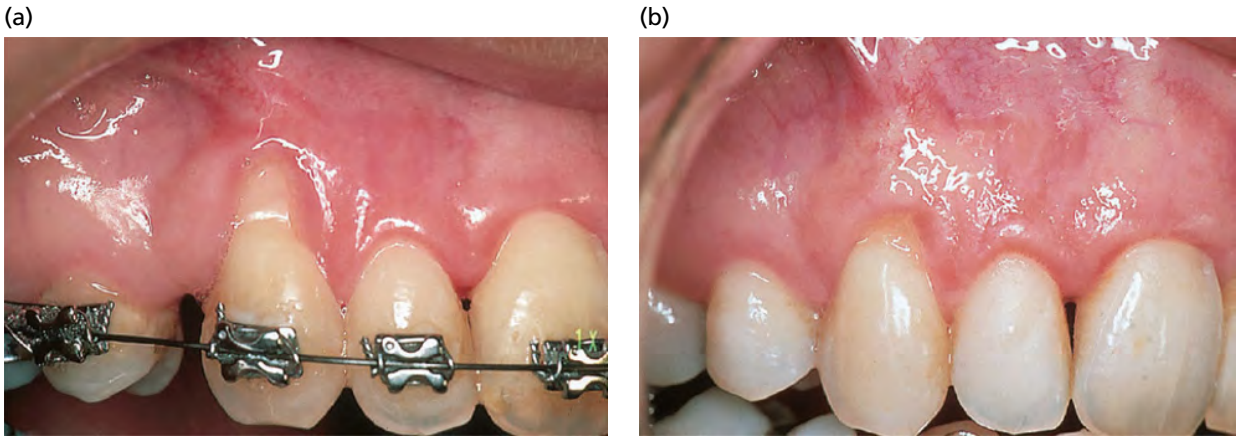

Fig. 39-16 (a) Prominently positioned tooth 13 showing soft tissue recession. (b) Same tooth following the completion of the orthodontic tooth movement. Note the reduction of the recession that has taken place as a consequence of the changed position of the tooth.

been moved into a more proper position within the alveolar process (Fig. 39-16) is also accompanied by bone formation.

Alterations occurring in gingival dimensions and marginal tissue position in conjunction with orthodontic therapy are related to the *direction of tooth movement*. Facial movement results in reduced facial gingival dimensions, while an increase is observed following lingual movement (Coatoam *et al*. 1981; Andlin-Sobocki & Bodin 1993). Recession of the labial gingival margin and loss of attachment were demonstrated in experimental studies in the monkey following either tipping and extrusion movements or bodily movements of incisors (Batenhorst *et al*. 1974; Steiner *et al*. 1981). However, similarly designed studies carried out in dogs (Karring *et al*. 1982; Nyman *et al*. 1982) and humans (Rateitschak *et al*. 1968) failed to demonstrate that labial tooth movement is accompanied by marginal tissue recession and attachment loss. The conflicting results may be related to differences with respect to, for example, (1) the amount of labial tooth displacement, (2) the presence/absence of plaque and gingival inflammation in the regions subjected to tooth movement, and/or (3) differences in gingival dimensions. Wennström *et al*. (1987) experimentally moved teeth orthodontically into areas with varying thickness and quality of the marginal soft tissue. Following extensive bodily movement of incisors in a labial direction through the alveolar bone, most teeth showed a small apical displacement of the soft tissue margin but no loss of connective tissue attachment (Fig. 39-17).

In other words, the apical displacement of the gingival margin was the result of a reduced height of the free gingiva (Fig. 39-18), which in turn may be related to tension ("stretching") in the soft tissues during the facial tooth movement and reduced buccolingual tissue thickness. Similar to results presented by Foushee *et al*. (1985) from a study in humans, no relationship was found between the initial apicocoronal width (height) of the gingiva and the degree of apical displacement of the soft tissue margin during orthodontic therapy. Thus, the findings do not lend support to the concept of a certain zone of gingiva as essential

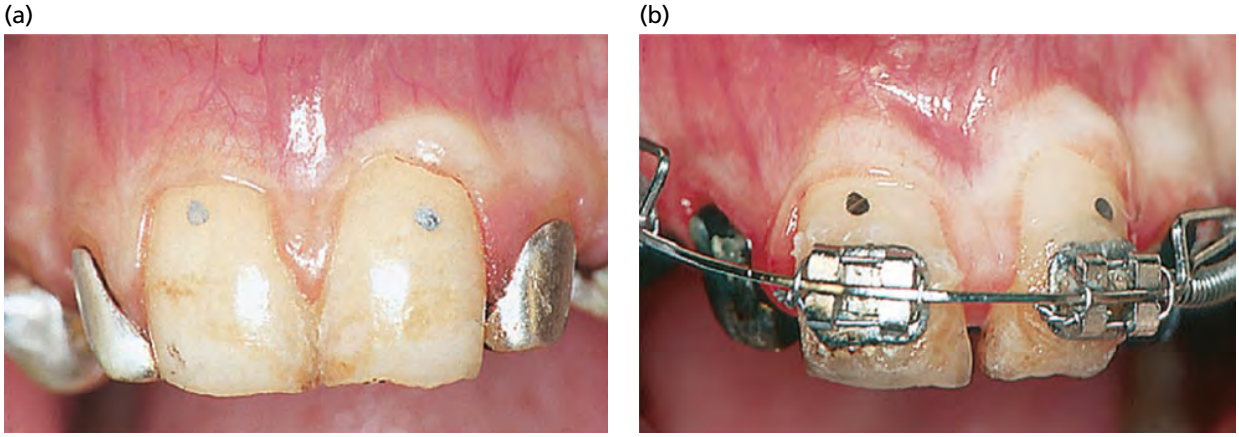

Fig. 39-17 Buccal aspect of the central incisors before (a) and after (b) the labial tooth movement. No obvious change in the location of the gingival margin has occurred despite the pronounced labial displacement of the incisors.

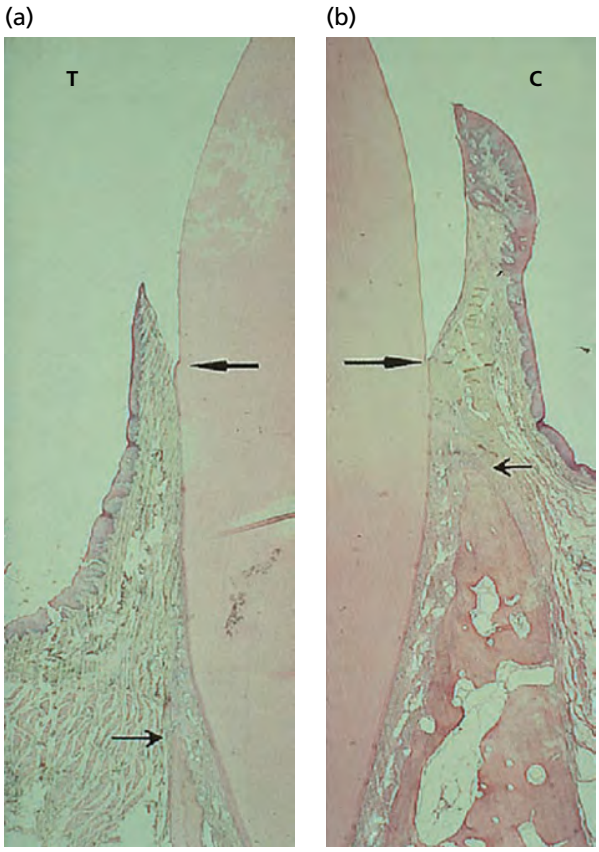

Fig. 39-18 Histologic specimens showing (a) reduced alveolar bone height at an incisor bodily moved in the labial direction and (b) normal alveolar bone height at a non-moved control tooth. Note the maintained level of connective tissue attachment and the reduced height of the free gingiva at the labially displaced incisor (a). Large arrows indicate the position of the cementoenamel junction and small arrows the position of the alveolar bone crest.

for the prevention of recession during orthodontic therapy, but rather corroborate observations reported by Coatoam *et al*. (1981) that the integrity of the periodontium can also be maintained during orthodontic therapy in areas which have only a minimal zone of gingiva.

In the experimental studies by Steiner *et al*. (1981) and Wennström *et al*. (1987), it was observed that teeth experiencing loss of connective tissue attachment when orthodontically moved facially showed obvious clinical signs of inflammation throughout the experimental period. Since it has been demonstrated that, in the presence of plaque-induced suprabony lesions, orthodontic forces generating bodily tooth movement are not capable of causing accelerated destruction of the connective tissue attachment (Ericsson *et al*. 1978), a decreased buccolingual dimension of the border tissue due to "stretching" of the facial gingiva may have favored the destructive effect of the plaque-associated inflammatory lesion. This assumption is validated by the observations that, in the presence of plaque-induced gingivitis, a thin marginal soft tissue is more susceptible to complete breakdown than a thick one (Baker & Seymour 1976). Furthermore, no difference in attachment loss was observed at plaque-infected teeth that were bodily moved *within the alveolar bone*, irrespective of the type of bordering soft tissue (gingiva or lining mucosa) (Wennström *et al*. 1987). Hence, the *thickness rather than the quality* of the marginal soft tissue on the pressure side of the tooth is the determining factor for the development of the recession. This interpretation is supported by findings of clinical studies in humans analyzing factors of importance for the development of recessions during labial movement of mandibular incisors. Melsen and Allais (2005) found that gingival inflammation and a "thin gingival biotype" were significant predictors for gingival recession, and Yared *et al*. (2006) reported that 93% of the teeth that developed recession had a gingival thickness of <0.5 mm. Hence, the observations made in the studies discussed strongly emphasize the importance of adequate infection control during orthodontic treatment.

Conclusion: The clinical implication of the results from the studies discussed is that labial tooth movement should be preceded by careful examination of the dimensions of the tissues covering the facial aspect of the teeth to be moved. As long as a tooth can be moved within the envelope of the alveolar process, the risk of harmful side effects on the marginal tissue is minimal, irrespective of the dimensions and quality of the soft tissue surrounding the tooth. If, however, the tooth movement is expected to result in the establishment of an alveolar bone dehiscence, the volume (thickness) of the covering soft tissue should be considered as a factor that may influence the development of soft tissue recession during, as well as after, the phase of active orthodontic therapy. A thin phenotype may serve as a *locus minorus resistentia* to developing soft tissue defects in the presence of plaque-induced inflammation or toothbrushing trauma.

Recessions associated with generalized forms of destructive periodontal disease

The loss of periodontal support at proximal sites may result in compensatory remodeling of the support at the buccal/lingual aspect of the teeth, leading to an apical shift of the soft tissue margin (Serino *et al*. 1994). In addition, apical displacement of the soft tissue margin is an inevitable consequence of the resolution of periodontal lesions following treatment and is independent of a non-surgical or a surgical treatment approach (Fig. 39-19).

Diagnosis of gingival recessions

Miller (1985a) described a classification of recession defects taking into consideration the anticipated root coverage that it is possible to obtain with the use of grafting techniques (Fig. 39-20);

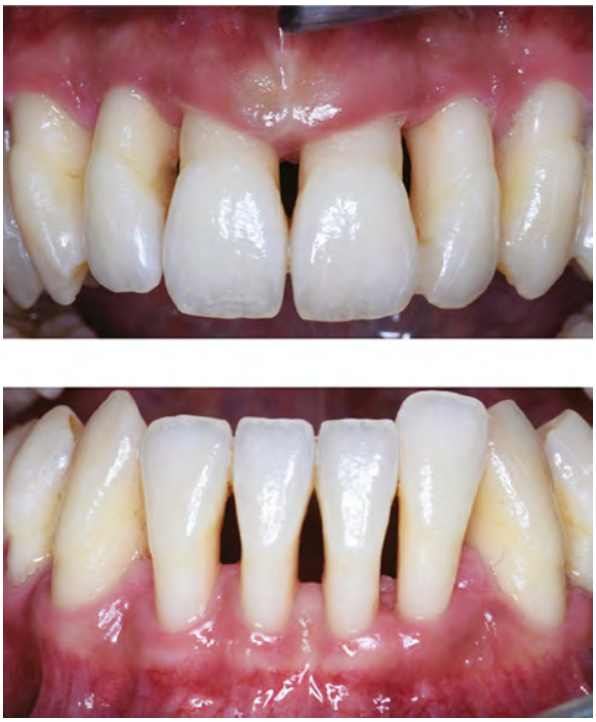

Fig. 39-19 Recessions associated with generalized forms of destructive periodontal disease. Recession of the soft tissue is found not only at the facial aspect of the teeth but also at proximal sites.

- *Class I*: marginal tissue recession not extending to the mucogingival junction; no loss of interdental bone or soft tissue
- *Class II*: marginal tissue recession extending to or beyond the mucogingival junction; no loss of interdental bone or soft tissue
- *Class III*: marginal tissue recession extending to or beyond the mucogingival junction; loss of interdental bone/soft tissue or malpositioning of the tooth
- *Class IV*: marginal tissue recession extending to or beyond the mucogingival junction; severe loss of interdental bone/soft tissue or severe malpositioning of the tooth.

While complete root coverage (CRC) was considered achievable in class I and II defects, only partial coverage could be expected in class III and IV recession defects. While there seems to be no reason to differentiate between class I and II recession defects, the critical clinical variable to determine the possible outcome of a root coverage procedure was the level of periodontal tissue support at the proximal sites of the tooth.

The recent 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions has adopted a classification of gingival recessions (Jepsen *et al*. 2018) based on the dimension of the buccal/lingual gingival recession in relation to the interdental clinical attachment loss (Cairo *et al*. 2011) (Fig. 39-21):

- *Recession Type 1 (RT1)*: Gingival recession with no loss of interproximal attachment. Interproximal CEJ is clinically not detectable at both mesial and distal aspects of the tooth.

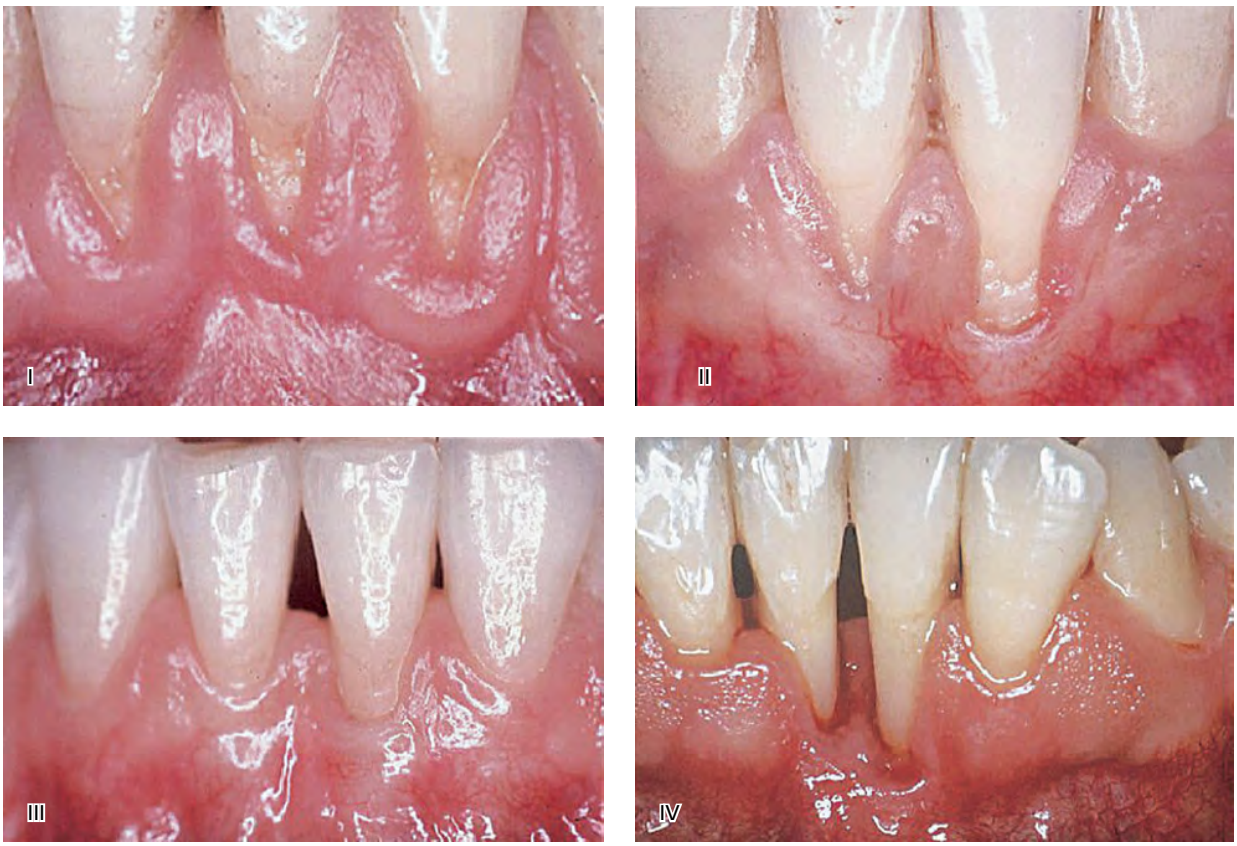

Fig. 39-20 Miller classification of recession defects (see text). (Source: Courtesy of Professor Giampaolo Pini Prato.)

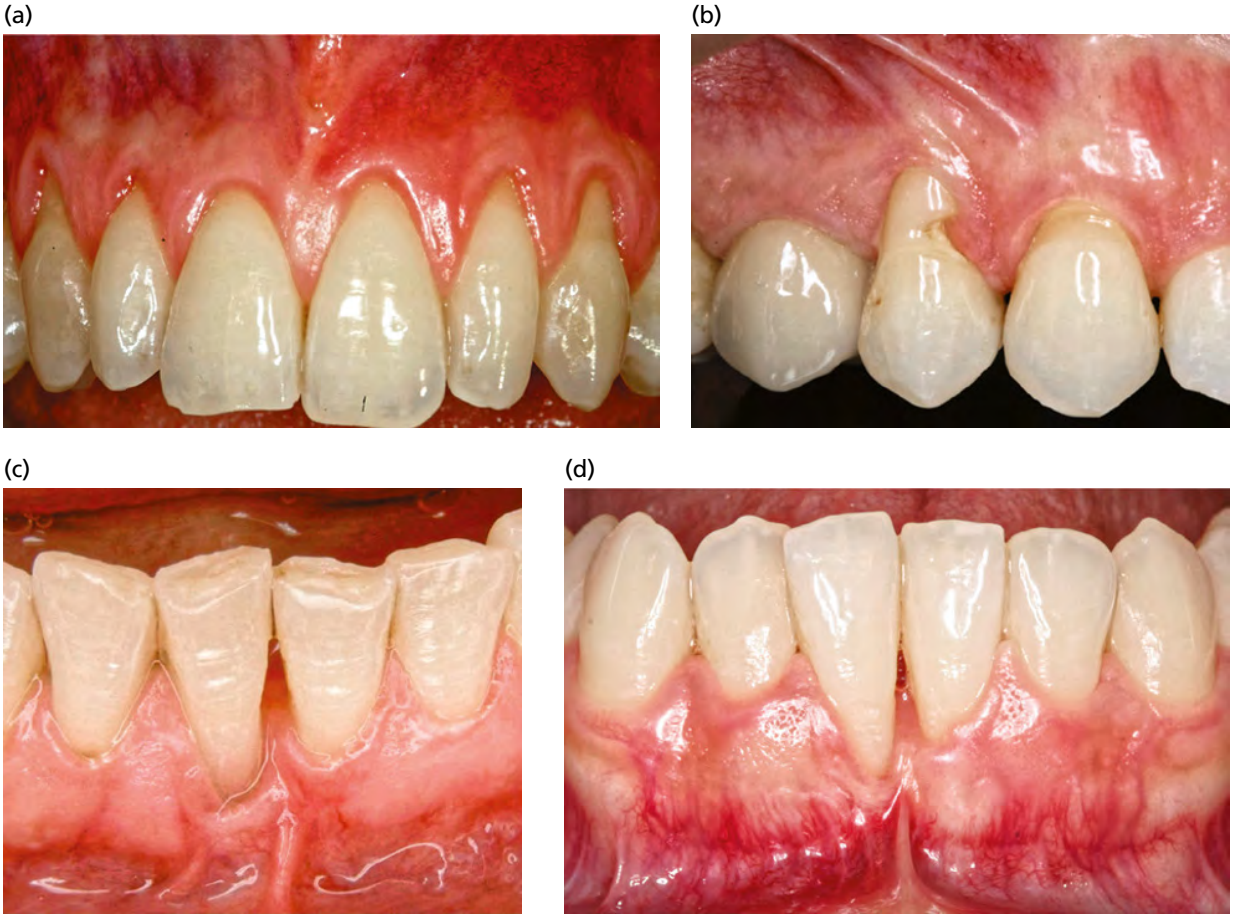

Fig. 39-21 Cairo classification of recession defects (see text). (a) RT1; (b) RT2; (c, d) RT3.

- *Recession Type 2 (RT2)*: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the depth of the interproximal sulcus/pocket) is less than or equal to the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).
- *Recession Type 3 (RT3)*: Gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss (measured from the interproximal CEJ to the apical end of the sulcus/pocket) is higher than the buccal attachment loss (measured from the buccal CEJ to the apical end of the buccal sulcus/pocket).

This classification is a treatment-oriented classification to forecast the potential for root coverage through the assessment of interdental CAL. In the RT1 (Miller Class I and II) 100% root coverage can be predicted; in the RT2 (overlapping the Miller class III) some randomized clinical trials indicate that depending on the degree of interdental CAL loss CRC may be predictable applying different root coverage procedures; in the Cairo RT3 (overlapping the Miller class IV) full root coverage is not achievable (Tonetti *et al*. 2014)

In order to account for other factors associated with the predictability of root coverage with the different mucogingival surgical interventions, this classification should be supplemented with other relevant diagnostic elements (depth of the gingival recession, gingival thickness, keratinized tissue width, presence of the CEJ, associated cervical lesions).

The development of NCCLs occurs frequently on exposed root surfaces and is associated with deeper gingival recessions. These NCCLs are usually accompanied by the loss of the CEJ and/or formation of lesions on the tooth surface (loss of substance with presence of a root surface concavity >0.5 mm [step]). In the new 2017 classification (Cortellini & Bissada 2018) it is possible to identify four different clinical situations: Class A, when the CEJ is still detectable, with presence/absence of cervical step >0.5 mm; and Class B, when the CEJ is not identifiable, with presence/absence of cervical step >0.5 mm. The diagnosis of these clinical situations should be associated to the type of recession (RT1, RT2, or RT3) and the other diagnostic elements (depth of the recession, gingival thickness, and amount of keratinized tissue) (see Table 39-2) to support the clinician with the decision making in relation to the choice of surgical intervention for root coverage (described later in this chapter).

Table 39-2 Diagnostic table for treatment support of gingival recessions.

Gingival site				Tooth site	
	REC depth	GT	KTW	CEJ (A/B)	Step (+/-)
No recession					
RT1					
RT2					
RT3					

CEJ, cementoenamel junction (Class A = detectable CEJ. Class B = undetectable CEJ); GT, gingival thickness; KTW, keratinized tissue width; RT, recession type; REC depth, depth of the gingival recession; Step, root surface concavity (Class + = presence of a cervical step >0.5 mm. Class – = absence of cervical step).

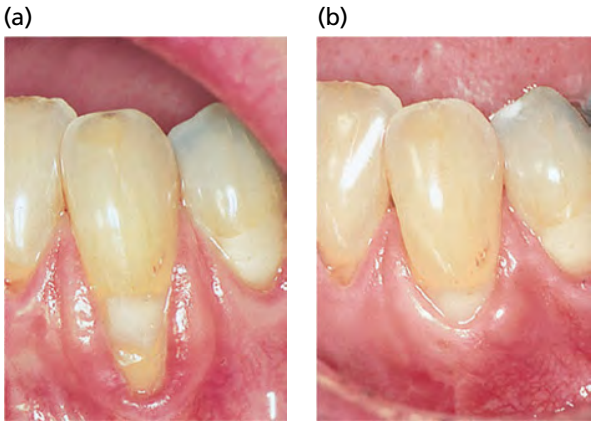

Fig. 39-23 (a) Mandibular canine with a deep recession, which makes self-performed plaque control difficult. (b) To facilitate plaque control, the position of the soft tissue margin was altered surgically.

Treatment of gingival recessions

The main indications for root coverage procedures are esthetic/cosmetic demands (Fig. 39-22). Root sensitivity and changing the topography of the marginal soft tissue in order to facilitate plaque control may also be an indication for root coverage procedures (Fig. 39-23).

Because gingival recessions are not pathological entities *per se* (in absence of gingival inflammation), it is important to justify the decision to treat them with root coverage procedures. A basic question to be answered is: what occurs if an existing gingival recession is left untreated? A systematic review with meta-analysis that assessed the long-term outcomes of untreated facial gingival recession (Chambrone & Tatakis 2016) reported that facial gingival recession in subjects with good oral hygiene is highly likely to result in an increase in the recession depth during long-term follow-up. Agudio *et al*. (2016) compared treated sites with homologous contralateral sites presenting with thin gingival phenotype with or without recessions in a population of highly motivated patients. At the end of the follow-up period (mean of 23.6 ± 3.9 years, range 18–35 years), the extent of the recession was reduced in 83% of the 64 treated sites, whereas it was increased in 48% of the 64 untreated sites. Thin gingival phenotypes augmented by grafting procedures remained more stable over time than thin gingival phenotypes. Even though progression of gingival recession seems not to impair the long-term survival of teeth, it may be associated with problems like esthetic impairment, dentin hypersensitivity, and tooth conditions that concern the patient and the clinician.

Recession defects in children need particular attention. In the growing child, recession defects may be eliminated spontaneously, provided adequate plaque control is established and maintained (Fig. 39-24). Andlin-Sobocki *et al*. (1991) reported from a 3-year prospective study that 25 of 35 recession defects with an initial depth of 0.5–3.0 mm healed spontaneously following improvement of the oral hygiene standard. Furthermore, all but three remaining recessions showed a decrease, and no site demonstrated an increase in depth. Hence, reparative surgical treatment of soft tissue recessions in the developing

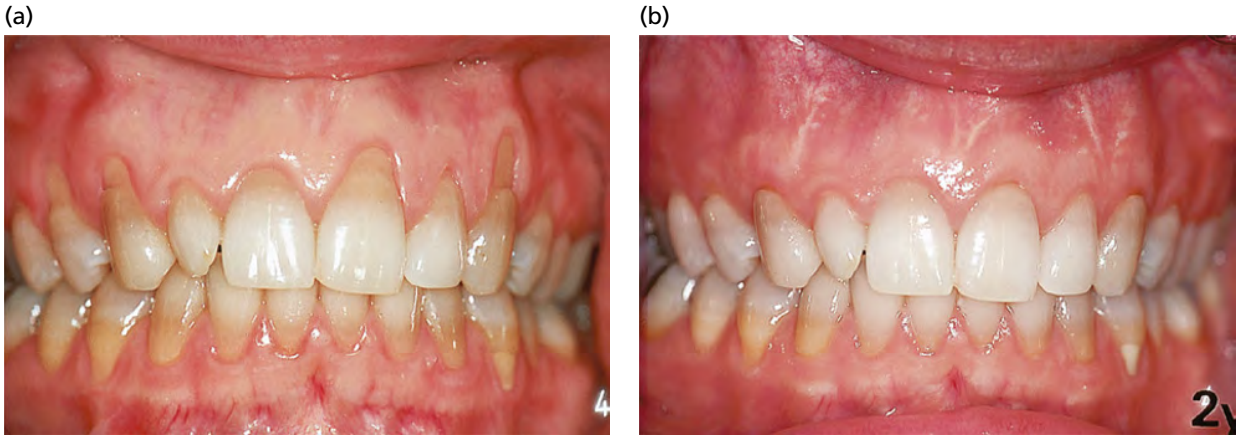

Fig. 39-22 (a) A 25-year-old woman with esthetic concerns due to multiple soft tissue recessions in the maxilla and a high lip line. The gingiva is healthy and several of the exposed root surfaces show abrasion defects, indicating toothbrushing trauma as the causative factor for the development of the recessions. The brushing technique was altered, and root coverage was achieved surgically. (b) Two-year post-treatment view.

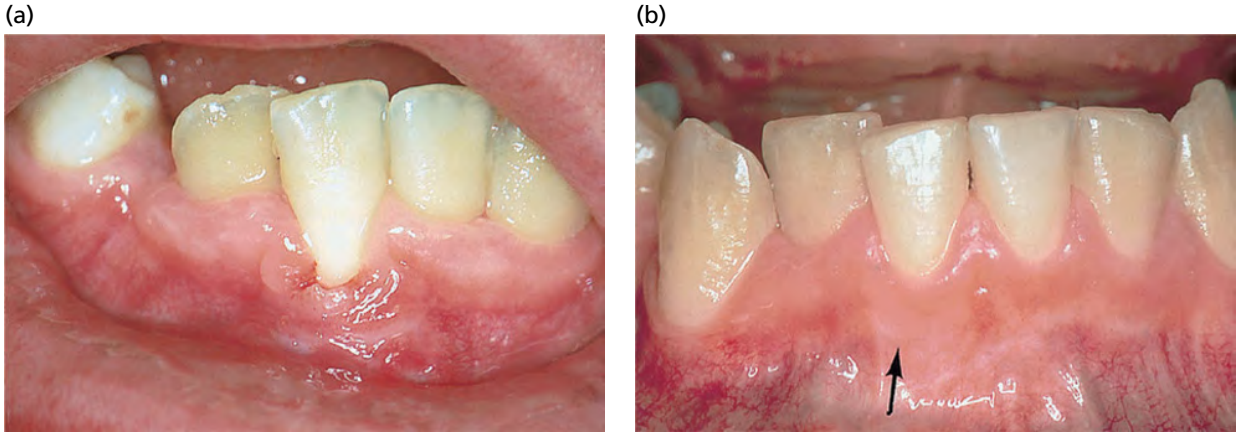

Fig. 39-24 A 9-year-old boy showing recession at tooth 41. (a) Tooth is rotated and buccally positioned. The minimal amount of gingiva found apical to the recession shows pronounced signs of inflammation. The plaque control in the region was improved but surgical intervention was postponed. (b) Same tooth area at the age of 14 years. Note the spontaneous soft tissue repair that has taken place at tooth 41 as a consequence of the improved plaque control and the growth in the alveolar process (arrow).

dentition may not be necessary and should preferably be postponed until the growth is completed.

In patients in need of orthodontic therapy with a gingival recession and a thin phenotype associated with a prominent, facially positioned tooth (Fig. 39-25a), surgical treatment for root coverage should be postponed until the orthodontic therapy is completed when lingual movement of the tooth into a more proper position within the alveolar bone is planned (Fig. 39-25b). In these cases, the recession, as well as the dehiscence, will decrease as a consequence of the orthodontic tooth movement. However, when expansion or rotational tooth movements are expected, the surgical treatment for root coverage should be done prior to the orthodontic treatment in order to prevent further attachment loss.

Root coverage procedures

It should be recalled that the two major causative factors in the development of marginal tissue recession are trauma caused by toothbrushing and plaque-induced periodontal inflammation. The control of these factors will prevent further progression of the recession in most cases. This means that in tooth regions with a thin covering of soft tissue, with or without an incipient recession, the patient should be encouraged to carry out effective, but at the same time non-traumatic, plaque-control measures. With respect to toothbrushing, the Bass method (see Chapter 28) should be avoided and the patient should be instructed to use a technique that creates as little apically directed pressure on the soft tissue margin as possible. A soft toothbrush should, of course, be used.

Before root coverage is attempted, the exposed portion of the root should be rendered free from bacterial biofilms. Preferably, this is achieved by the use of a rubber cup and a polishing paste. Controlled clinical trials showed no differences in terms of root coverage or residual probing depth between teeth that had been instrumented (root planed) or polished only (Oles *et al*. 1988; Pini Prato *et al*. 1999).

The mucogingival surgical procedures used in the treatment of recession defects are classified as (1) pedicle soft tissue graft procedures, (2) free soft tissue

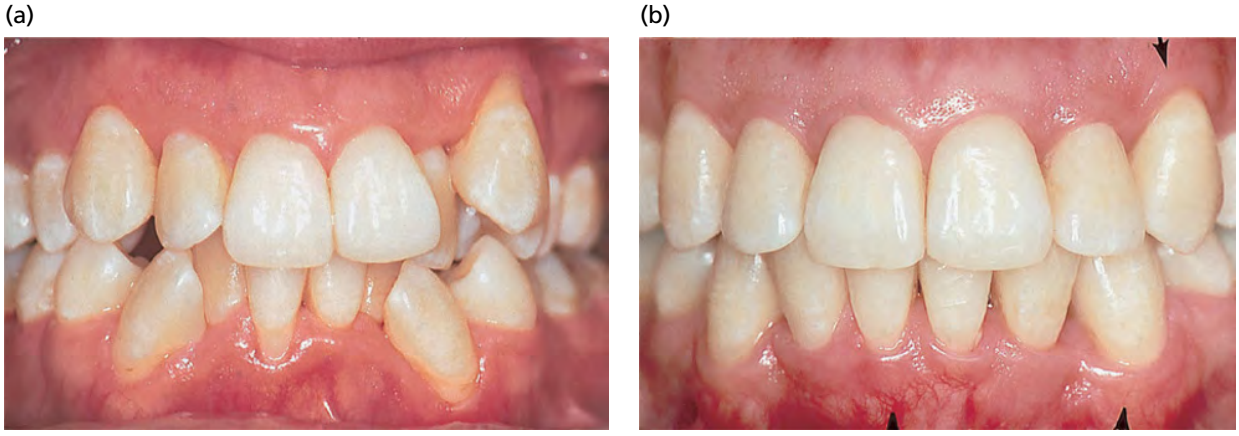

Fig. 39-25 Spontaneous repair of soft tissue recessions following orthodontic tooth movement. (a) A 22-year-old woman showing recessions and thin marginal tissues at prominently positioned teeth, particularly 23, 33, 41, and 43. (b) Following proper alignment of the teeth, the recessions have spontaneously been resolved and an increased gingival height can be noted.

graft procedures combined with either pedicle grafts or envelope/tunnel flaps.

The *pedicle graft procedures* are, depending on the direction of transfer, grouped as (1) *rotational flap procedures* (e.g. laterally sliding flap, double papilla flap, oblique rotated flap) or (2) *advanced flap procedures* (e.g. coronally repositioned flap, semilunar coronally repositioned flap) when there is no rotation or lateral movement of the pedicle graft. Regenerative procedures are also included within the group of pedicle graft procedures, that is, rotational and advanced flap procedures involving the placement of a barrier membrane between the graft and the root or the application of enamel matrix proteins over the root surface.

Free soft tissue autogenous graft procedures may be performed as (1) an epithelialized graft or (2) a subepithelial CTG (non-epithelialized graft), both usually taken from the area of the masticatory mucosa in the palate.

The choice of a root coverage surgical technique depends on several factors that can be categorized essentially as belonging to three groups: the local anatomical characteristics of the site to be treated, the patient's requests, and the surgeon's preferences.

Within the local factors it is important to assess:

- The number of recession defects to be treated
- The size of the recession defect
- The height and width of the interdental soft tissue, and the dimension of papillae near the recession
- The height, thickness, and color of the KT apical and lateral to the root exposure
- The presence of root caries or cervical abrasions
- The depth of the vestibulum
- The presence of marginal frenuli or muscle insertions.

Irrespective of the surgical technique, either using a pedicle flap, an autogenous graft, or a combination, the root surface must be adequately prepared to obtain the adhesion of the soft tissue to the root and a stable clinical result in terms of recession coverage. Root preparation is usually done by scaling and root planing intrasurgically, although extensive root planing should only be performed in situations where a reduced root prominence would be considered beneficial for graft survival or tissue regeneration, or if a shallow root caries lesion is diagnosed. The presence of a filling in the root does not preclude the possibility of root coverage (Fig. 39-26), but preferably the filling should be removed before the root is covered with soft tissue.

The use of root surface demineralization agents has been advocated, not only for the removal of the smear layer, but also to improve the fibrous attachment by exposing the collagen fibrils of the dentin matrix and thus allowing direct interaction with those in the covering connective tissue. However, controlled clinical trials comparing the clinical outcome of root coverage procedures with and without root conditioning (Ibbott *et al*. 1985; Oles *et al*. 1985; Bertrand & Dunlap 1988; Laney *et al*. 1992; Bouchard *et al*. 1997; Caffesse *et al*. 2000) failed to demonstrate a beneficial effect from the use of acid root biomodification. Gottlow *et al*. (1986) evaluated the healing following treatment of localized gingival recessions with coronally positioned flaps and citric acid root biomodification in a controlled study in dogs. Histologic analysis after 3 months of healing disclosed no differences in the amount of root coverage or new connective tissue attachment between citric acid-treated sites and saline-treated control sites. Although root resorption was a common finding among the citric acid-treated teeth in this dog model, such a finding has not been reported to be common in humans. Based on a systematic review on the efficacy of root surface conditioning, Oliveira and Muncinelli (2012) concluded that there is no evidence that root surface biomodification by, for example, citric acid, EDTA, or laser prior to soft tissue root coverage improves the clinical outcome of root coverage procedures.

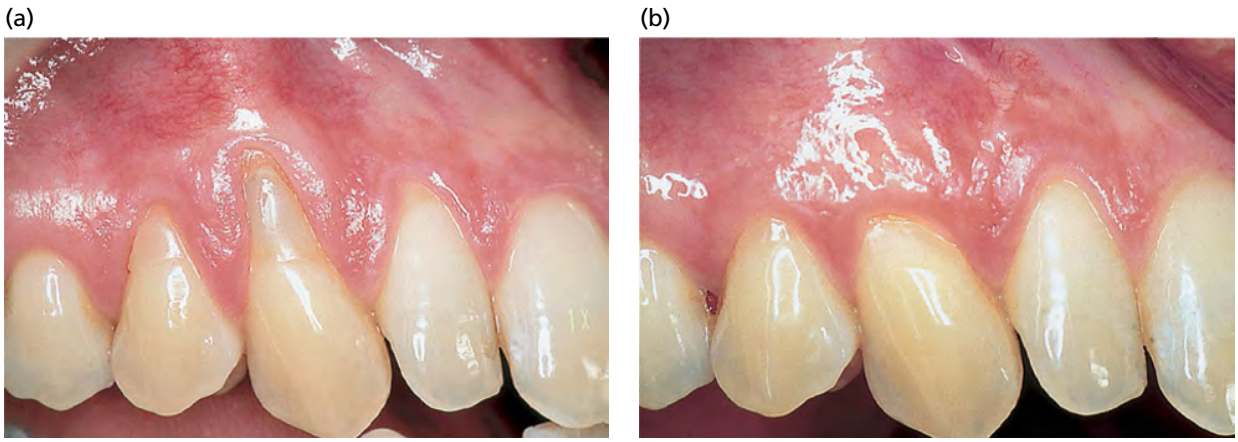

Fig. 39-26 (a) Canine showing pronounced recession and a composite resin restoration in the exposed root. Following removal of the restoration, the exposed root was surgically covered with soft tissue (pedicle graft). (b) Two-year postoperative healing result.

The biological potential of enamel matrix derivatives (EMD) as a differentiation and proliferation factor for mesenchymal cells and fibroblasts derived from the periodontal ligament has been demonstrated in both *in vitro;* and *in vivo;* studies. Furthermore, EMD promotes the transformation of gingival fibroblasts to actively participate in new connective tissue attachment to root surfaces (see detailed biological activity in Chapter 38 on Periodontal Regeneration). There is, however, scarce human histological information on the use of EMD and the coronally advanced flap to treat recession defects, and this data is derived from case reports in hopeless teeth and Miller class III–IV defects. These extreme cases are probably far from the expected clinical use and therefore do not provide histological evidence of the biological potential of this biomimetic approach when applied to the treatment of gingival recessions. The possible added value of EMD to the CTG has also been studied histologically in humans (Carnio *et al*. 2002), but the combination of EMD and CTG did not have a beneficial effect on the nature of the attachment achieved and did not promote regeneration. Similar outcomes were reported by McGuire and Cochran (2003) also reporting that the combination of EMD and CTG did not have a beneficial effect on the nature of the attachment achieved and did not promote regeneration.

Different surgical techniques have been proposed for the treatment of single or multiple gingival recessions.

Pedicle grafts

The following pedicle graft procedures have been used as root coverage procedures to treat single recession defects.

Advanced flaps

Advanced flaps are pedicle flaps that, using elasticity of the alveolar mucosa and gingival tissues, are positioned coronally to the CEJ, thus covering the exposed root surface. The more widely used is the *coronally advanced flap* (CAF), originally proposed by Allen and Miller (1989) (Fig. 39-27). The technique consists of two vertical divergent incisions positioned laterally to the involved tooth at the level of the CEJ and extending into the alveolar mucosa; the incision is connected by a horizontal intrasulcular incision. A split thickness incision is then utilized to raise the flap from the underlying periosteum and the flap is positioned coronal to the CEJ. Pini Prato *et al*. (1992) modified this design by augmenting the dimension of the surgical papillae utilizing a horizontal marginal incision with a "golf club" shape. Two divergent incisions are then executed deep into the alveolar mucosa. These modifications were essentially made

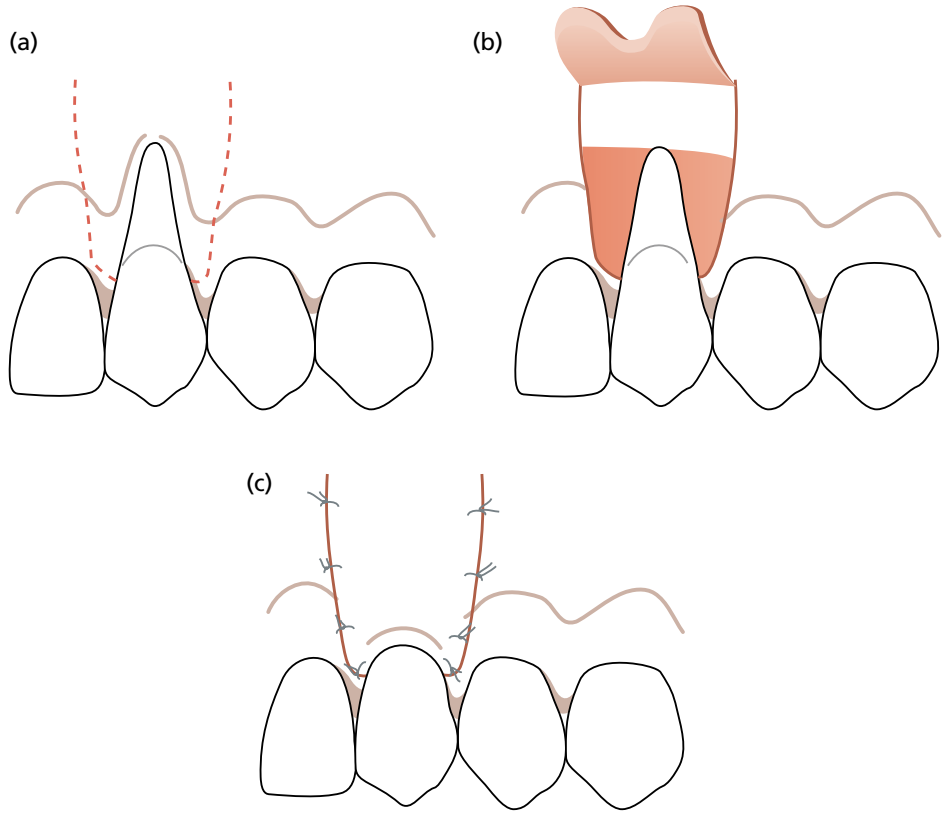

Fig. 39-27 (a–c) Coronally advanced flap procedure. The surgical technique for utilizing coronally advanced pedicle grafts to cover localized recession defects. (Source: Based on Allen & Miller 1989. Reproduced with permission from John Wiley & Sons.)

to increase the dimension of the flap to augment vascularization and thus postsurgical stability.

The design of the CAF has been further modified by De Sanctis and Zucchelli (2007) (Fig. 39-28). The two horizontal incisions must be 3 mm long and should be positioned at a distance from the tip of the papilla that is equivalent to the dimension of the recession plus 1 mm. With these dimensions, the margin of the flap will be stabilized at the end of the coronal advancement, in a position coronal to the CEJ, allowing for postsurgical shrinkage. Two vertical slightly divergent beveled incision are then made deep in the alveolar mucosa in such a way that the bone and the periosteal tissues are not included in the superficial cut and are therefore not involved in the healing process, in an attempt to avoid unsightly scars. The flap is then raised in a split-full-split manner, first raising the surgical papillae with a sharp dissection as far as the gingival sulcus. Using a periosteum elevator, full thickness flap elevation is then performed from the sulcus as far as the buccal bone, thus achieving a thicker tissue for covering the dimension equivalent to the recession. Finally, the last and most apical part of the flap is raised, split thickness, using a blade. Care is taken to detach all muscle insertions from the flap to enable flap mobility.

The flap is then positioned 1–2 mm coronal to the CEJ in such a way that the surgical papillae reaches the tip of the de-epithelialized anatomical papillae and is secured at a level 1-2 mm coronal to the CEJ by suturing the flap to the connective tissue bed in the papilla regions. Additional lateral sutures are placed to carefully close the releasing incisions.

This flap design takes into consideration several biological factors. The vascular support of the flap provided by the pedicle is usually not enough for tissue stability and requires an additional vascular bed provided by the dimensions

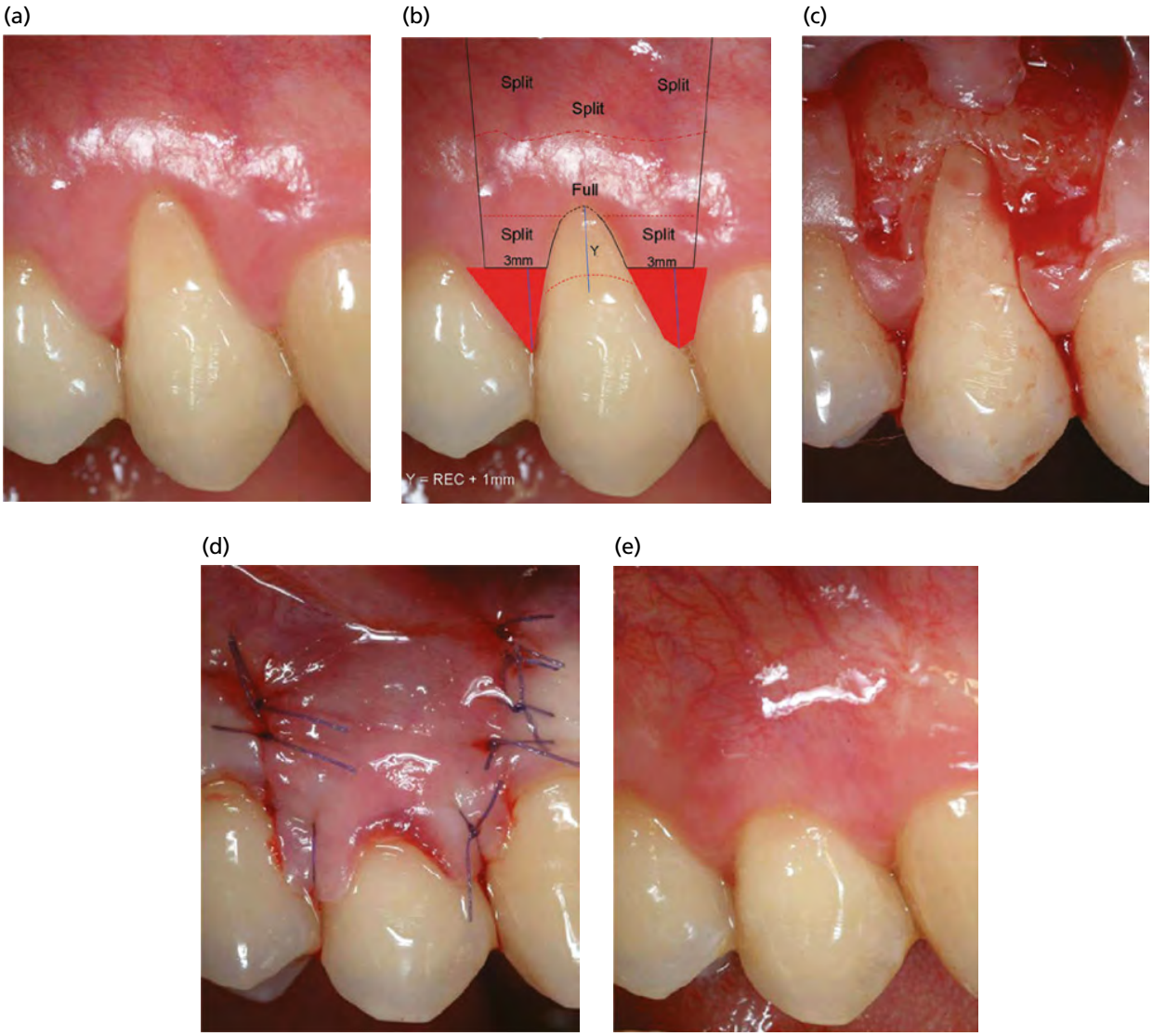

Fig. 39-28 Coronally advanced flap procedure. (a) Recession defect affecting a first premolar. (b) Schematic outline of the flap preparation. Blue line, amount (mm) of intended coronal advancement of the flap; dotted red area, de-epithelialized papillae; split, split-thickness elevation; full, full-thickness elevation. (c) Flap elevated. The papilla areas are then de-epithelialized to allow anchorage of the flap coronal to the cementoenamel junction (CEJ). (d) Flap is advanced and anchored at a level coronal to the CEJ with a sling suture. (e) Clinical healing at 1 year.

of the de-epithelialized papilla and the peripheral area beveled with the two vertical incisions. This combination of internal/external vascular supply provides effective vascular support to the flap. The thin surgical papillae improves the marginal vascular exchange with the recipient bed, while the apical split thickness guarantees flap mobility because of the excision of all muscular insertions. The modulation of the thickness of the flap (split-full-split) also enables the inclusion of the periosteum where it is needed most – to cover the avascular root surface – and provides not only increased thickness but also enhanced healing capacity because of the specific characteristic of the cells within this tissue.

Semilunar coronally positioned flap

The semilunar flap (Sumner 1969; Tarnow 1986; Sorrentino & Tarnow 2009) essentially consists of a semilunar incision, following the outline of the gingival margin. The semilunar incision should be positioned at least 3 mm from the tissue margin in keratinized tissue, the curvature of the flap should be parallel to the curvature of the gingival margin, and the incision should be extended into the adjacent papillae. The flap is then raised split thickness with an intrasulcular incision that will allow for the coronal movement of the flap. This is then positioned coronal to the CEJ and stabilized with slight manual pressure. No sutures are used. This technique can be utilized for the treatment of shallow recessions in the presence of a wide band of thick marginal keratinized tissue (Fig. 39-29).

Rotational flap procedures (e.g. laterally sliding flap, double papilla flap, oblique rotated flap) are those in which the raised flap is mobilized in directions other than coronal, which will require modifying the marginal position of the tissues.

Laterally positioned flap

The laterally positioned flap was first proposed by Grupe and Warren (1956) (Fig. 39-30) and essentially consists of the utilization of the keratinized tissue of a tooth adjacent to a gingival recession and the design of a pedicle flap that is repositioned laterally to cover the exposed root. This flap is designed with two vertical oblique incisions starting from the base of the papillae of the tooth next to the recession (generally the distal tooth), and is extended deep into the alveolar mucosa. The flap is then raised full thickness. In order to reduce the risk of recession on the donor tooth, Grupe (1966) suggested that the marginal soft tissue should not be included in the flap. Staffileno (1964) and Pfeifer and Heller (1971) advocated the use of a split-thickness flap to minimize the potential risk for development of dehiscence at the donor tooth. To mobilize the flap a so-called cut back incision is made at the bottom of the distal vertical incision. The cut back is an oblique incision made in the direction of the movement of the flap. This technique provided an efficient solution in the treatment of localized gingival recession (Smukler 1976; Guinard & Caffesse 1978; Ricci *et al*. 1996).

A *laterally moved coronally advanced flap* (Zucchelli *et al*. 2004) is a modified surgical technique, coupling the lateral and coronal advancement of the flap (Fig. 39-31). The flap is designed starting with a horizontal incision from the CEJ of the tooth to be treated. This incision is continued with a vertical incision parallel to the mesial margin of the recession that extends into the alveolar mucosa. At the opposite edge of the recession, another incision extending to the alveolar mucosa will join the previous incision, thus constructing a wide recipient triangular periosteal bed area where the flap will be secured in place. The flap is then designed with a submarginal

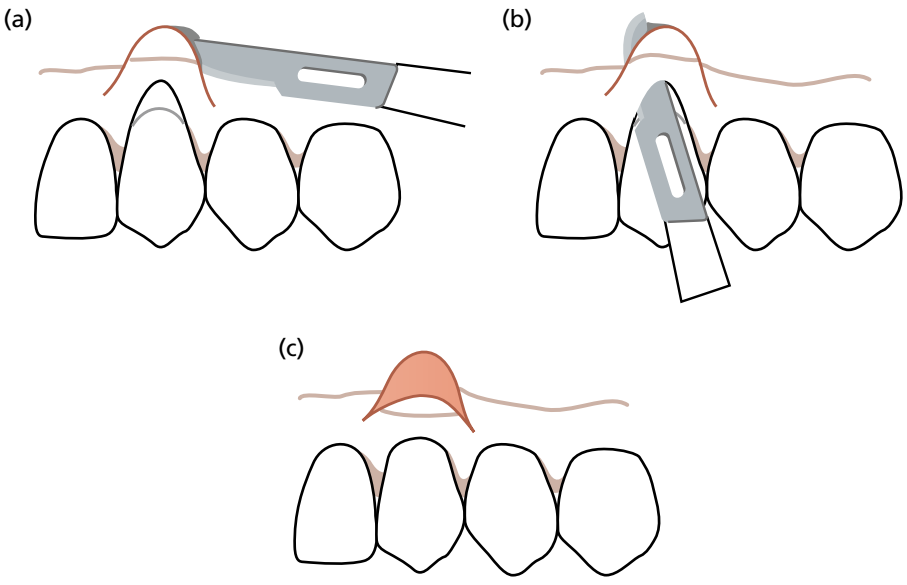

Fig. 39-29 Semilunar coronally repositioned flap procedure. The surgical technique for utilizing coronally displaced pedicle grafts to cover shallow localized recession defects (see text for explanation).

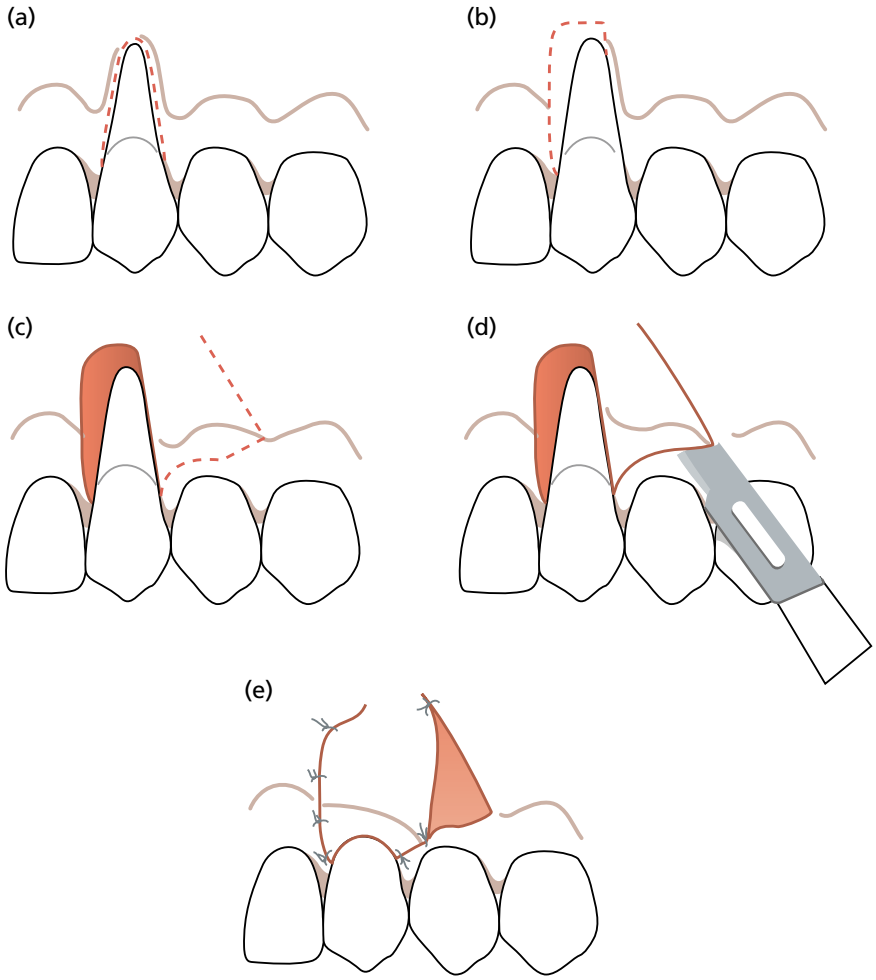

Fig. 39-30 (a–e) Rotational flap procedure. The surgical technique for utilizing rotational pedicle grafts to cover localized recession defects (see text for explanation). (Source: Based on Grupe & Warren 1956. Reproduced with permission from John Wiley & Sons.)

semilunar incision that maintains a collar of keratinized tissue around the donor tooth to avoid any risk of recession on this tooth. The final vertical incision is positioned at the end of the flap and is obliquely oriented in the direction of the movement to facilitate the positioning of the flap over the denuded root. At this point the anatomical papillae mesial and distal to the involved tooth are de-epithelialized and the flap coronally advanced after releasing all muscle insertions. The flap is then coronally positioned in such a way that the surgical papillae will be placed over the de-epithelialized anatomical papillae and secured with a modified suspended suture and single suture on the edge. This technique was compared in a randomized clinical trial with and without a CTG in the treatment of gingival recession at the buccal aspect of upper first molars (Zucchelli *et al*. 2012). The authors concluded that full root coverage and high aesthetic scores can be achieved by both techniques, with no statistically significant difference between them.

The double papilla flap (Cohen & Ross 1968)

The procedure starts with a beveled incision on the margin of the recession. The beveled incision must be reciprocal, that is, internal in one side and external in the opposite one This is due to the fact that the two edges will be overlapped at the end of the papillae movement.

Two oblique incision are than performed 1–2 mm coronal to the CEJ and the two papillae are detached with a split thickness incision. The two parts of the flap are subsequently joined together with single interrupted sutures over the midline of the tooth, taking care that the two parts perfectly overlap. The flap is finally secured by means of a suspended suture (Fig. 39-32).

Several critical factors may explain the infrequent application of this technique: because the integrity of the flap depends on a very small area of anchorage, the sutures are positioned in the most critical area, over an avascular surface, and over the convexity of the root, which is the area of maximum tension.

Other modifications of the procedure are the oblique rotational flap (Pennel *et al*. 1965), the rotation flap (Patur 1977), and the transpositioned flap (Bahat *et al*. 1990).

Gingival recession seldom appears as a single defect. The recessions are more often multiple, affecting an entire quadrant and sometimes the entire mouth. Zucchelli and De Sanctis (2000) have described a flap design for the treatment of multiple

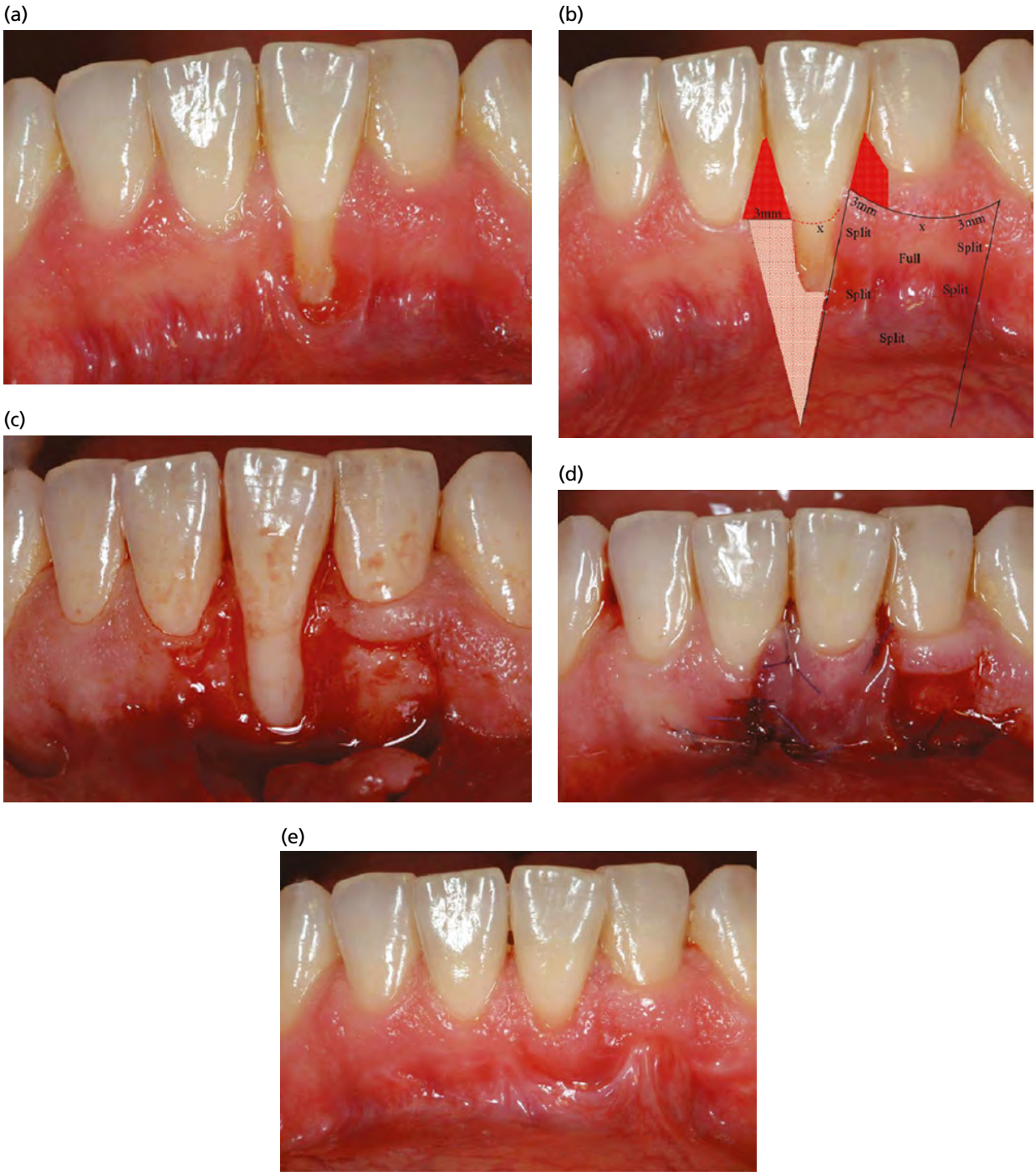

Fig. 39-31 Laterally moved, coronally advanced flap (see text for explanation). (a) A central incisor with recession defect. (b) Schematic outline of the preparation of the recipient site and the pedicle graft. Dotted pink area, receiving area for lateral flap; dotted red area, de-epithelialized papillae; x, recession width at the level of the cementoenamel junction; split, split-thickness elevation; full, full-thickness elevation. (c, d) Flap is transpositioned laterally and coronally, and secured in position by sutures. A horizontal double mattress suture is performed to reduce lip tension on the marginal portion of the flap. (e) Clinical healing at 1 year.

recessions, which allows for optimal adaptation of the flap, following its coronal advancement without placement of vertical releasing incisions

The multiple coronally advanced flap (MCAF)

This flap design consists of an envelope flap without releasing vertical incisions, comprising several teeth or an entire quadrant. The flap design is influenced by the coronal movement of the flap without vertical incisions and is dependent on the tension caused by the anchoring of the flap to the fixed adjacent tissues, thus causing a mesial rotation in all the papillae mesial to the center of the flap and a distal rotation in all distal papillae. In light of this, the flap design starts with two oblique incisions in the tooth positioned at the center of the flap, directed from the mesial and distal papillae to the bottom of the recession of the adjacent teeth (Fig. 39-33). This incision begins at a distance from the tip of the papillae that

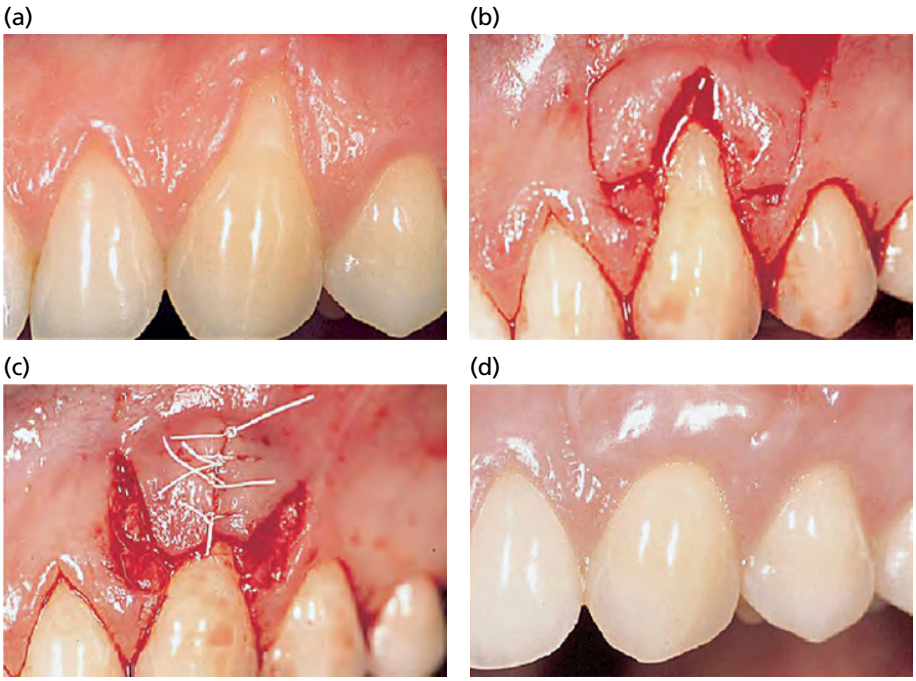

Fig. 39-32 Double papilla flap procedure. (a) Pretreatment view of a maxillary canine with facial soft tissue recession. Using split incisions, soft tissue flaps are mobilized from both sides of the recession (b) and sutured together for coverage of the exposed root (c). The healing result 6-month postoperatively shows complete root coverage (d). (Source: Courtesy of Professor Giampaolo Pini Prato.)

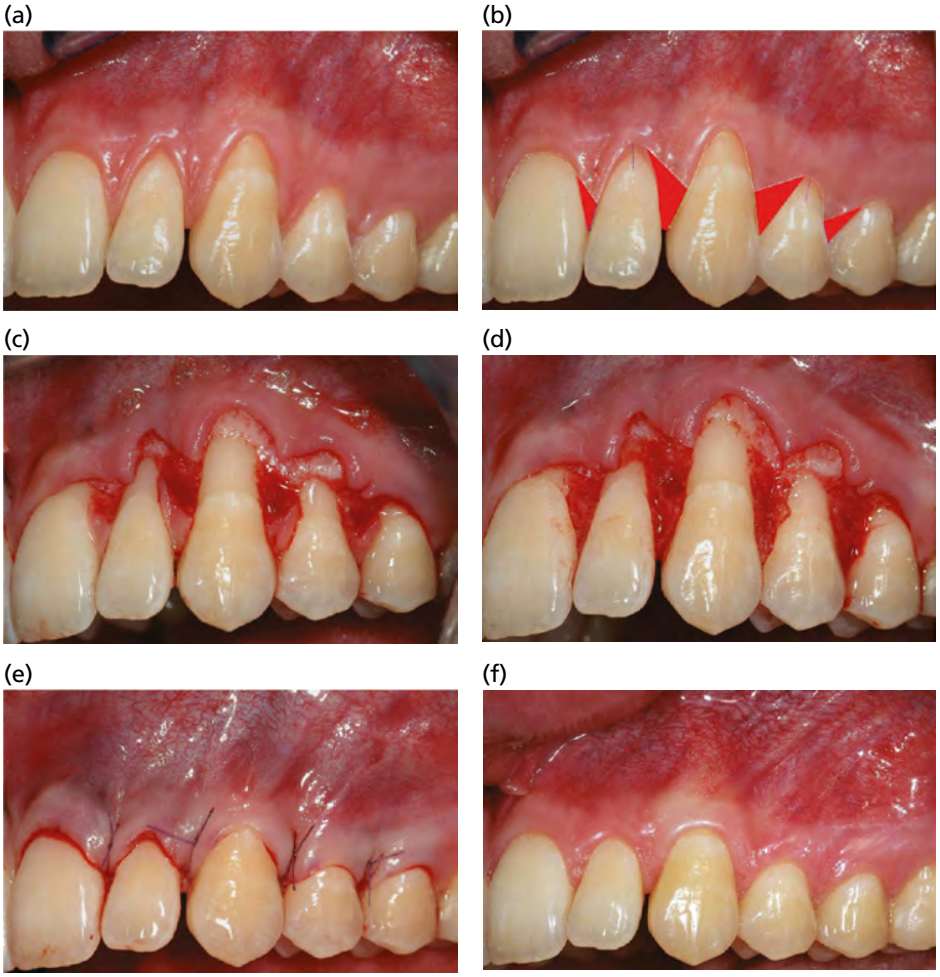

Fig. 39-33 Coronally advanced flap procedure for multiple recessions (see text for explanation). (a–e) Oblique incisions over the interdental areas are placed in such a manner that the "surgically created papillae" mesial to the midline of the surgical field are dislocated apically and distally, while the papillae of the flap distal to the midline are shifted to a more apical and mesial position. (f) One-year post-treatment view.

is commensurate with the size of the recession. These incisions are made in such way that the tip of surgical papillae will be directed mesially in all the papilla of the teeth mesial to the centre of the flap and distally at the distal teeth. The inclination of the papilla will take into account their rotation with the coronal displacement of the flap.

The area of the surgical papillae is then dissected split thickness, taking care not to sever the bottom of the recession with the blade. A periosteum elevator is then placed at the bottom of the sulcus to raise a full thickness flap, thus comprising the entire thickness of the free gingiva, taking care that at least 2 mm of periosteum is included. Finally, the more apical part of the flap is dissected split thickness, and all the muscle insertions are carefully detached from their insertion to the flap. The remaining facial portion of the interdental papillae is de-epithelialized to create connective tissue beds to which the flap can be stabilized and sutured. Following a thorough debridement of root surfaces, the flap is advanced coronally, taking care that the flap margin is positioned at least 1 mm coronal to the CEJ. The flap is then secured in position by means of single modified suspended sutures. Care has to be taken for a perfect adaptation of the flap over the root surface and the de-epithelialized papillae.

The possible impact of vertical releasing incisions was evaluated by Zucchelli *et al*. (2009) comparing the same flap design (CAF for multiple recessions) with and without releasing incisions. The presence of vertical releasing incisions did not influence the patient's perception of the results, because the patient was not able to discern the presence of scars, although CRC was more likely with the flap designed without vertical releasing incisions. Zucchelli *et al*. (2009) and De Sanctis *et al*. (2011) have proposed the multiple coronal advanced flap with a vertical releasing incision as the treatment of choice for recessions affecting mandibular posterior teeth.

Pedicle soft tissue graft procedures combined with a barrier membrane

The use of a barrier membrane, according to the principles of guided tissue regeneration (GTR; see Chapter 38), in conjunction with pedicle soft tissue graft procedures, was introduced as a treatment modality for root coverage by Pini Prato *et al*. (1992). In order to create space for tissue formation between the facial root surface and the membrane, the authors suggested that extensive root planing should be carried out to produce concave root morphology. Both non-absorbable titanium-reinforced expanded polytetra-fluoroethylene (e-PTFE) membranes as well as bioresorbable membranes have been utilized in combination with coronally advanced flaps. Zucchelli *et al*. (1998) compared three different modalities to treat deep recessions utilizing a non-resorbable barrier, a resorbable barrier, and a CTG in conjunction with a coronal advancement of the flap. It was concluded that the mucogingival bilaminar technique is at least as effective as GTR procedures in the treatment of gingival recession ≥4 mm (Fig. 39-34). Furthermore, systematic reviews from randomized clinical trials have not been able to demonstrate any added value on the use of barrier membranes in terms of both the percentage of root coverage and the percentage of CRC when compared with CAF alone or CAF plus CTG (Rocuzzo *et al* 2002; Cairo *et al*. 2014).

Healing of pedicle soft tissue grafts over denuded root surfaces

In the areas surrounding the recession defect, where the recipient bed consists of bone covered by connective tissue, the pattern of healing is similar to that observed following a traditional flap operation. Cells and blood vessels from the recipient bed as well as from the tissue graft invade the fibrin layer, which is gradually replaced by connective tissue. After 1 week,

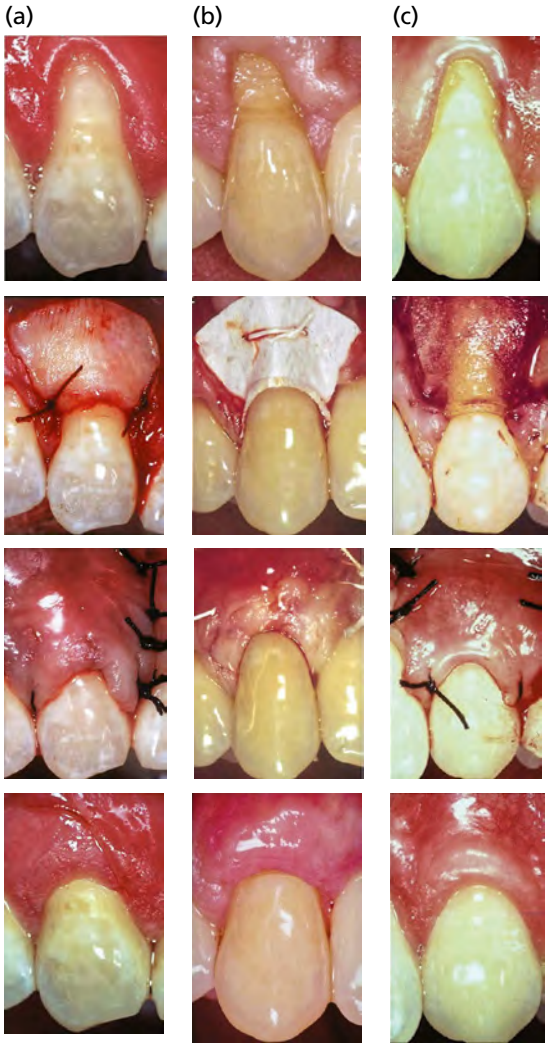

Fig. 39-34 Comparison between three diferent surgical techniques. Column (a) Coronal advanced flap plus connective tissue graft. Column (b) Coronal advanced flap plus non resorbable barrier membrane. Column (c) Coronal advanced flap plus resorbable membrane. Healing at 1 year.

a fibrous reunion is already established between the graft and the underlying tissue.

Healing in the area where the pedicle graft is in contact with the denuded root surface was studied by Wilderman and Wentz (1965) in dogs. According to these authors, the healing process can be divided into four different stages (Fig. 39-35):

1. *Adaptation stage (from 0 to 4 days)*. The laterally repositioned flap is separated from the exposed root surface by a thin fibrin layer. The epithelium covering the transplanted tissue flap starts to proliferate and reaches the tooth surface at the coronal edge of the flap after a few days.
2. *Proliferation stage (from 4 to 21 days)*. In the early phase of this stage, the fibrin layer between the root surface and the flap is invaded by connective tissue proliferating from the subsurface of the flap. In contrast to areas where healing occurs between two connective tissue surfaces, growth of connective tissue into the fibrin layer can only take place from one surface. After 6–10 days, a layer of fibroblasts is seen in apposition to the root surface. These cells are believed to differentiate into cementoblasts at a later stage of healing. At the end of the proliferation stage, thin collagen fibers are formed adjacent to the root surface, but a fibrous union between the connective tissue and the root has not been observed. From the coronal edge of the wound, epithelium proliferates apically along the root surface. According to Wilderman and Wentz (1965), the apical proliferation of epithelium may stop within the coronal half of the defect, although further down-growth of epithelium was also frequently observed.
3. *Attachment stage (from 27 to 28 days)*. During this stage of healing, thin collagen fibers become inserted into a layer of new cementum formed at the root surface in the apical portion of the recession.
4. *Maturation stage*. This last stage of healing is characterized by continuous formation of collagen fibers. After 2–3 months, bundles of collagen fibers insert into the cementum layer on the curetted root surface in the apical portion of the recession.

Results of experimental studies in monkeys and dogs on the healing characteristics of the periodontal wound have been interpreted to indicate that gingival connective tissue lacks the ability to form a new connective tissue attachment to the root but may induce root resorption (see Chapter 21). This finding is of particular interest when considering the rationale for the treatment of recession defects by free or pedicle soft tissue grafts. Since, in these surgical

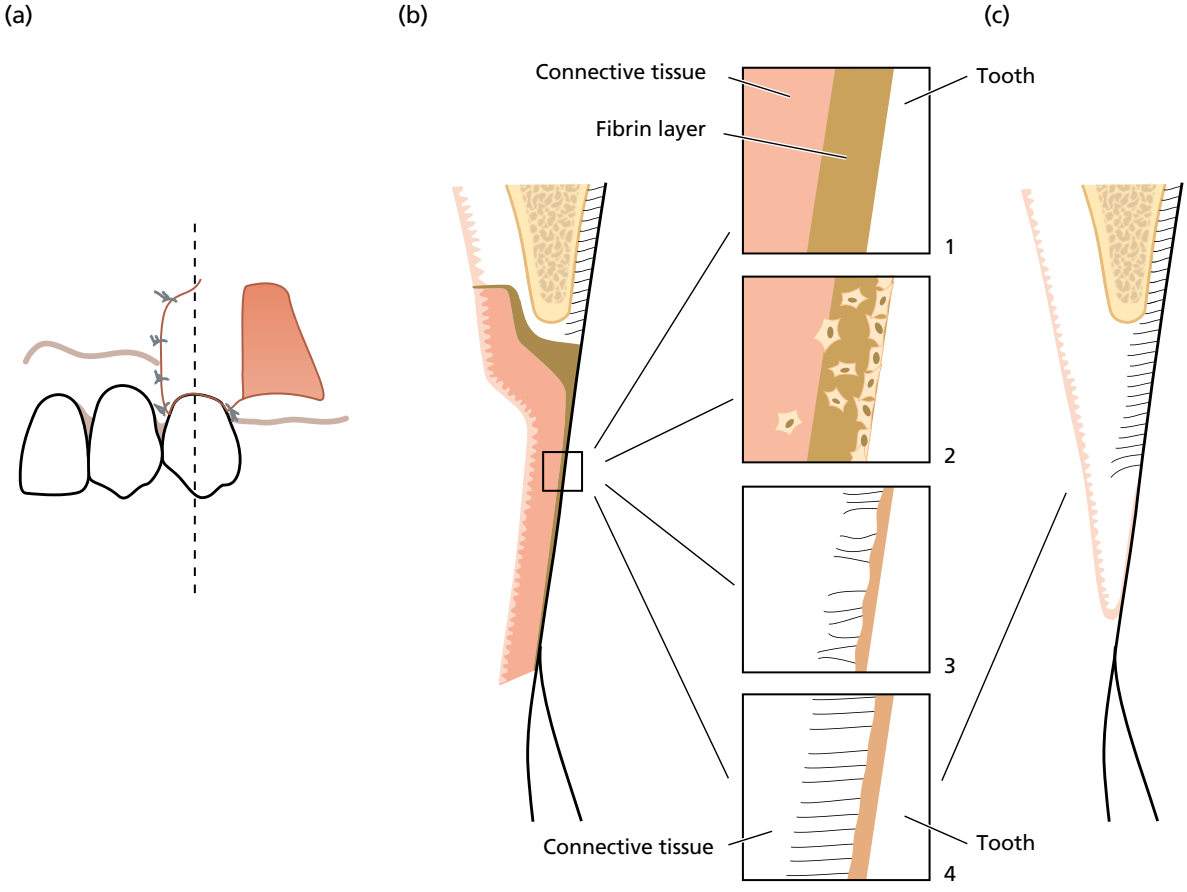

Fig. 39-35 (a) Healing following treatment of a localized soft tissue recession with a pedicle graft. (b) Cross-section through the area immediately after operation. The framed areas (1–4) illustrate the four stages into which the healing process can be divided. (c) Area after healing. Approximately 50% of the successfully covered defect may show new connective tissue attachment.

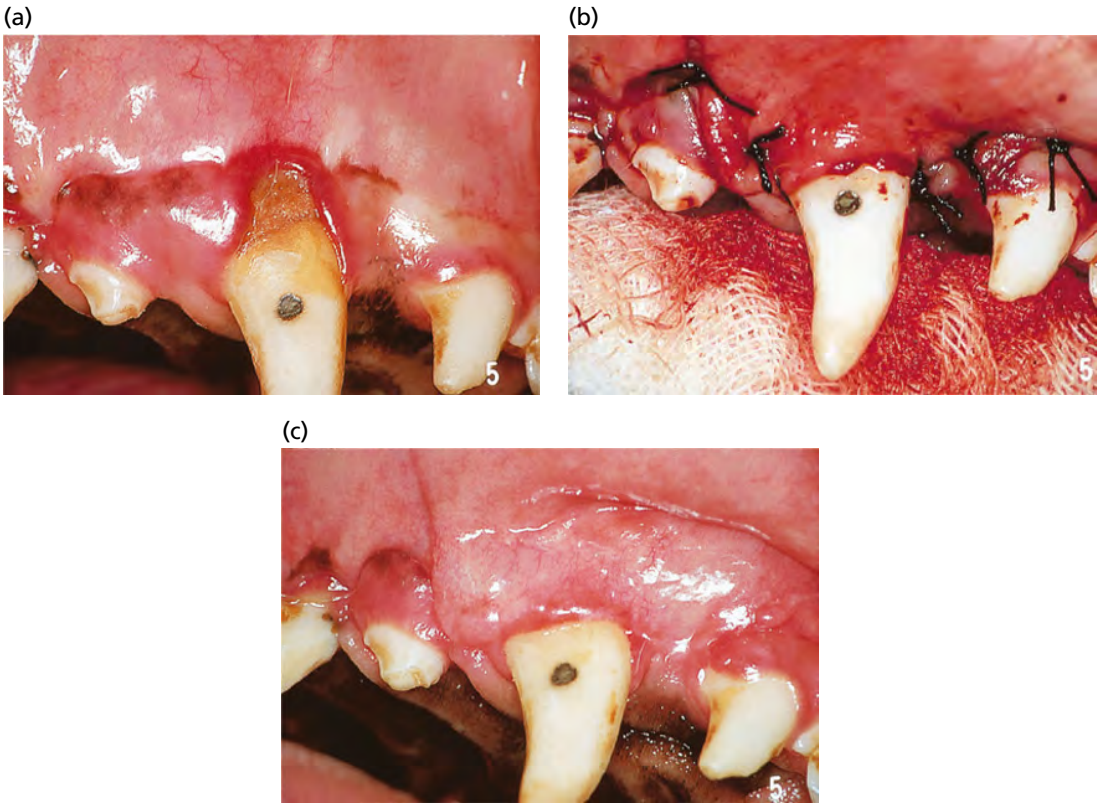

Fig. 39-36 Treatment of an experimentally induced localized recession defect in a dog with a coronally displaced flap. (a) Presurgical appearance of the localized recession defect. (b) Site following flap closure of the defect and (c) following 3 months of healing.

procedures, gingival connective tissue is placed in contact with a denuded root surface, root resorption should be expected to occur. The reason why it is not a common complication following this type of treatment can be explained by two possible events: either cells from the periodontal ligament form a fibrous attachment to the root surface or epithelial cells proliferate apically, forming a root-protective barrier (long junctional epithelium) towards the gingival connective tissue. Histologic studies to determine whether it is one or the other type of attachment that results following treatment of recessions with pedicle grafts indicate that new connective tissue attachment may form in the most apical part of the defect. In the study by Wilderman and Wentz (1965), a connective tissue attachment of around 2 mm and an epithelial attachment of the same height had formed in the soft tissue-covered portion of the defect, that is about 50% of the successfully covered defect showed new connective tissue attachment. Gottlow *et al*. (1986) examined the result of healing following treatment of experimentally produced recession type defects with a coronally advanced flap in dogs (Fig. 39-36). The histologic analysis after 3 months of healing disclosed that, on average, 20% of the apicocoronal length of the original defect had been exposed due to recession during healing (i.e. about 80% root coverage was achieved), 40% was covered by epithelium, and 40% demonstrated connective tissue attachment with cementum formation (Fig. 39-37). Determining

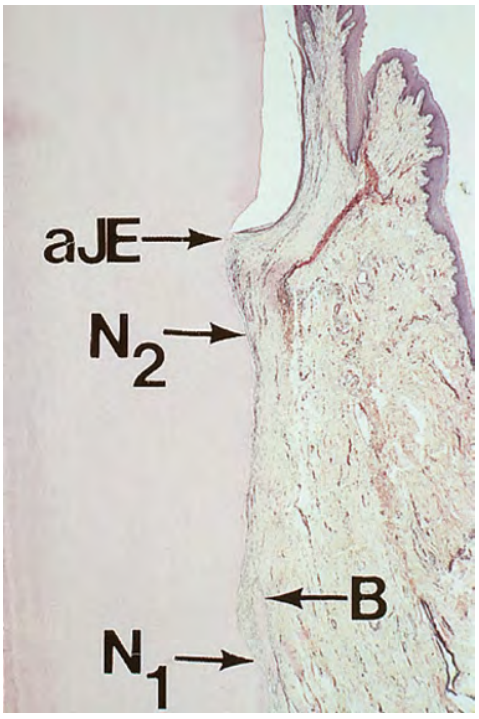

Fig. 39-37 Microphotograph of the healing following a coronally displaced flap in the same dog as in Fig. 39-36. A new connective tissue attachment is formed and extends coronally from the apical border of the notch prepared at the bottom of the bone dehiscence (N_1) to the apical termination of the epithelium (aJE) located within the notch indicating the presurgical level of the soft tissue margin (N_2). B, alveolar bone crest.

factors for the type of healing result were the size and the shape of the defect. The possibility of achieving a new connective tissue attachment in the apical portion of the defect seemed to be considerably better in narrow recession defects than in wider ones, most likely because the periodontal ligament at the lateral parts of the defect will serve as a source of granulation tissue from which a new connective tissue attachment can develop.

Healing following pedicle graft procedures has also been histologically studied in monkeys (Caffesse *et al*. 1984; Gottlow *et al*. 1990), and in these studies 38–44% of the successfully covered recession defects demonstrated formation of new connective tissue attachment. The study by Gottlow *et al*. (1990) also showed that the use of a GTR membrane between the root surface and the pedicle graft generated significantly more new connective tissue attachment (79% of the covered part of the recession defect). A significantly increased amount of cementum formation with inserting collagen fibers was also demonstrated following the utilization of enamel matrix proteins in combination with a coronally advanced flap for treatment of experimentally produced recession defects in dogs (Sallum *et al*. 2004).

Some case reports with human block sections provide further evidence that new connective tissue attachment may be formed following pedicle graft procedures. Histologic evaluation of two teeth treated with a laterally positioned flap revealed that connective tissue attachment was re-established in the apical quarter of the successfully covered portion of the root (Sugarman 1969). Cortellini *et al*. (1993) examined histologically a tooth treated with the GTR procedure and showed that connective tissue faced 74% of the length of the recession defect. New cementum with inserting collagen fibers, that is new connective tissue attachment, covered 48% of the distance between the apical border of the root instrumentation and the soft tissue margin. In addition, histomorphometric assessments of a tooth treated with enamel matrix proteins revealed that new cementum covered 73% of the original defect (Heijl 1997).

Use of free soft tissue graft procedures

A free soft tissue graft of masticatory mucosa is usually selected when there is no acceptable donor tissue present in the area adjacent to the recession defect or when a thicker marginal tissue is desirable. The procedure can be used for the treatment of a single tooth as well as for several adjacent teeth. The graft used may either be (1) an epithelialized graft or (2) a subepithelial CTG of palatal masticatory mucosa.

Epithelialized soft tissue graft

The epithelialized free soft tissue graft procedure can be performed either as a two-step surgical technique, where an epithelialized free soft tissue graft is placed apical to the recession and following healing is positioned coronally over the denuded root (Fig. 39-38) (Bernimoulin *et al*. 1975; Guinard & Caffesse 1978), or as a one-step technique by which the graft is placed directly over the root surface (Sullivan & Atkins 1968a, b; Miller 1982) (see Fig. 39-42). The latter technique has been the most commonly used.

Zucchelli and De Sanctis (2013) proposed a modification of the original two-stage technique to overcome the esthetic problems due to the excess of marginal keratinized tissue in the transplanted area (Fig. 39-39). This modification could be useful in lower anterior cases where the recession has reached the base of the vestibule or in instances with shallow vestibule when adjacent teeth do not have a large band of keratinized tissue to perform a lateral sliding flap. The procedure starts with the preparation of a recipient bed at the base of the recession, then the epithelialized graft is harvested from the palate. Care should be taken to design the correct dimension of the graft: (1) the height of the graft should be equal to the height of the keratinized tissue present on teeth

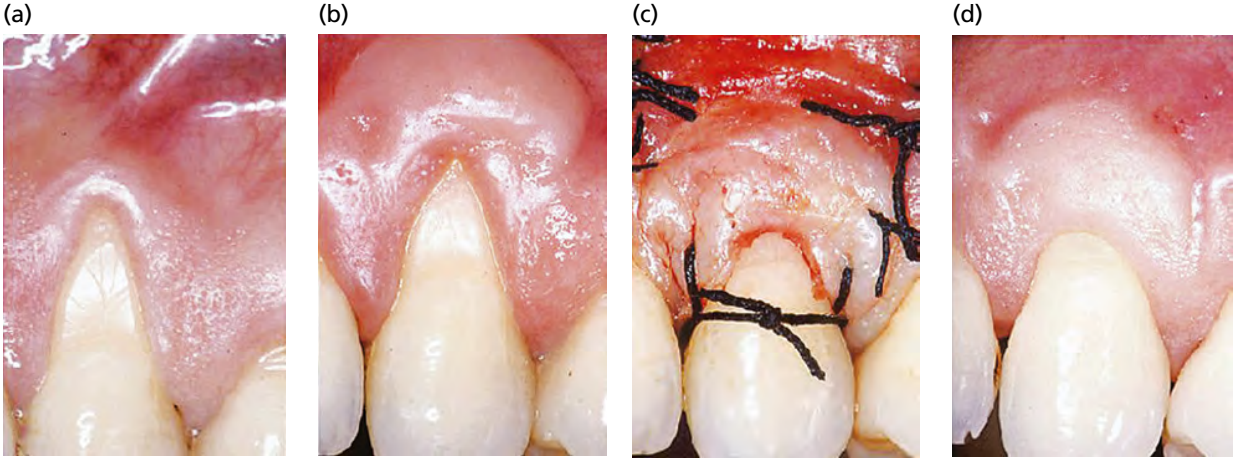

Fig. 39-38 Two-stage epithelialized free soft tissue graft procedure. (a–c) Epithelialized soft tissue graft is placed apical to the recession and allowed to heal. At a second-stage surgery, a coronally advanced flap procedure is performed to achieve coverage of the denuded root. (d) One-year postoperative result. (Source: Courtesy of Professor Giampaolo Pini Prato.)

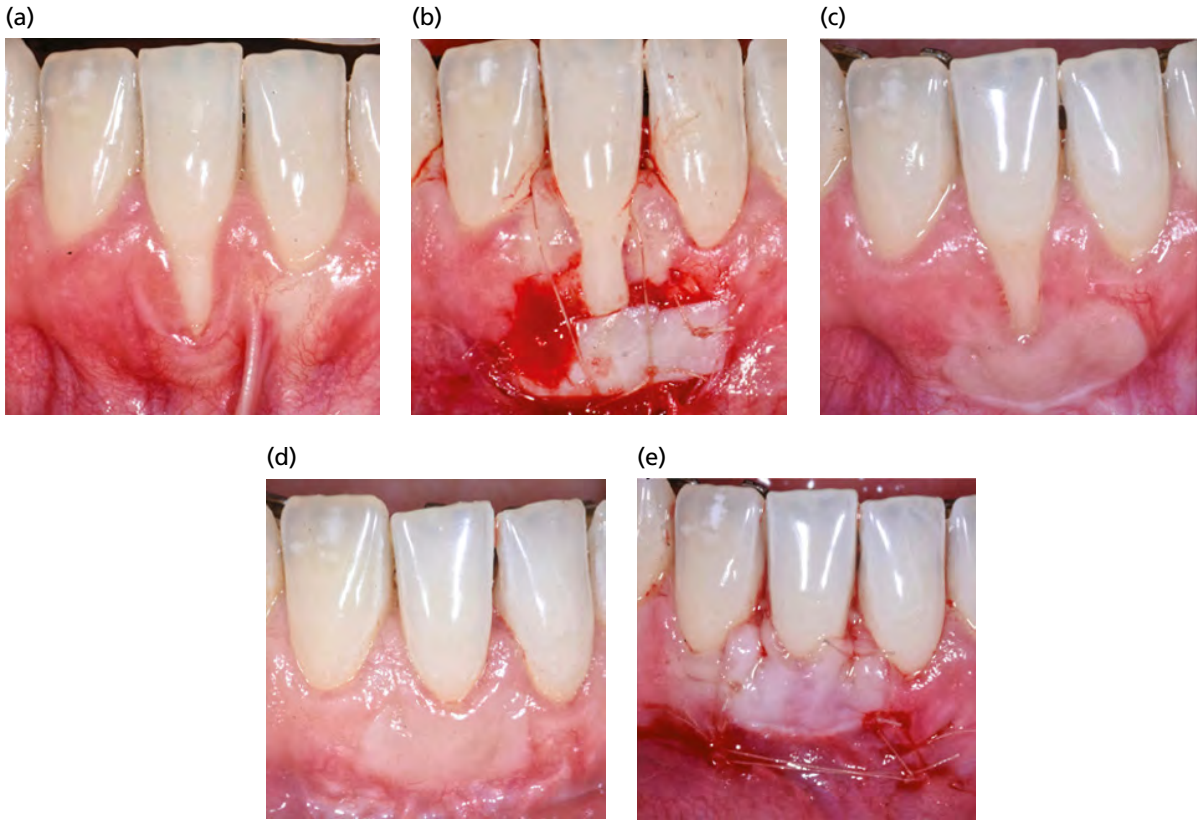

Fig. 39-39 Two stage coronally advanced flap. (a) Deep recession on lower central incisor. (b) Free gingival graft positioned over periosteum at the base of the defect. (c) Three months healing. (d) Second stage, coronally positioned flap. (e) One-year healing

adjacent to the treated area; (2) the width should correspond to the width of the recession plus the dimension of the anatomical interdental papillae.

Once the graft is harvested it is stabilized apical to the recession over the prepared periosteal bed. Three months after the first surgery, a flap is raised with the same technique described for CAF with a split-full-split approach and positioned 1–2 mm coronal to the CEJ.

The same authors also proposed utilizing a laterally moved and coronally advanced flap with the same two-step approach but positioning the free gingival graft apical to the band of keratinized tissue of the tooth adjacent to the one to be treated (Fig. 39-40). This design is indicated when the vestibule is too shallow or the recession reaches the bottom of the vestibule, that is, in a situation where positioning of a free gingival graft is very difficult or impossible. Three months later a lateral and coronal sliding flap is performed to treat the recession defect. Using the one-step technique, the surgical principles of utilizing free mucosal grafts were outlined by Sullivan and Atkins (1968a, b) and later modified by Miller (1982):

1. Before any incisions, the exposed root surface is carefully scaled and root planed (Fig. 39-41a). The convexity of the root may be reduced to minimize the mesiodistal avascular recipient bed.
2. As in the treatment with pedicle grafts, the preparation of the *recipient bed* is crucial for the success of the free graft procedure. A 3–4-mm wide recipient connective tissue bed should be prepared apical and lateral to the recession defect (Fig. 39-41b). The area is demarcated by first

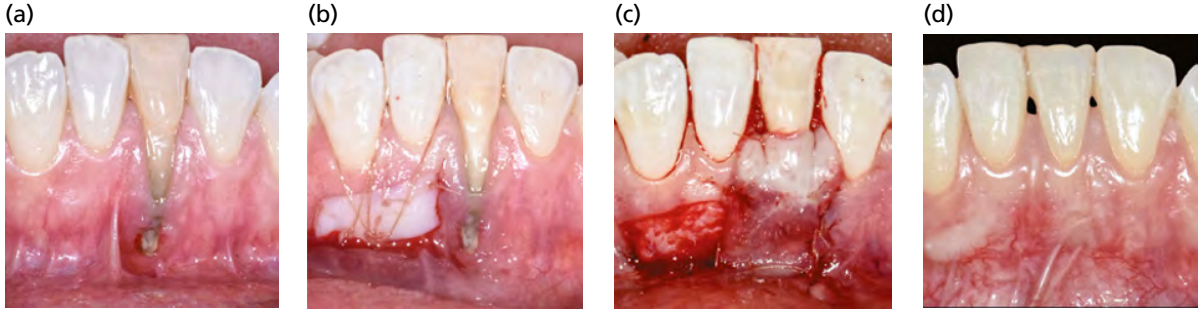

Fig. 39-40 Two stage laterally moved and coronally advanced flap. (a) Very deep recession on a mandibular central incisor. (b) Epithelio-connective free gingival graft on adjacent area. (c) Laterally moved and coronally advanced flap. (d) One-year healing.

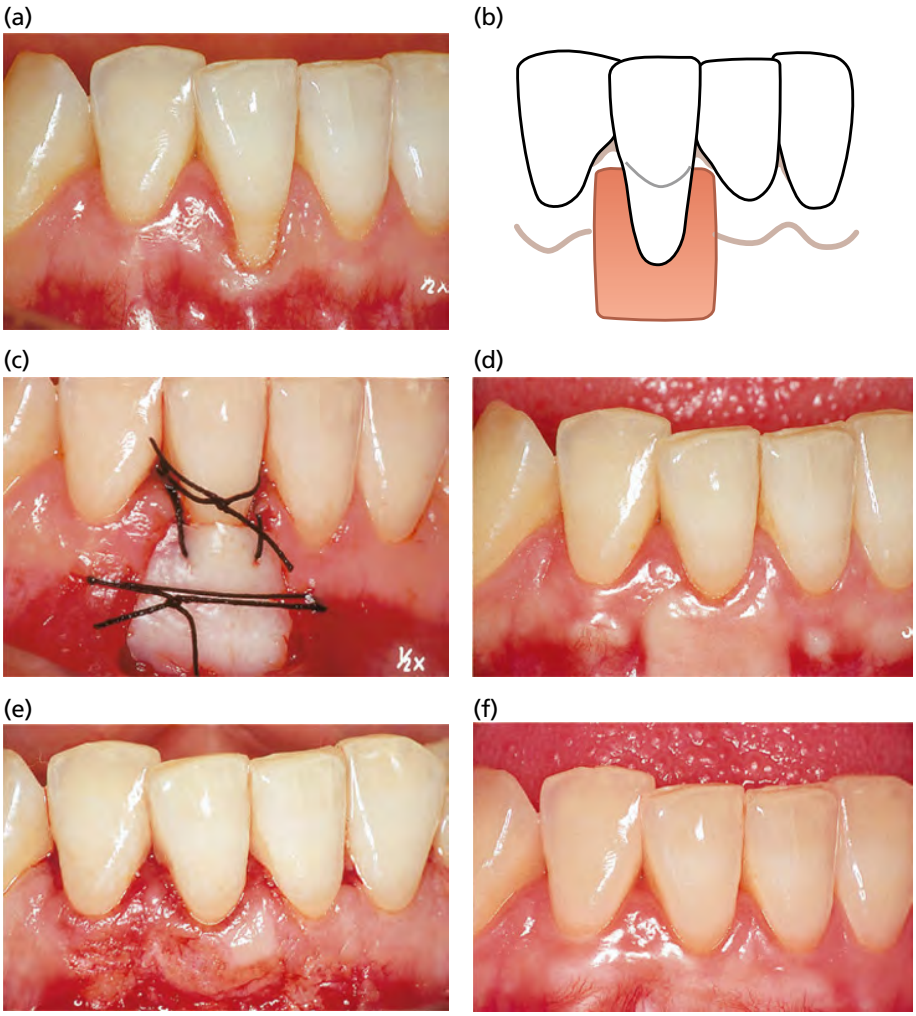

Fig. 39-41 (a–f) Epithelialized free soft tissue graft procedure. A recession defect at a mandibular central incisor treated with the free graft procedure (see text for explanation).

placing a horizontal incision, at the level of the CEJ, in the interdental tissue on each side of the tooth to be treated. Subsequently, two vertical incisions, extending from the incision line placed in the interdental tissue to a level approximately 4–5 mm apical to the recession, are placed. A horizontal incision is then made connecting the two vertical incisions at their apical termination. Starting from an intracrevicular incision, a split incision is made to sharply dissect the epithelium and the outer portion of the connective tissue within the demarcated area.

3. To ensure that a graft of sufficient size and proper contour is removed from the donor area, a foil template of the recipient site is prepared. This template is transferred to the donor site, the palatal mucosa in the region of the premolars, and the required size of the graft is outlined by a shallow incision. A graft with a thickness of 2–3 mm is then dissected from the donor area. It is advocated to place sutures in the graft before it is cut completely free from the donor area because this may facilitate its transfer to the recipient site. Following the removal of the graft, pressure is applied to the wound area for control of bleeding.
4. The graft is immediately placed on the prepared recipient bed. In order to immobilize the graft at the recipient site, sutures must be anchored in the periosteum or in the adjacent attached gingiva. Adequate numbers of sutures are placed to secure close adaptation of the graft to the underlying connective tissue bed and root surface. Pressure is exerted against the graft for some minutes in order to eliminate blood from between the graft and the recipient bed.
5. The sutures are usually maintained for 2 weeks. The appearance of a grafted area after 3 months of healing is shown in Fig. 39-41d. A gingivoplasty may be indicated to achieve a satisfactory esthetic appearance of the grafted area (Fig. 39-41e, f).

Connective tissue grafts combined with pedicle grafts

This technique involves utilizing a CTG placed directly over the exposed root and then covered with a mucosal flap mobilized coronally (Fig. 39-42) (Langer & Langer 1985; Nelson 1987; Harris 1992; Bruno 1994; Zucchelli *et al*. 2003). These designs are generally termed as *bilaminar techniques* since their

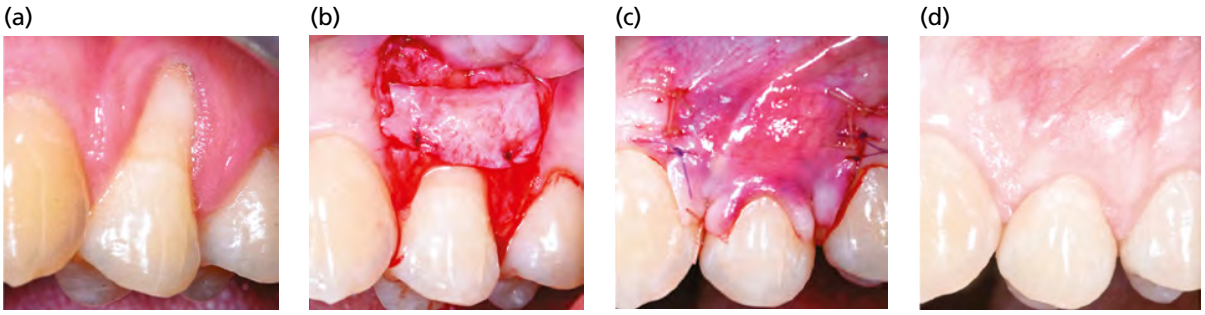

Fig. 39-42 Free connective tissue graft combined with a coronally advanced flap procedure for the treatment of a single recession defect. (a) Deep gingival recession at a premolar with minimal height of keratinized tissue apical to the root exposure. (b) Flap is raised split-full-split and graft has been sutured at the base of de-epithelialized papillae. (c) Flap has been advanced coronally and sutured. (d) Clinical healing at 1 year.

rationale is to use the coronally advanced flap to assure appropriate vascular supply and to use the CTG to modify the gingival phenotype by increasing the thickness of the tissue in the marginal area, thus augmenting the postsurgical stability of the newly formed tissues over the root. A literature review (Graziani *et al*. 2014) has indicated that when the phenotype is increased, the effectiveness of root covering is enhanced. Compared with the epithelialized graft, the CTG is preferable due to a less invasive palatal wound and an improved esthetic result. As an alternative to the CTG, xenogenic collagen matrixes may be used (McGuire & Scheyer 2010; Jepsen *et al*. 2013).

The flap design is the same as described for the CAF. Although it may be raised split thickness, the use of a split-full-split approach is suggested to ensure the maximum stability for the marginal soft tissue.

The connective tissue is harvested from the palate or the retromolar area. Several techniques have been proposed to harvest palatal connective tissue using one, two, or three incisions to raise a primary flap to "open the door" that gives access to the deeper layer of the tissue that is harvested with a fourth incision and withdrawn, making sure that the periosteum is left in position (Fig. 39-43). The primary flap is then closed, and the wound will heal by primary intention.

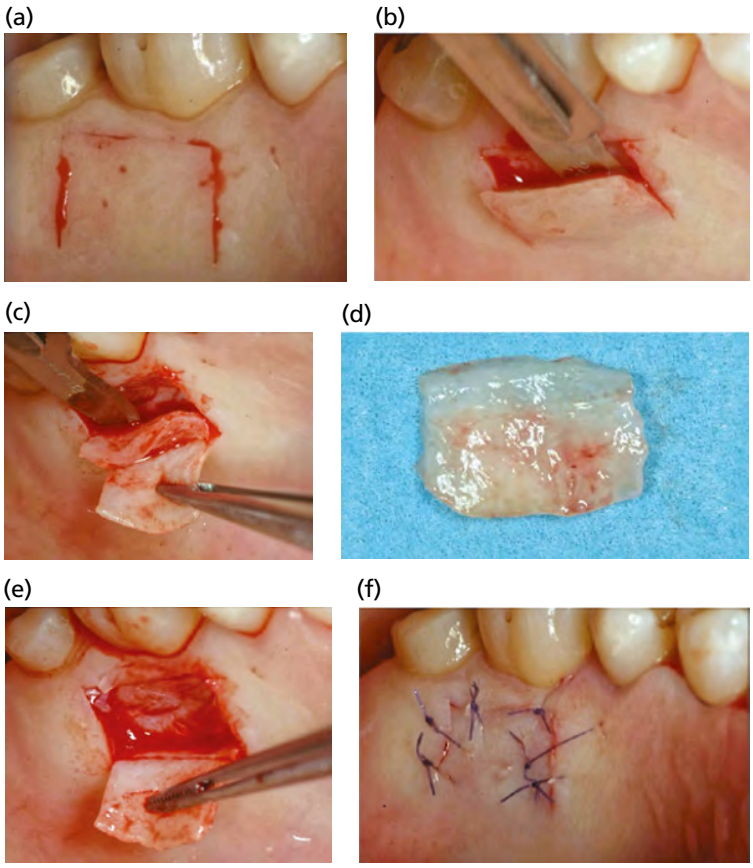

Fig. 39-43 "Trap door technique". (a) Three incisions are performed. (b) Primary flap is raised with a superficial incision. (c) Deep incision to delineate the thickness of the graft. (d) Connective tissue is harvested. (e) Epithelial-connective superficial flap. (f) "Trap door" is closed.

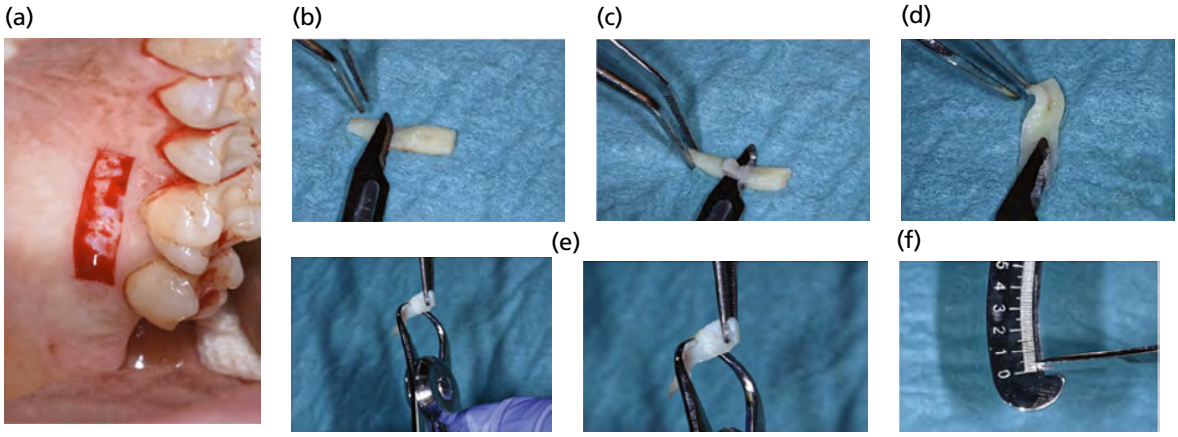

Fig. 39-44 (a) Epithelial-connective tissue is harvested from the palate. (b, c, d) De-epithelization. (e, f) Thickness.

An alternative technique is to harvest epithelial-connective tissue, which is subsequently de-epithelialized out of the mouth (Fig. 39-44). The wound in this case will heal by secondary intention. This technique is suggested to avoid the inclusion of fatty or glandular tissue and to include only dense connective tissue because only the more superficial connective tissue is withdrawn. Zucchelli *et al*. (2010) reported that patient discomfort depends more on the depth of the wound that on the healing modality.

The harvested connective tissue is immediately positioned over the exposed root that has been previously treated and stabilized with marginal sutures at the base of the anatomical papilla at both sides of the recession. According to the authors (Zucchelli *et al*. 2003), the connective tissue should be positioned slightly apical to the CEJ, so it does not interfere with the positioning of the marginal portion of the flap. Finally, the flap is positioned coronal to the CEJ, which is similar to the CAF technique.

The CAF plus connective tissue is a technique that has shown successful results for the root coverage of isolated RT1 and RT2 single recession type defects (Rocuzzo *et al*. 2002; Cairo *et al*. 2014). This surgical approach (CAF plus CTG) may also be utilized to treat multiple recession defects. The approach for multiple recessions is the same as described for the MCAF and once the flap is raised in a split-full-split manner, a connective graft is harvested from the palate and positioned over the previously treated roots (Fig. 39-45). The dimension of the flap is dependent on the number of recessions to be treated.

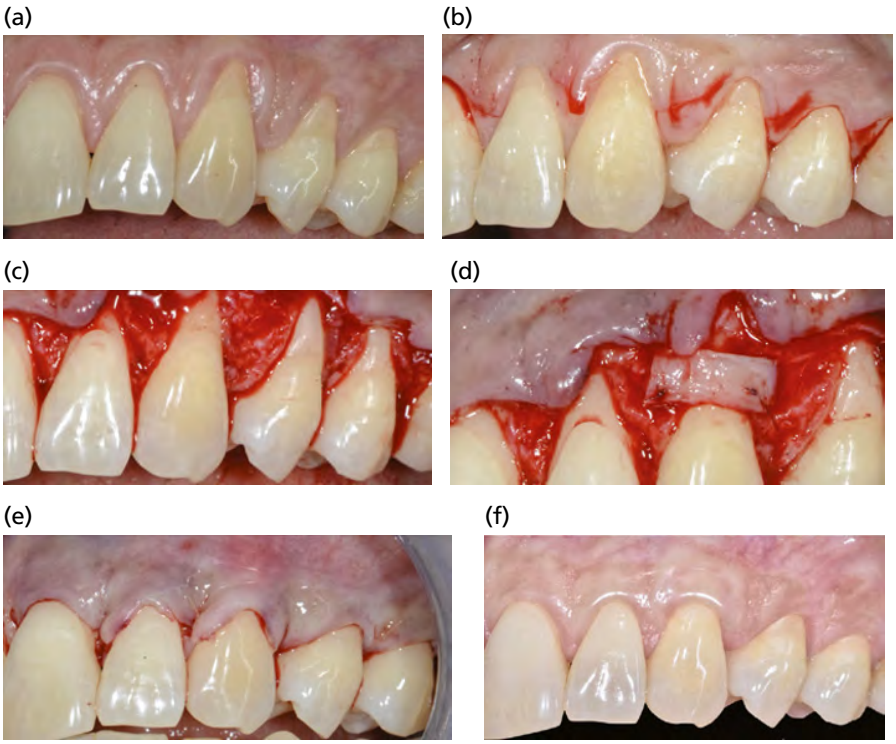

Fig. 39-45 Free connective tissue graft combined with a coronally advanced flap procedure. (a) Multiple recessions; (b) incisions; (c) split-full-split flap elevation with de-epithelialization of the anatomical papilla; (d) free connective tissue graft placed on the canine root surface; (e) coronally positioned flap and sutured; (f) one-year post-treatment result.

A literature review on the treatment of multiple recessions (Graziani *et al*. 2014) reported that the technique of choice should be MCAF combined with the use of CTGs. CTGs are not needed in all recessions, but only in those sites where the phenotypic condition of the gingiva is thin. In these sites this combination has yielded better esthetic and long-term predictable results, with minimal patient discomfort (Cairo *et al*. 2014; Stefanini *et al*. 2018; De Sanctis *et al*. 2020).

Tunnel approaches for the treatment of gingival recessions

In 1985 Raetze described the so called "*envelope technique*" for covering localized areas of root exposure using palatal subepithelial connective tissue grafts (SCTG). The technique implies the preparation of a supraperiosteal "envelope" or "*pouch*" using an undermining partial thickness incision in the tissues surrounding the defect, in order to accommodate a SCTG (Fig. 39-46). The graft is positioned directly over the exposed root and fixed to the underlying surfaces by means of tissue glue (i.e. cyanoacrylate) without the use of sutures. Because its major part is placed in the "envelope", adequate protection, stability, and blood supply originating from the surrounding tissues is ensured. In a retrospective study, Rossberg *et al*. (2008) have assessed the long-term clinical and patient-centered esthetic outcomes following treatment of single recessions by means of the envelope technique and SCTG. Clinical re-examinations made at 6–22 years (mean, 11.4 ± 5.4 years) revealed a mean root coverage (MRC) of 89.7% ± 25.1% while CRC was obtained in 82% (i.e. in 32 out of 39) of the defects.

Further developments in the "envelope" technique resulted in the various types of tunnel approaches. Allen (1994) and Zabalegui *et al*. (1999) described a further extension of the supraperiosteal envelope over several teeth, thus enabling the coverage of multiple adjacent gingival recessions (Fig. 39-47).

The technique described by Zabalegui *et al*. (1999) implied the placement of intrasulcular incisions, followed by preparation of supraperiosteal envelopes at the respective teeth, which subsequently are connected with each other following careful undermining of the papillae. Following preparation of the tunnel, a large SCTG is harvested from the palate, carefully pulled in the tunnel, and adapted so that the gingival recessions are covered. When using this technique, no attempts are made to coronally advance the tunnel to cover the graft and the exposed root surfaces, thus leaving the coronal part of the graft exposed. At 1 year following therapy, the authors reported an MRC of 91.6% and a CRC of 66.7% respectively, thus pointing to the clinical relevance of this surgical approach.

Later, the tunnel approach described by Allen (1994) and Zabalegui *et al*. (1999) was further modified to coronally displace the tunneled flap to completely cover the soft tissue graft with the purpose of improving graft survival and aesthetics (Zuhr *et al*. 2007). A number of case series and randomized clinical studies have evaluated the outcome of this

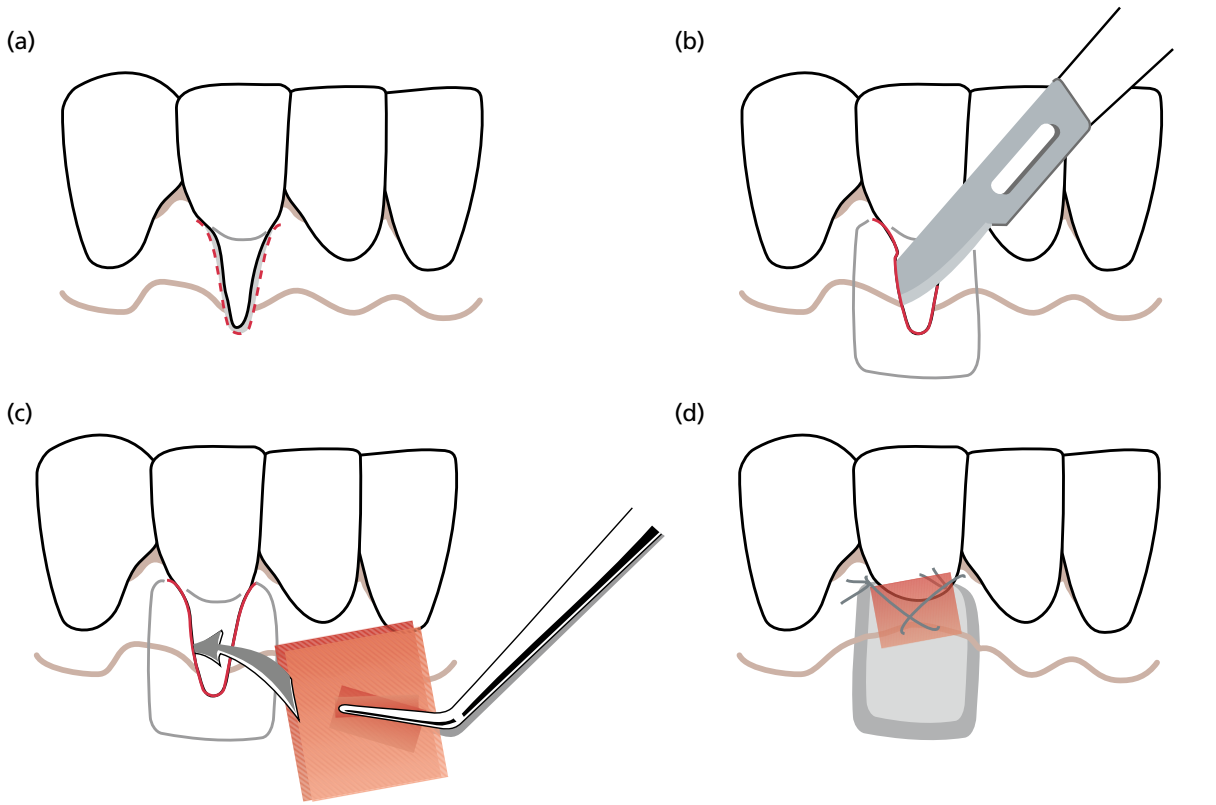

Fig. 39-46 (a–d) The "envelope technique".

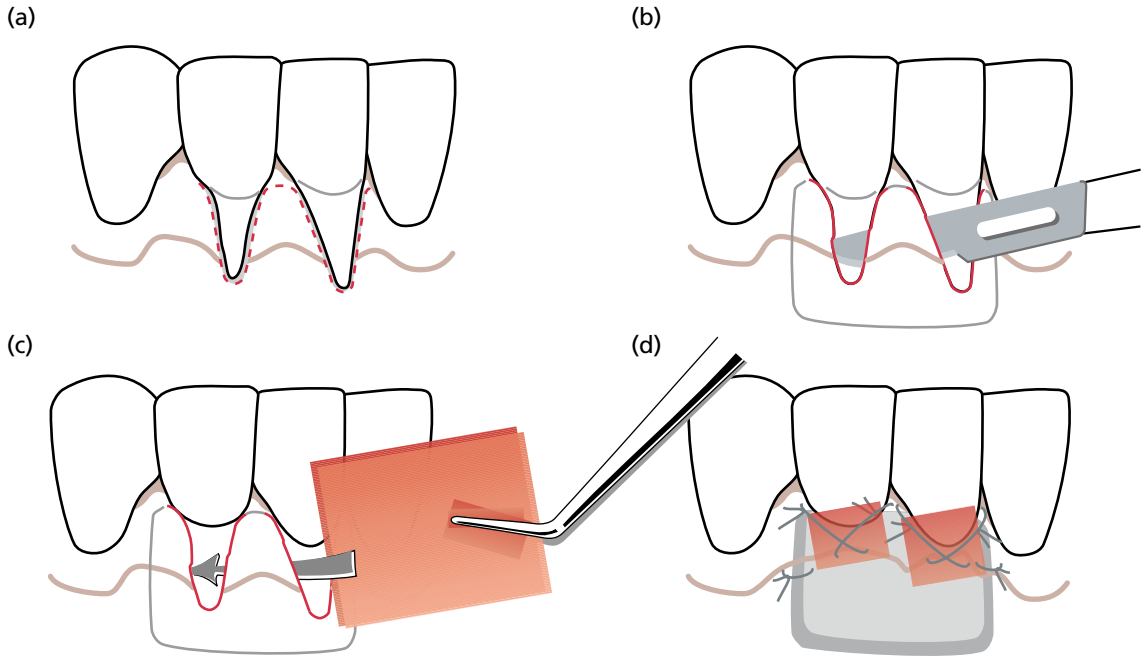

Fig. 39-47 (a–d) Free connective tissue graft procedure: the "tunnel technique". (Sources: Allen 1994; Zabalegul *et al*. 1999. Reproduced with permission from John Wiley & Sons.)

"so called" modified coronally advanced tunnel (MCAT) for the treatment of maxillary multiple adjacent gingival recessions and also for the treatment of single mandibular recessions (Aroca *et al*. 2010, 2013; Sculean *et al*. 2014, 2016, 2017). The major advantage of MCAT is because the prepared tunnel (pouch) is coronally advanced to cover the graft and the exposed root surfaces, thus improving the vascular supply of the graft and subsequently its potential for survival. The most important steps in the design of MCAT are depicted in Fig. 39-48. Following local anesthesia, gentle root planing of the exposed root surface is performed to remove the biofilm using Gracey curettes. Subsequently, intrasulcular incisions at the treated teeth are placed using microsurgical blades and, if needed, extended one tooth mesially or distally. Using specially designed tunneling knives, a full-thickness pouch is raised and prepared beyond the level of the mucogingival junction leaving the interdental papillae intact. The mucoperiosteal pouch is then carefully extended mesially and distally under the neighbouring papillae until the adjacent recessions are connected. Attaching inserting collagen fibres are removed from the inner aspect of the tunneled flap (i.e. connected pouches) using 15c surgical and/or microsurgical blades until tension-free coronal mobilization is obtained. If needed, the interdental parts of the papillae are also gently undermined using specially designed tunneling knifes. Care should be taken not to disrupt the interdental papillary tissues and/or to avoid perforation of the tunnel. After tunnel preparation, a palatal SCTG 1–1.5 mm thick is harvested using the single incision technique described by Hürzeler and Weng (1999) and Lorenzana and Allen (2000). Immediately after closure of the palatal wound, the SCGT is pulled into the tunnel using single or mattress sutures and fixed at the inner surface of the tunnel flap. Subsequently, the graft is imobilized at the CEJ or slightly below using a sling suture to obtain complete stability. Finally, the tunnel flap is advanced coronally to completely cover the graft and the exposed root surface using sling sutures. Sutures are usually removed 14 days after surgery. In a case series consisting of a total or 54 adjacent maxillary RT1 and RT2 (i.e. Miller Class I, II, or III) they were consecutively treated with the MCAT in conjunction with an EMD and SCTG (Sculean *et al*. 2016). Out of 54 recessions, 49 were classified as RT1 and 5 as RT2 recessions. At 12 months following surgery, statistically and clinically significant root coverage was obtained in all patients and defects. CRC was obtained in 40 RT 1 recessions and in one Miller Class III recession representing an MRC of 96% (Fig. 39-48). Follow-up examinations have shown that the obtained results can be maintained on a long-term basis provided that an adequate level of oral hygiene is maintained.

Comparable results were also obtained by Aroca *et al*. (2010), who treated RT2 multiple adjacent gingival recessions by means of MCAT in conjunction with SCTG either with or without an EMD. In that study, the MRC was 82% in the test group (i.e. MCAT + SCGT + EMD) and 83% in the control group (i.e. MCAT + SCGT) respectively, while CRC amounted to 38% in both groups. Interestingly, the additional use of EMD did not seem to influence the clinical outcomes.

Recently, the MCAT was also successfully applied for the coverage of single and multiple RT1 and RT2 gingival recessions at crown-restored teeth in the aesthetic area (Sculean *et al*. 2017) (Fig. 39-49). A total of 23 single or multiple maxillary RT1 and RT2

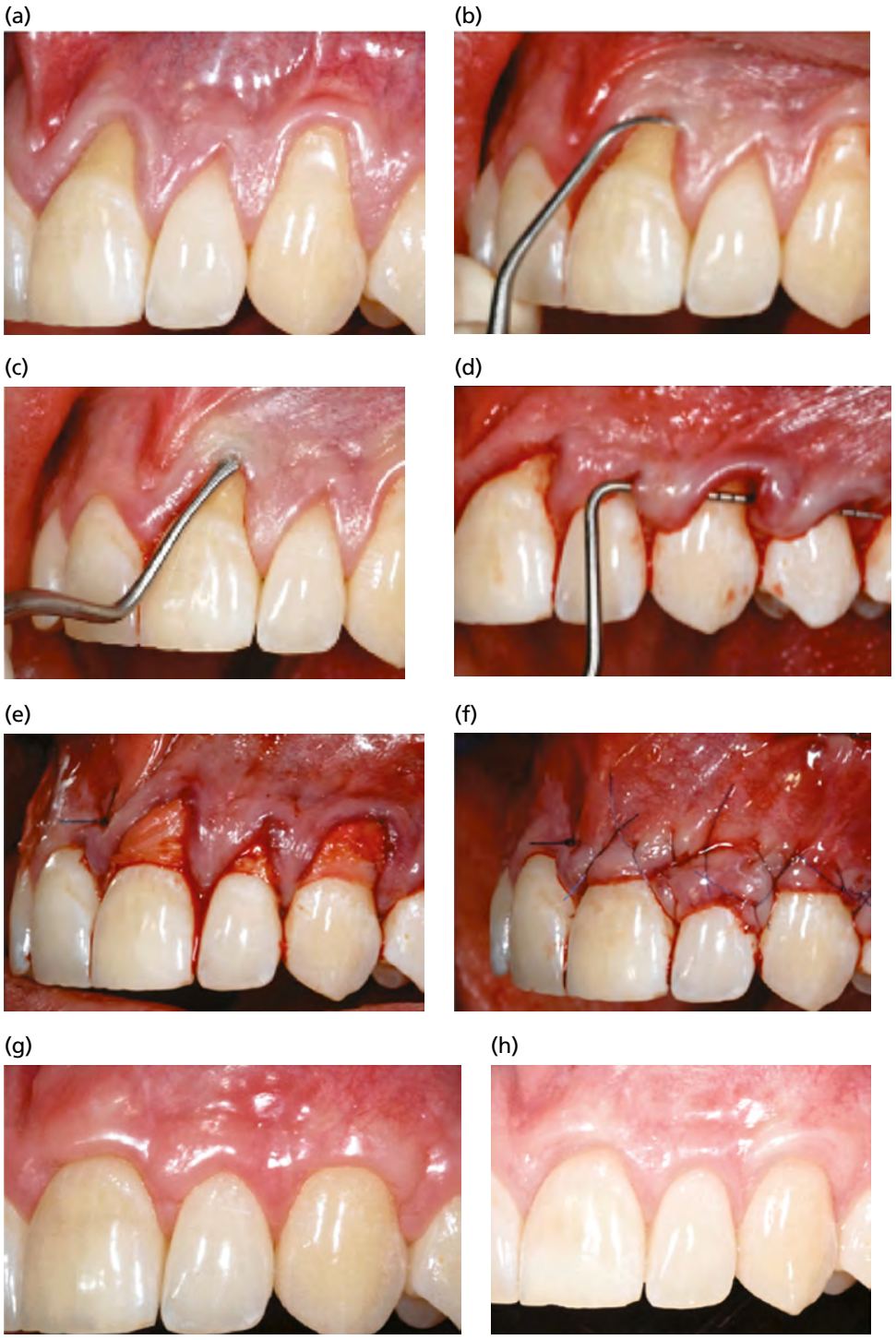

Fig. 39-48 (a) Preoperative view depicting RT1 multiple adjacent gingival recessions. (b) Gentle scaling of the root surfaces to remove the biofilm. (c) Preparation of the tunnel with specially developed tunnel instruments. (d) Prepared tunnel. Please note the tension free mobilization. (e) Subepithelial palatal connective tissue graft (SCTG) sutured at the cementoenamel junction. (f) The tunneled flap is sutured coronally to completely cover the recessions and the SCTG. (g) At 2-years postoperatively, complete recession coverage is evident. (h) At 11 years postoperatively a stable clinical situation is still visible. A slight relapse of the soft tissue can be observed at tooth at 21.

gingival recessions were consecutively treated with MCAT in conjunction with SCTG. Out of the 23 recessions, 16 were classified as RT1 and seven as RT2. All patients presented at least one facial gingival recession at a crown-restored tooth, located in the maxillary anterior area. In all cases, the facial recession was associated with an impaired esthetic appearance. At 12 months, statistically highly significant (P <0.0001) root coverage was obtained in all patients and defects. CRC was obtained in 22 out of the 23 recessions (e.g. in all 16 RT1 and in six out of the seven RT2 recessions) (Fig. 39-49). Taken together, the available results suggest that the use of the MCAT in conjunction with SCTG represents a valuable option for treating RT1 and RT2 multiple gingival recessions in the maxillary aesthetic area.

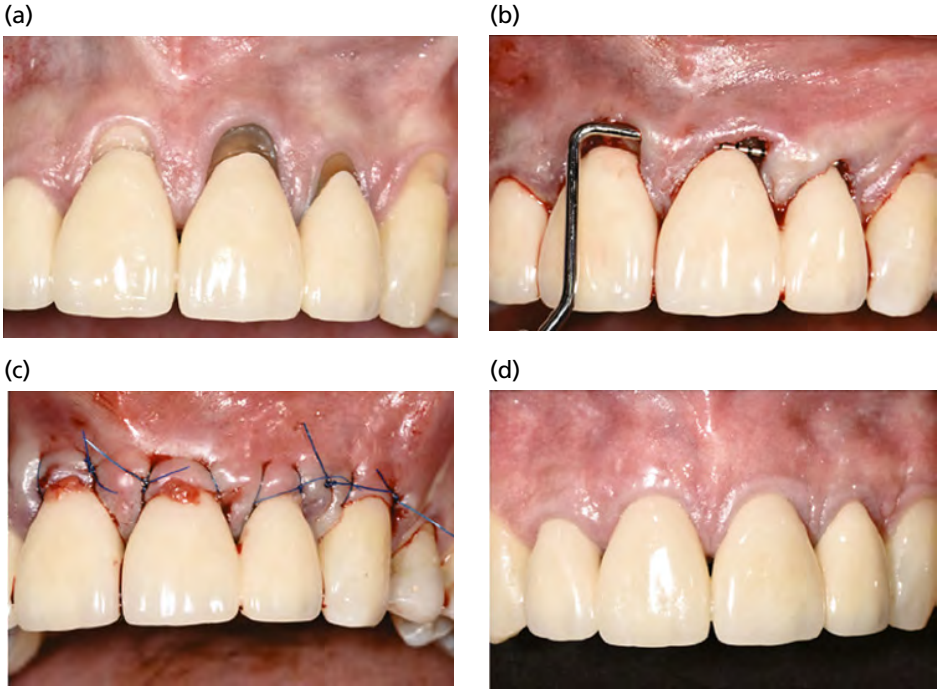

Fig. 39-49 (a) Preoperative view depicting multiple adjacent gingival recessions at crown-restored teeth in the maxillary esthetic area. (b) Prepared tunnel. (c) Coronally sutured tunnel to completely cover the exposed root surfaces and the SCTG. (d) At 2 years post-treatment, complete coverage of the exposed surfaces is evident.

The clinical relevance of the MCAT has also been evaluated in the treatment of isolated mandibular recessions (Sculean *et al*. 2014; Nart & Valles. 2016). In a case series including 16 patients with one isolated RT1 and RT2 mandibular recession, treatment was performed by means of MACT combined with EMD and SCTG (Sculean *et al*. 2014). At 12 months following surgery, statistically and clinically significant root coverage was obtained in all 16 defects. MRC amounted to 96.25% while CRC was measured in 12 out of the 16 defects (75%).

However, in deep isolated mandibular recessions located in the anterior area, tension free coronal displacement of the tunnel flap can be extremely difficult and may result in decreased vestibulum depth and/or flap dehiscence due to increased flap tension. In order to minimize these potential shortcomings, a novel surgical technique (e.g. the laterally closed tunnel or LCT) has been specifically designed and tested for the treatment of deep isolated mandibular RT1 and RT2 recessions (Fig. 39-50) (Sculean & Allen 2018). The LCT implies the placement of slightly beveled intrasulcular incisions by means of microsurgical blades followed by the preparation of a mucoperiosteal pouch (e.g. tunnel) using specially designed microtunnelling instruments. No special attempts are usually made to additionally remove the epithelium surrounding the margins of the pouch, because this is removed by means of the bevelled intrasulcular incisions. The pouch is then mobilized apically beyond the mucogingival line and extended mesially and distally from the recession defect by undermining the facial surface of the interdental papillae (Fig. 39-50). Collagen fibres inserting apically and laterally at the inner surface of the pouch are released using conventional and microsurgical blades until tension-free mesial and distal displacement of the pouch margins is obtained. Special attention needs to be paid in order not to disrupt the interdental papillae or to perforate the tunneled flap. As a result of this procedure, the margins of the pouch can be approximated without tension mesially and distally to cover either completely or the greatest part of the graft and the exposed root surface. Subsequently, a palatal SCTG is harvested as described earlier and pulled into the tunnel using mattress sutures and fixed mesially and distally at the inner aspect of the tunnel. The graft is additionally adapted to the CEJ by means of a sling suture and, finally, the margins of the pouch are pulled together over the graft and sutured with interrupted sutures to accomplish tension free complete or partial coverage of the graft and of the denuded root surface.

This novel surgical technique has been evaluated in a consecutive case series including 24 patients exhibiting one single deep mandibular RT1 or RT2 gingival recession at a depth of ≥4 mm. At 12 months, CRC was obtained in 17 out of the 24 defects representing 70.83% of the defects, whereas in the remaining seven defects RC amounted to 80–90% (in six cases) and 79% (in one case), respectively. The results obtained at isolated mandibular recessions with both MCAT and LCT compared well with those reported by Zucchelli *et al*. (2014) using the CAF. In a randomized controlled clinical study, Zucchelli *et al*. (2014) have evaluated the treatment of isolated RT1 gingival recessions located at mandibular incisors by means of CAF + SGCT with or without removal

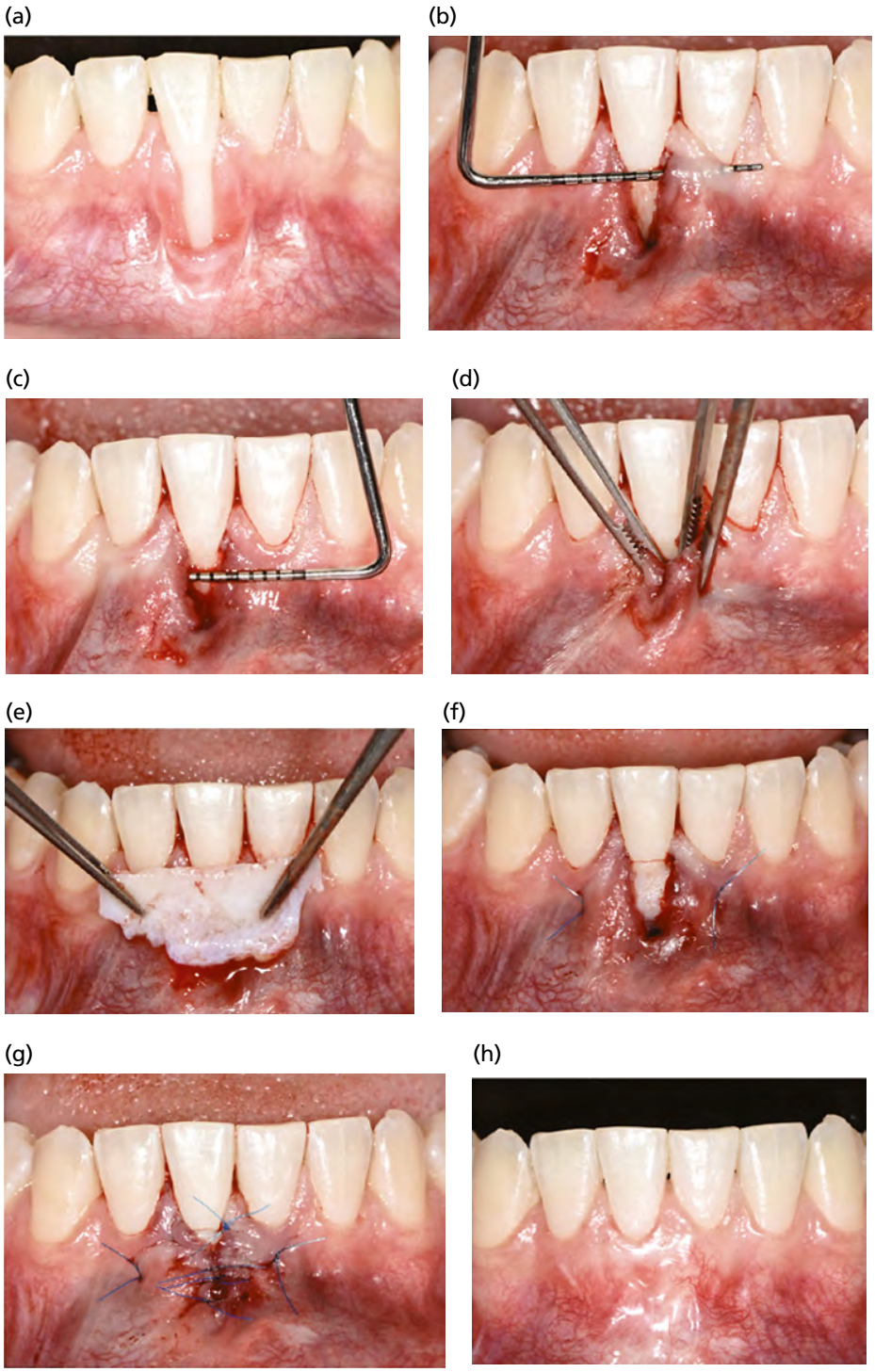

Fig. 39-50 (a) Preoperative view depicting a deep RT1 gingival recession located at tooth 41. (b) Prepared mesial tunnel. (c) Prepared distal tunnel. (d) Following tunnel preparation, tension free mobility of the soft tissue margins is evident. (e) Harvested subepithelial connective tissue graft (SCTG). (f) SCTG sutured at the cementoenamel junction. (g) Tension-free, lateral closure of the tunnel enabling an almost complete coverage of the SCTG. (h) At 1 year after treatment, complete root coverage is evident.

of labial submucosal tissue (LST). The results have shown predictable recession coverage, while the additional removal of LST yielded a tesion-free flap, thus resulting in less graft exposure and statistically significantly better CRC (e.g. 48% vs. 88%). Despite the fact that is is difficult to directly compare the results obtained at mandibular isolated recessions following the use of a CAF with those obtained with MACT or LCT, the results point to the pivotal role of a tension-free coronal mobilization of the soft tissues surrounding the recessions to obtain predictable CRC.

A number of clinical studies have been conducted to compare the outcomes following coverage of single and multiple gingival recessions by means or either the tunnel technique or CAF. The data indicate that CAF+CTG and MCAT+CTG provided comparable clinical and aesthetic improvements in

the treatment of single maxillary gingival recessions (Neves *et al*. 2020). A recent systematic review with meta-analysis has evaluated the efficacy of the tunnel technique in the treatment of localized and multiple gingival recessions and compared the outcomes with those obtained with CAF (Tavelli *et al*. 2018). The overall calculated MRC of the tunnel technique for localized gingival recessions was 82.75% ± 19.7% and 87.87% ± 16.45% for multiple recessions, respectively. Taken together, despite the still limited evidence comparing the tunnel technique with CAF, the available data indicate that both the tunnel approach and CAF may lead to excellent and comparable clinical outcomes in terms of root coverage and esthetics. However, when the same types of grafts were used, CAF was associated with a higher percentage of CRC compared with the tunnel approaches (Tavelli *et al*. 2018).

The use of soft tissue substitutes for the treatment of gingival recessions

Because use of SGCT always requires a second surgical site for harvesting the autogenous tissue graft, with its associated increased patient morbidity and more frequent postsurgical complications such as pain and/or bleeding (Chackartchi *et al*. 2019), a number of soft tissue replacement materials have been developed and investigated for replacing autologous grafts in root coverage procedures. These include mainly the use of ADM or various types of xenogeneic collagen matrices (Bohac *et al*. 2018; de Carvalho Formiga *et al*. 2020).

ADM is an allograft obtained from human skin that is chemically processed to remove all cells while preserving the extracellular dermal matrix (Bohac *et al*. 2018; de Carvalho Formiga *et al*. 2020). ADM has been frequently used for tooth recession coverage using either the CAF or tunnel approaches (Ozenci *et al*. 2015; Tavelli *et al*. 2019). In a randomized clinical trial, Woodyard *et al*. (2004) have shown that on a short-term basis (i.e. at 6 months), the use of ADM in conjunction with CAF resulted in higher recession coverage and increased soft tissue thickness than treatment with CAF alone. Very recent data suggest, however, that on a long-term basis (i.e. up to 12 years) a statistically significant relapse of the gingival margin may occur, irrespective of the used surgical technique (CAF or tunnel) (Tavelli *et al*. 2019).

A 3D xenogeneic porcine-derived bioresorbable collagen matrix (CM) has been evaluated in a histological (Vignoletti *et al*. 2011) and in randomized controlled clinical studies comparing treatment of RT1 single recessions by means of CAF alone or in conjunction with either CM or CTG (McGuire & Scheyer 2010; Cardaropoli *et al*. 2012; Jepsen *et al*. 2013; Moreira *et al*. 2016; Tonetti *et al*. 2018). The results from these studies have provided evidence that in RT1 recessions, the treatment with CAF + CM may result in higher gains of keratinized tissue compared to CAF alone (Jepsen *et al*. 2013; Moreira *et al*. 2016). However, in terms of root coverage, CM yielded either comparable or slightly less results compared with the outcomes obtained with CTG (de Carvalho Formiga *et al*. 2020). However, the use of CM was associated with statistically significantly reduced surgical time and patient morbidity compared with the use of CTG (McGuire & Scheyer 2010; Cardaropoli *et al*. 2012; Tonetti *et al*. 2018; de Carvalho Formiga *et al*. 2020).

The use of CM has also been evaluated in case series and in an RCT for the treatment of RT1 multiple adjacent recessions using MCAT (Aroca *et al*. 2013; Molnár *et al*. 2013). When compared with SCTG (Aroca *et al*. 2013), both treatments resulted in statistically significant improvements of CRC, MRC, KTW, and GT compared with baseline (P <0.05). However, CRC was found at 42% of test sites and at 85% of control sites, respectively (P <0.05) thus indicating superior results for SCTG. However, duration of surgery and patient morbidity were statistically significantly lower in the test compared with the control group. The long-term (i.e. up to 5 years) outcomes following treatment of isolated gingival recession by means of CAF + CM or CAF + SCTG have been evaluated by McGuire and Scheyer (2016). The results have failed to show statistically significant differences in terms of keratinized tissue width, probing depths, and recession coverage between the two groups indicating similar outcomes for both types of grafts.

Another type of collagen matrix is a porcine-derived acellular dermal collagen matrix (PADM) (Cosgarea *et al*. 2016; Pietruska *et al*. 2019). Pietruska *et al*. (2019) have compared the outcomes of the MCAT technique used in conjunction with either PADM or SCTG for the treatment of mandibular RT1 MAGR. The results revealed statistically significant recession coverage in both groups, but CRC was achieved in nine out of 45 (20%) defects treated with PADM and in 31 out of 39 (67%) treated with SCTG, thus indicating superior results for SCTG.

Taken together, the available evidence suggests that the use of the available soft tissue replacement materials may lead to short-term outcomes comparable with the use of autogenous grafts and also to less patient morbidity. However, the long-term stability of the results still needs to be demonstrated.

Healing of free soft tissue grafts

Survival of a free soft tissue graft placed over a denuded root surface depends on diffusion of plasma and subsequent revascularization from those parts of the graft that are resting on the connective tissue bed surrounding the dehiscence. The establishment of collateral circulation from adjacent vascular borders of the bed allows the healing phenomenon of "bridging" (Sullivan & Atkins 1968a). Hence, the amount of tissue that can be maintained over the root surface is limited by the size of the avascular area (Oliver

et al. 1968; Sullivan & Atkins 1968a). Other factors considered critical for the survival of the tissue graft placed over the root surface are that a sufficient vascular bed is prepared around the dehiscence and that a thick graft is used (Miller 1985b).

Another healing phenomenon frequently observed following free graft procedures is "creeping attachment", that is, coronal migration of the soft tissue margin. This occurs as a consequence of tissue maturation over a period of about 1-year post-treatment.

There are few histologic evaluations of the nature of the attachment established to the root surface following the use of free grafts for root coverage. Sugarman (1969) reported from a histologic evaluation of a human tooth treated with a free soft tissue graft that new connective tissue attachment was found in the apical quarter of the successfully covered recession defect. Harris (1999) and Majzoub *et al*. (2001), each reporting the histologic outcome of free CTGs in two cases, found only minimal amounts of new cementum formation in the most apical part of the recession defect and that healing resulted in a long junctional epithelium occupying the interface between the covering soft tissue and the root. Carnio *et al*. (2002) performed a histologic evaluation of four cases of root coverage with a CTG combined with application of enamel matrix proteins (Emdogain®). They reported that the healing resulted in connective tissue adhesion to the root surface and that the formation of new cementum was observed only in the most apical end of the grafted area.

Thus, the limited histologic information available from humans on the healing of free soft tissue grafts indicates that a healing pattern similar to the one discussed above following pedicle graft procedures may result, namely that connective tissue attachment may be established in the most apical and lateral parts of the recession defect, but that an epithelial attachment is formed along the major portion of the root. Further, the application of enamel matrix proteins may prevent the apical migration of the epithelium but may not favor the formation of a true connective tissue attachment between the free graft and the root surface.

Selection of surgical procedure for root coverage

For each individual case, several factors have to be taken into consideration when selecting the surgical procedure for achieving root coverage, for example jaw, tooth position, recession depth and width, tissue thickness and quality apical and lateral to the recession, esthetic demands, and compliance. From an esthetic point of view, the soft tissue coverage of exposed root surfaces should be in harmony with the adjacent tissue and hence a pedicle graft would be the preference.

For maxillary teeth, the coronally advanced flap may be considered as the basic procedure to be used for single as well as multiple recessions. If the quality of the mucosa apical to the recessions is considered inadequate for root coverage, the procedure is combined with the placement of a CTG.

In the mandible, the placement of a free CTG with an "envelope" or a "tunnel" preparation is preferred because of a thin mucosa apical to the recession and often the presence of multiple frenula, that is, conditions not suitable for a coronally advanced flap. In case of a localized single recession defect of moderate depth, a rotational flap may be used if keratinized mucosa of sufficient dimensions is available lateral to the recession.

Clinical outcomes of root coverage procedures

Independent of the modality of surgical procedure used to attain soft tissue root coverage, shallow residual probing depths, gain in clinical attachment, and increase in gingival height are the common characteristics of treatment outcome. Although the major indications for performing root coverage procedures are esthetic/cosmetic demands and root sensitivity, few studies have used assessments of these criteria as end points of treatment success. Instead, the common outcome variables used are the amount of root coverage achieved, expressed as a percentage of the initial depth of the recession defect, and the proportion of treated sites showing complete root coverage. Whereas CRC may be a successful outcome with respect to root sensitivity, it is not necessarily equivalent to treatment success from an esthetic point of view because, besides root coverage in harmony with adjacent teeth, factors such as tissue thickness, color, and texture influence the appreciation of the esthetic result.

An overall comparison of the treatment outcome of various root coverage procedures is hampered by the fact that there is substantial heterogeneity between studies (Cairo *et al*. 2008; Chambrone *et al*. 2009). The variability in the treatment outcome for the various procedures, both within and between studies, is large, indicating that the procedures are operator sensitive and that various factors influencing the treatment outcome have not been adequately considered. An analysis with regard to initial Miller class I–II recession defects that may be successfully covered following treatment with coronally advanced flaps, based on the data from randomized controlled studies included in recent systematic reviews (Cairo *et al*. 2008; Chambrone *et al*. 2009), shows that on average about 70% root coverage may be expected (range 34–87%). Complete coverage of the recession defect, which is the ultimate goal of the therapy, may be reached in approximately 35% of treated cases (range 15–60%).

Evidence suggests that the treatment outcome can be improved by adjunctive use of CTG or enamel matrix proteins, with an estimated mean absolute

adjunctive effect of 15–25% for CRC and 13–17% for reduction in recession depth (Cairo *et al*. 2008; Chambrone *et al*. 2009; Buti *et al*. 2013).

Systematic reviews were prepared for the EFP and AAP consensus workshops, respectively (Cairo *et al*. 2014; Chambrone & Tatakis 2015) and it was reported that bilaminar techniques using subepithelial CTGs achieved superior percentages of mean and CRC as well as a significant increase in keratinized tissue. The outcome of these consensus workshops indicated that: CAF was associated with higher probability of CRC and a higher amount of recession reduction than the SCPF. The combination of CAF+CTG seems to be the more effective technique to reach a CRC and recession reduction, when compared with other techniques (CAF plus collagen matrix, free gingival graft, laterally positioned flap, CAF plus barrier membranes). GTR was not able to improve the clinical efficacy of CAF. Studies adding ADM under CAF showed a large heterogeneity and no significant benefits compared with CAF alone. Multiple combinations, using more than a single graft/biomaterial under the flap, usually provide similar or less benefits than simpler, control procedures in term of root coverage outcomes. In the same workshop, Graziani *et al*. (2014) carried out a metanalysis for multiple gingival recessions, with similar outcomes in relation to the different surgical treatment modalities, although with lesser evidence. An even more recent systematic review (Chambrone *et al*. 2019) corroborated these results, reporting that the CAF with or without the use of CTGs or other biomaterials, can be used for the successful treatment of single or multiple recession type defects. The modified CAF and tunnel approaches show the highest percentages of CRC.

Factors influencing the degree of root coverage

Patient-related factors. As with other surgical periodontal treatment procedures, poor oral hygiene will negatively influence the success of root coverage procedures (Caffesse *et al*. 1987). Further, a predominant causative factor in the development of gingival recession is toothbrushing trauma, and hence this factor has to be corrected to secure an optimal outcome for any root coverage procedure. Treatment outcome in terms of root coverage is usually less favorable in smokers than in non-smokers (Trombelli & Scabbia 1997; Zucchelli *et al*. 1998; Martins *et al*. 2004; Erley *et al*. 2006; Silva *et al*. 2006), although some studies showed no differences between these groups (Tolmie *et al*. 1991; Harris 1994).

Site related factors. Among site-specific factors, the level of interdental periodontal support may be of greatest significance for the outcome of root coverage procedures. From a biologic point of view, CRC is achievable in RT1–2 recession defects (Fig. 39-51), whereas when loss of connective tissue attachment and soft tissue height also involves proximal tooth sites (RT3), only partial facial root coverage may be obtainable (Fig. 39-52). An additional factor shown to influence the degree of attainable root coverage is the dimensions of the recession defect. A less favorable treatment outcome has been reported at sites with wide (>3 mm) and deep (≥5 mm) recessions (Holbrook & Ochsenbein 1983; Pini Prato *et al*. 1992; Trombelli *et al*. 1995). In a study comparing the treatment effect of coronally advanced flap and free CTG procedures, Wennström and Zucchelli (1996) reported that CRC was observed in only 50% of the defects with an

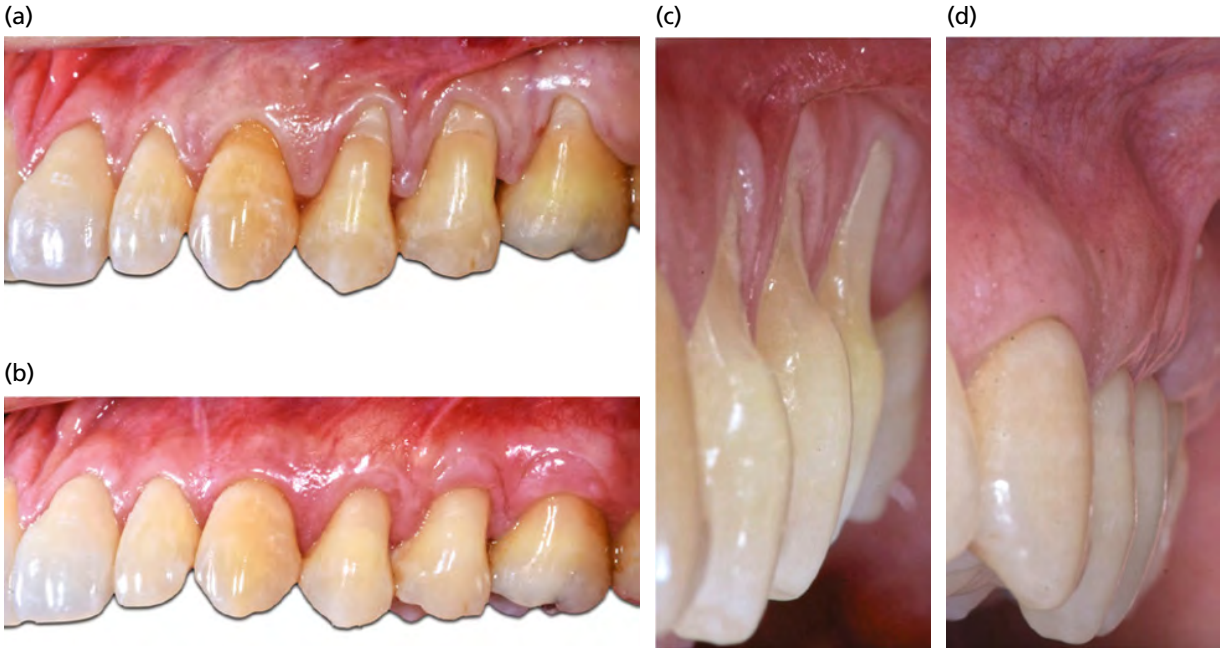

Fig. 39-51 (a) Preoperative view depicting NCCL lesions associated with multiple adjacent gingival recessions restored with composite restorations. (b) One year after treatment, root coverage is evident over the composite restorations. (c) Lateral view of multiple adjacent recessions. (d) Root coverage 1 year after treatment

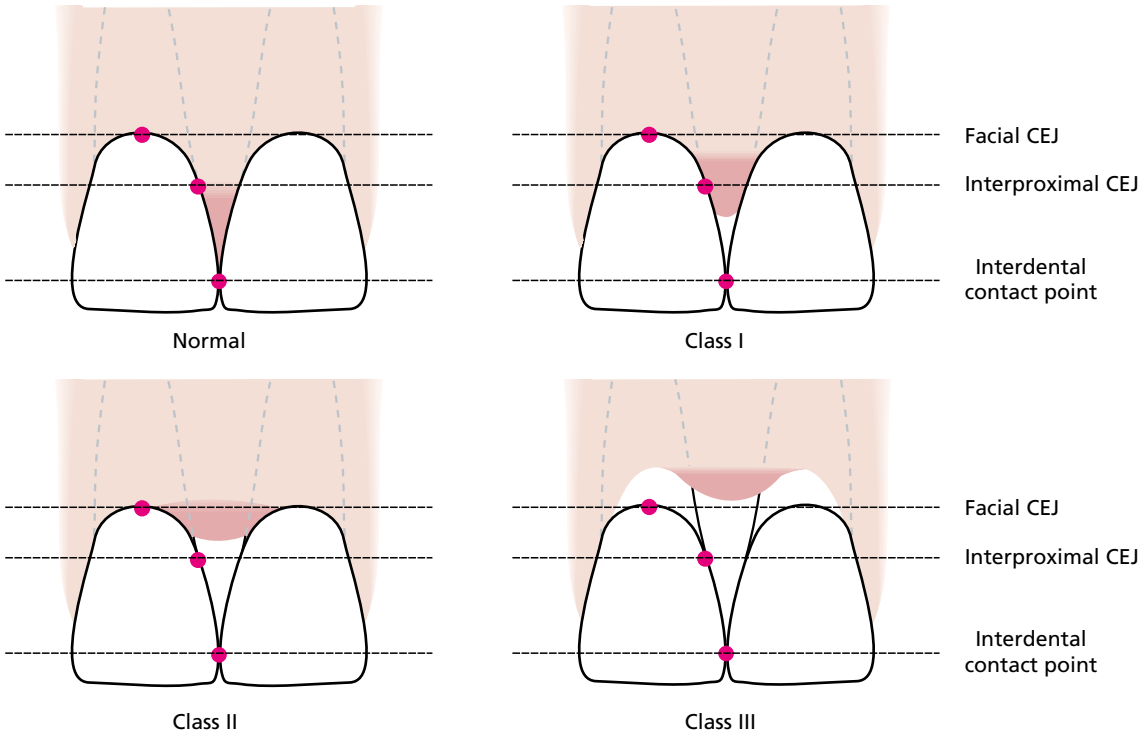

Fig. 39-52 The classification system for papilla height. CEJ, cementoenamel junction. (Source: Modified from Nordland & Tarnow 1998. Reproduced with permission from John Wiley & Sons.)

initial depth of ≥5 mm compared with 96% for shallower defects.

Technique-related factors. Several technique-related factors may influence the treatment outcome of a pedicle graft procedure. In a systematic review including data from 15 studies (Hwang & Wang 2006), a positive correlation was demonstrated between the thickness of the tissue flap and recession reduction. For complete root coverage, the critical threshold thickness was found to be about 1 mm. However, whether a full- or a split-thickness pedicle graft is used for root coverage may not influence the treatment outcome (Espinel & Caffesse 1981). Elimination of flap tension is considered an important factor for the outcome of the coronally advanced flap procedure. Pini Prato *et al*. (2000a) measured the tension in coronally advanced flaps to compare the amount of root coverage in sites with and without residual flap tension. At sites that had residual tension (mean 6.5 g), the root coverage amounted to 78% 3 months postsurgically and 18% of the treated sites showed complete root coverage. Sites without tension demonstrated MRC of 87% and CRC in 45% of the cases. Furthermore, a statistically significant negative association was shown between the magnitude of residual tension in the flap and the amount of recession reduction. Although the connective tissue areas lateral to the recession defect are considered important for the retention of the advanced flap when positioned over the root surface, the dimension of the interdental papilla area is not a prognostic factor for the clinical outcome of the root coverage procedure (Saletta *et al*. 2001). As can be expected, the position of the gingival margin relative to the CEJ after suturing affects the probability of CRC following healing. Pini Prato *et al*. (2005) demonstrated that for 100% predictability of CRC in the treatment of Miller class I recessions with a coronally advanced flap procedure, the flap margin has to be positioned at least 2 mm coronal to the CEJ.

With regard to free graft procedures, the thickness of the graft influences their success (Borghetti & Gardella 1990). A thickness of the free graft of about 2 mm is recommended.

Tooth-related factors. The development of NCCLs occurs frequently on exposed root surfaces. Several studies showed that these lesions are associated with deeper gingival recessions and with a reduced probability for CRC (Jepsen *et al*. 2018). When NCCLs are present in a site with a gingival recession, a multidisciplinary approach should be considered including mucogingival surgery for root coverage and CEJ reconstruction. It is not yet clear whether the hard tissue damage should be restored before or after the surgical phase, although there is evidence that restorative materials, such as glass ionomer cements or composites, can be combined with a coronal advanced flap (Santamaria *et al*. 2008, 2009, 20 14, 2016, 2018; Silveira *et al*. 2017) (Fig. 39-51). When restoring the CEJ several techniques have been proposed (Zucchelli *et al*. 2006; Cairo *et al*. 2010; Zucchelli *et al*. 2011; Silveira *et al*. 2017; Santamaria *et al*. 2018), although there is not a consensus where to establish the new CEJ. Some authors suggest positioning the composite restoration 1–2 mm apical to the original position in order to allow for an apical shift of the soft tissue margin following the

root coverage procedure and for the restoration to still be effective in reducing the root sensitivity (Silveira *et al*. 2017; Santamaria *et al*. 2018). De Sanctis *et al*. (2020) proposed a combined approach in the treatment of multiple recession presenting NCCL consisting of the re-establishment of the CEJ with the composite restoration extending 1 mm apical to the original anatomical T position combined with the MCAF with or without a vertical releasing incision, utilizing the site-specific application of a CTG as previously discussed. Using this approach, CRC was attained in 90% of all the treated sites at 12 months follow-up

Interdental papilla reconstruction

The loss of papilla height and the establishment of "black triangles" between teeth may occur due to several reasons. In adults the most common reason is loss of periodontal support due to periodontitis, but other factors, such as abnormal tooth shape, improper contours of prosthetic restorations, and traumatic oral hygiene procedures, may also negatively influence the outline of the interdental soft tissues.

Nordland and Tarnow (1998) proposed a classification system regarding the papillary height adjacent to natural teeth, based on three anatomic landmarks: the interdental contact point, the apical extent of the facial CEJ, and the coronal extent of the proximal CEJ (Fig. 39-52):

- *Normal*: the interdental papilla occupies the entire embrasure space apical to the interdental contact point/area
- *Class I*: the tip of the interdental papilla is located between the interdental contact point and the level of the CEJ on the proximal surface of the tooth
- *Class II*: the tip of the interdental papilla is located at or apical to the level of the CEJ on the proximal surface of the tooth but coronal to the level of the CEJ mid-buccally
- *Class III*: the tip of the interdental papilla is located at or apical to the level of the CEJ mid-buccally.

In an observational study in humans, Tarnow *et al*. (1992) analyzed the correlation between the presence of interproximal papillae and the vertical distance between the contact point and the interproximal bone crest. When the vertical distance from the contact point to the crest of bone was ≤5 mm, the papilla was present almost 100% of the time, whereas if the distance was ≥6 mm only partial papilla fill of the embrasure between the teeth was most commonly found. Considering that a supracrestal connective tissue attachment zone of approximately 1 mm is normally found (Gargiulo 1961), the observation indicates that the biologic height of the interdental papilla may be limited to about 4 mm. This interpretation is supported by the observation that in interdental areas denuded following an apically repositioned flap procedure, an up growth of around 4 mm of soft tissue had taken place 3 years after surgery (Van der Velden 1982). Hence, before attempts are made to surgically reconstruct an interdental papilla, it is important to carefully assess (1) the vertical distance between the bone crest and the apical point of the contact area between the crowns and (2) the soft tissue height in the interdental area. If the bone crest–contact point distance is ≤5 mm and the papilla height is <4 mm, surgical intervention for increasing the volume of the papilla could be justified in order to solve the problem of an interdental "black triangle". However, if the contact point is located >5 mm from the bone crest, because of loss of periodontal support and/or an inappropriate interdental contact relationship between the crowns, methods to lengthen the contact area apically between the teeth should be selected rather than a surgical attempt to improve the topography of the papilla.

If loss of papilla height is only caused by soft tissue damage from oral hygiene devices, interproximal hygiene procedures must be initially discontinued to allow soft tissue recovery and then successively modified in order to eliminate/minimize traumatic injury to the papillae.

Surgical techniques

Several case reports have been published regarding surgical techniques for the reconstruction of deficient papillae (e.g. Beagle 1992; Han & Takei 1996; Azzi *et al*. 1998). However, the predictability of the various procedures has not been documented and no data are available in the literature providing information on the long-term stability of surgically regained interdental papillae.

Beagle (1992) described a pedicle graft procedure utilizing the soft tissues palatal to the interdental area (Fig. 39-53). A split-thickness flap is dissected on the palatal aspect of the interdental area. The flap is elevated labially, folded, and sutured to create the new papilla at the facial part of the interdental area. A periodontal dressing is applied on the palatal aspect only, in order to support the papilla.

Han and Takei (1996) proposed an approach for papilla reconstruction ("semilunar coronally repositioned papilla") based on the use of a free CTG (Fig. 39-54). A semilunar incision is placed in the alveolar mucosa facial to the interdental area and a pouch-like preparation is performed into the interdental area. Intrasulcular incisions are made around the mesial and distal half of the two adjacent teeth to free the connective tissue from the root surfaces to allow coronal displacement of the gingival–papillary unit. A CTG, taken from the palate, is placed into the pouch to support the coronally positioned interdental tissue.

Azzi *et al*. (1998) described a technique in which an envelope-type flap is prepared for coverage of a

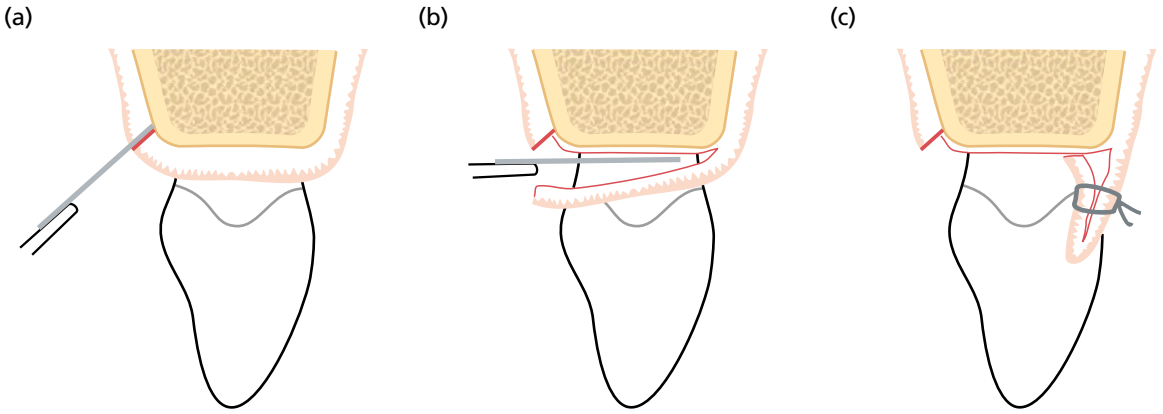

Fig. 39-53 (a–c) Papilla reconstruction: pedicle graft technique (see text for explanation). (Source: Based on Beagle 1992. Reproduced with permission from John Wiley & Sons.)

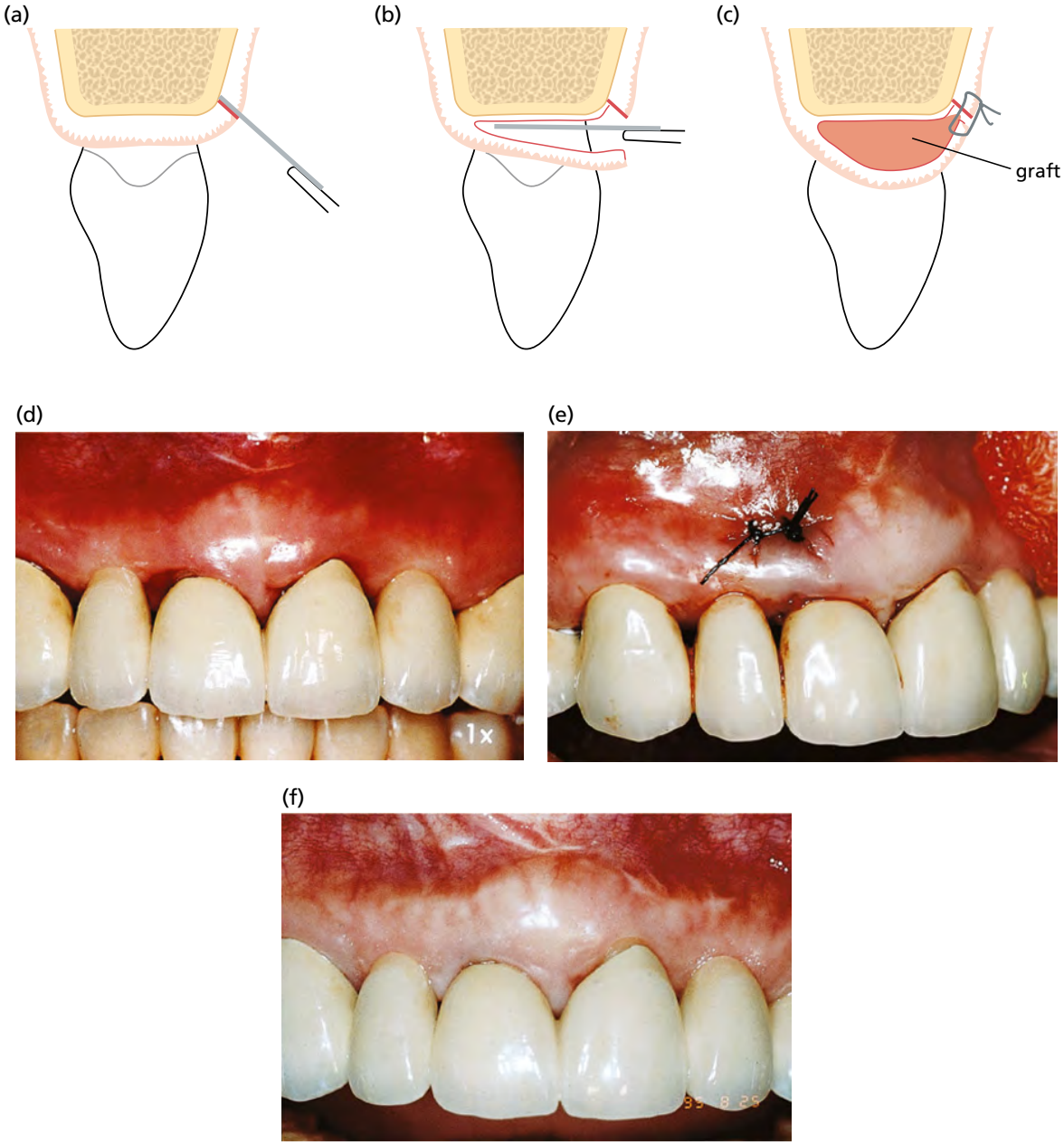

Fig. 39-54 Papilla reconstruction: "semilunar coronally repositioned papilla" technique. (a–c) Surgical technique (see text for explanation). (d–f) Reconstruction of papillae distal to the central incisors with the use of the semilunar coronally repositioned papilla technique in a patient with a fixed bridge reconstruction. (Source: Based on Han & Takei 1996. Reproduced with permission from John Wiley & Sons.)

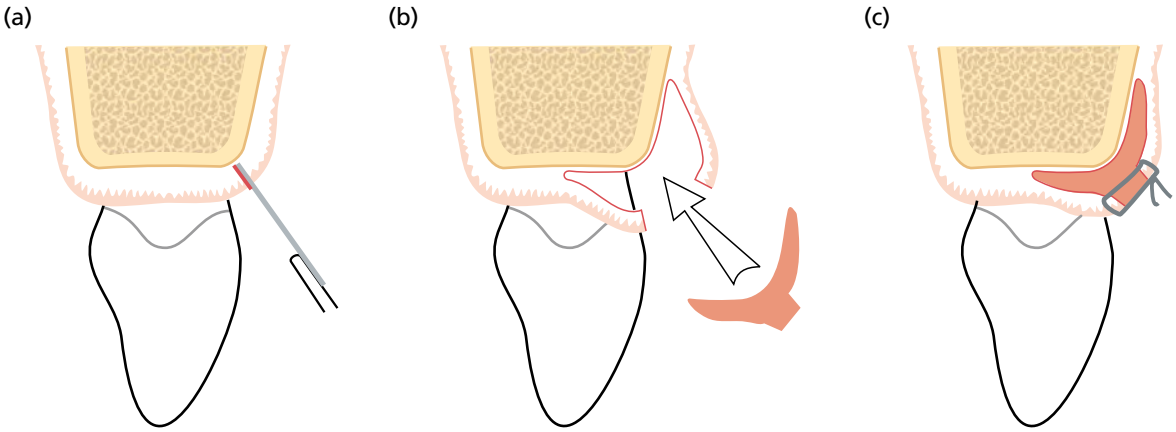

Fig. 39-55 (a–c) Papilla reconstruction: "envelope" technique (see text for explanation).

CTG (Fig. 39-55). An intrasulcular incision is made at the tooth surfaces facing the interdental area to be reconstructed. Subsequently, an incision is made across the facial aspect of the interdental area and an envelope-type split-thickness flap is elevated into the proximal site as well as apically to a level beyond the mucogingival line. A CTG is harvested from the tuberosity area, trimmed to adequate size and shape, and placed under the flaps in the interdental papilla area. The flaps are brought together and sutured with the CTG underneath.

Crown-lengthening procedures

Crown lengthening (CL) is a surgical procedure used to either facilitate restorative dentistry or to satisfy a patient's esthetic demands when there is excessive gingival display when smiling or when gingival enlargement prevents adequate oral hygiene practices (Lee 2004).

Depending on the main objective, whether the aim is to improve esthetic outcomes or for restorative purposes, CL surgical interventions have been categorized as esthetic, in situations of excessive gingival display and/or altered passive eruption, or functional, in situations where subgingival caries or fractures require the exposure of subcrestal sound tooth structure. Both have, however, the common objective of the re-establishment of the biologic width in a more apical position. Although biologic width has been the commonly used clinical term to describe the distance between the base of the gingival sulcus and the height of the alveolar bone, this distance corresponds to the apico-coronal variable dimensions of the junctional epithelium and supracrestal connective tissue attachment, and hence the dimension of the supracrestal attached tissues is currently the preferred term (Jepsen *et al*. 2018). The rationale of crown lengthening is, therefore, to re-establish the supracrestal attached tissues in a more apical position, thus avoiding the violation of this space, since there is available evidence from human and animal studies that its infringement is associated with inflammation and subsequent loss of periodontal supporting tissues, accompanied by an apical shift of the junctional epithelium and supracrestal connective tissue attachment (Jepsen *et al*. 2018).

Excessive gingival display

In most patients, the upper lip line limits the amount of gingiva that is exposed when a person smiles. Patients who have a high lip line expose a broad zone of gingival tissue and may often express concern about their "gummy smile" (Fig. 39-56).

The form of the lips and the position of the lips during speech and smiling cannot be easily changed, but the dentist may, if necessary, modify/control the form of the teeth and interdental papillae as well as the position of the gingival margins and the incisal edges of the teeth. In other words, it is possible by a combination of periodontal and prosthetic treatment measures to improve dentofacial esthetics in this category of patient.

As a base for treatment decisions, a careful analysis of the dentofacial structures and how these may affect esthetics should be performed. It should include the following features:

- Facial symmetry
- Interpupillary line; even or uneven
- Smile line: low, median or high
- Dental midline in relation to facial midline

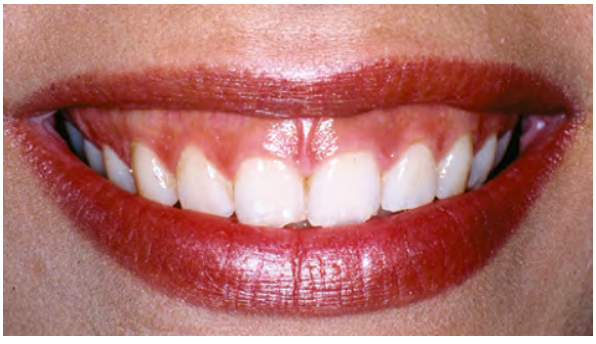

Fig. 39-56 "Gummy smile" patient exhibiting excessive gingival display when smiling.

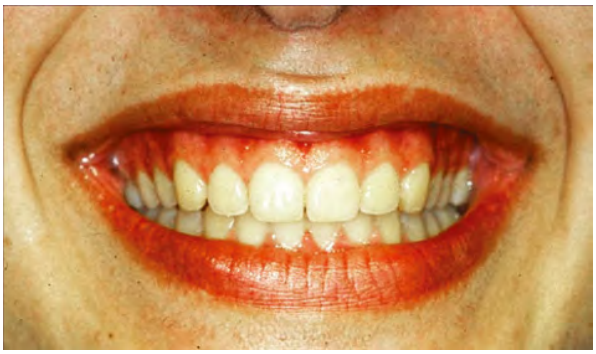

Fig. 39-57 "Gummy smile" patient exhibiting excessive gingival display when smiling due to an altered passive eruption

- Gingival display during speech and during a broad, relaxed smile
- Harmony of gingival margins
- Location of gingival margins in relation to the CEJ
- Periodontal phenotype
- Tooth size and proportions/harmony
- Incisal plane/occlusal plane.

Excess gingival display can occur when passive eruption has been delayed. Altered passive eruption is a developmental condition with abnormal dentoalveolar relationships. In the young adult with an intact periodontium, the gingival margin normally resides about 1 mm coronal to the CEJ. However, these patients may have a height of free gingiva that is >1 mm, resulting clinically with an insufficient length of the clinical crowns, with gingival margins (and sometimes bone) located at a more coronal level. In fact, when the bone is located more coronally, the alveolar crest may be located at the level of the CEJ or even beyond, which does not allow appropriate space for the supracrestal connective tissue attachment, which leads to pseudopockets and esthetic concerns. The result is the appearance of short clinical crowns and the usual patient complaint of "small front teeth". In the presence of a medium or high lip line, this condition will be more noticeable, combining the short teeth with an excessive gingival display (Fig. 39-57).

Exposure of sound tooth structure

In some clinical situations, conditions are unfavorable for successful restorative procedures. These include: deep subgingivally located carious lesions, crown and root fractures, pre-existing deep preparation margins, perforations during endodontic therapy, and root resorptions. Similarly, although supragingival placement of restorative margins is generally preferred because it facilitates impression making, finishing of the restoration, verification of its marginal integrity, and maintenance of gingival health, there are certain esthetically demanding clinical situations that require placing the restoration margins deep subgingivally. In these situations when there is not enough available tooth structure, the violation of the supracrestal tissue attachment may result in a periodontal lesion characterized by gingival inflammation, attachment loss, and alveolar bone resorption.

Surgical lengthening of the clinical crown will improve the anatomical conditions and facilitate restorative procedures in these patients that can be divided into two categories:

1. *Subjects who have normal occlusal relationships and incisal guidance*. In this category, the incisal line of the front teeth must remain unaltered, but the clinical crowns can be made longer by surgically exposing the root structure and by locating the cervical margins of the restorations apical to the CEJ (Fig. 39-57).
2. *Subjects who have abnormal occlusal relationships with excessive interocclusal space in the posterior dentition when the anterior teeth are in edge-to-edge contact*. In this category, the length of the maxillary front teeth can be reduced without inducing posterior occlusal interferences. In addition, the marginal gingiva can be resected or relocated to an apical position before crown restorations are made (Fig. 39-58).

In some individuals with an excessive display of gingiva, the size and shape of the teeth and the location of the gingival margins may be perfectly normal. The excessive display of gingiva in these cases is

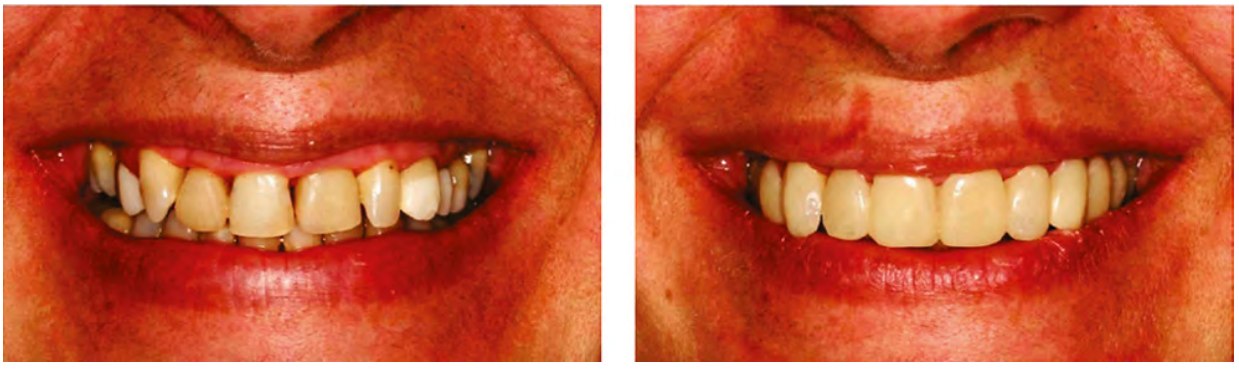

Fig. 39-58 Patient with a "gummy smile" and restorative needs with a mock-up on depicting planned final tooth shapes and sizes

often caused by vertical maxillary excess and a long mid-face. Periodontal crown-lengthening procedures will not suffice to solve their problems, but rather the maxilla must be altered by a major maxillofacial surgical procedure. The risk-to-benefit and cost-to-benefit ratios must be thoroughly evaluated before recommending this type of surgical therapy to correct esthetic problems.

Selection of the crown lengthening procedure

To select the proper procedure for crown lengthening, there is a need for indidualized analysis of crown–root–alveolar bone relationships. When restorative work is planned, an acrylic *mock-up* should be fabricated depicting the ideal tooth sizes and shapes. This *mock-up* is useful not only for adequate diagnosis and treatment planning, but also for patient acceptance, since the final result is evident (Fig. 39-58).

Gingivectomy

In clinical situations where the excessive gingival display is due only to excessive apical displacement of the gingival tissues (pseudopockets) with a normal dimension of the root–alveolar bone relationships (adequate space for the supracrestal connective tissue attachment from the alveolar crest to the CEJ), the full exposure of the anatomic crown can be accomplished by a gingivectomy/gingivoplasty procedure. In a study by Monefeldt and Zachrisson (1977), the effect of gingivectomies on the clinical facial crown height was assessed on study models from first bicuspids scheduled for extraction for orthodontic reasons. It was observed that the mean clinical crown height increased by 1 mm, whereas the mean probing pocket depth was reduced by 1 mm. In the histologic analyses, no apical migration of the epithelium beyond the CEJ was observed. This led to the conclusion that gingivectomy resulted in a reduction of pseudo pockets and did not displace the connective tissue attachment level apically. Therefore, gingivectomies can only be recommended for the controlled apical dislocation of the soft marginal tissues without altering the alveolar bone crest and connective tissue attachment level. In these situations, the gingivectomy procedure can be carried out either with an externally beveled path of incision what will frequently need extending across the midline and leaving a wide area of gingival tissue to heal by secondary intention, or alternatively, an internally beveled path of incision (internal gingivectomy) usually finished at the gingival margin area with a minimal gingivoplasty for achieving knife edge gingival margins (Fig. 39-59).

Apically positioned flaps

Conventional crown lengthening procedures are typically accomplished by an apically positioned flap (APF) with/without osseous resection (Palomo & Kopczyk 1978). In CL surgical interventions aimed at satisfying high esthetic demands, it is imperative to achieve an ideal position for the gingival margins (Herrero *et al*. 1995) and maintain this position long term (Deas *et al*. 2014). As a general rule, at least 4 mm of sound tooth structure must be exposed at the time of surgery, since during healing, the supracrestal soft tissues will proliferate coronally to cover 2–3 mm of the root (Herrero *et al*. 1995; Pontoriero & Carnevale 2001; Lanning *et al*. 2003), thereby leaving only 1–2 mm of supragingivally located sound tooth structure. When this technique is used for crown lengthening, it must also be realized that gingival tissues have an inherent tendency to bridge abrupt

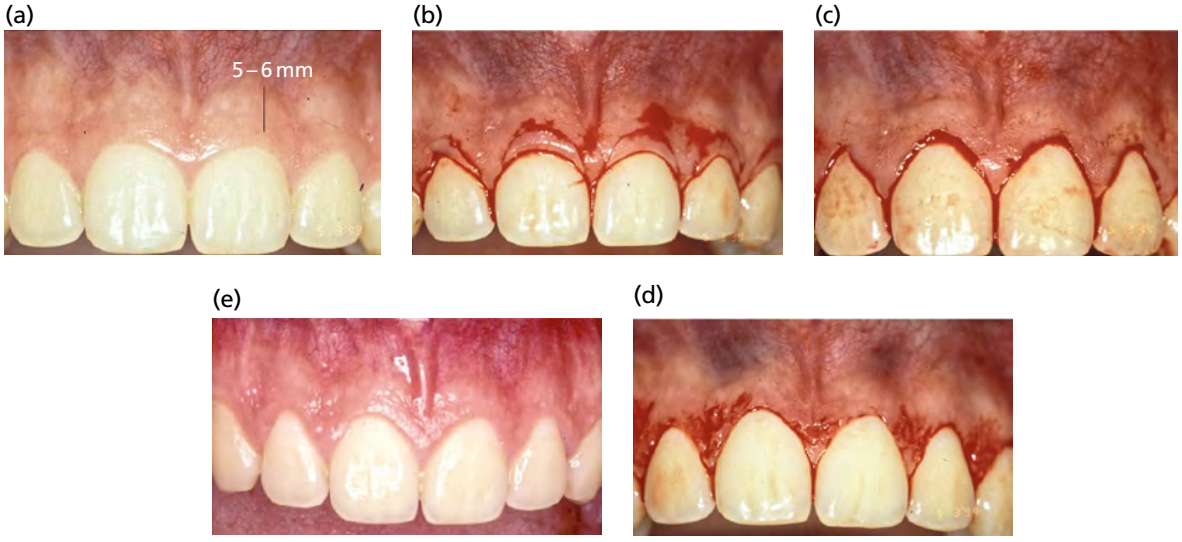

Fig. 39-59 Crown lengthening by *internal bevel gingivivectomy*. (a) Preoperative view depicting wide area of keratinized gingiva. (b) Internal bevel incisions. (c) Removal of excessive gingival tissue. (d) Minimal gingivoplasty to achieve knife edge gingival margins. (e) Three-month postoperative result.

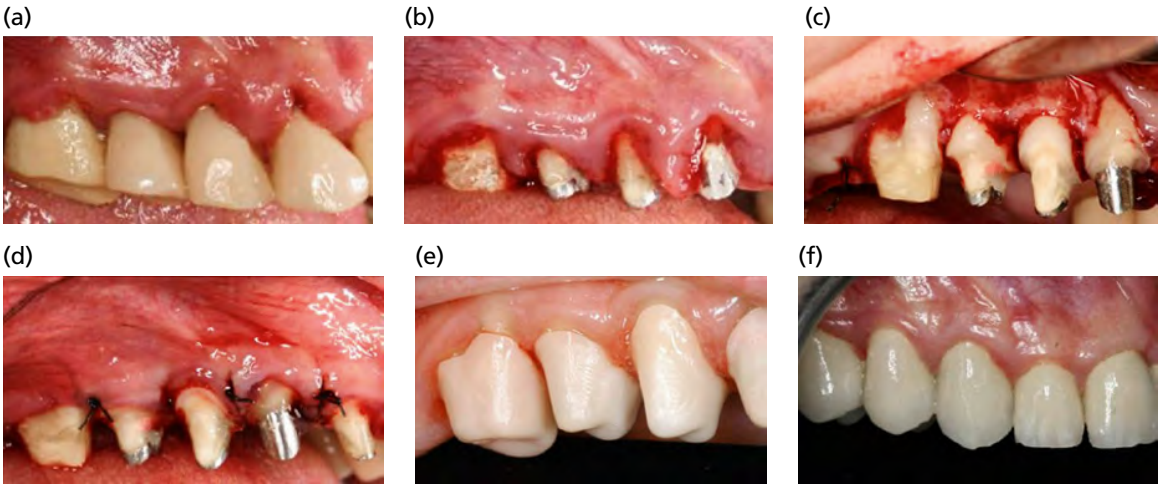

Fig. 39-60 (a) Marked gingival inflammation around prosthetic restoration in posterior right upper sextant. (b) Lack of retention and invasion of the biological width by the existing restoration. (c) Apically positioned flap crown lengthening procedure ensuring enough tooth surface for the retention of the restoration without invading the biological width. (d) Sutures positioning the flap over the bone crest. (e) New crown preparations using the available tooth structure. (f) Final prosthetic restoration with healthy gingival tissues.

changes in the contour of the bone crest. Thus, in order to retain the gingival margin at its new and more apical position, bone recontouring must be performed not only at the problem tooth but also at the adjacent teeth to gradually reduce the osseous profile (Fig. 39-60). Consequently, substantial amounts of attachment may have to be sacrificed when crown lengthening is accomplished with an APF technique. It is also important to remember that, for esthetic reasons, symmetry of tooth length must be maintained between the right and left sides of the dental arch. This may, in some situations, call for the inclusion of even more teeth in the surgical procedure.

In CL surgical interventions aimed at providing enough tooth structure to enable adequate retention for the prosthetic restoration, the amount of ostectomy is guided by the restorative needs. In these situations, it is imperative to consider the remaining periodontium and the presence of furcation entrances, since frequently these interventions must sacrifice supporting bone not only in the affected teeth, but also in adjacent teeth (Fig. 39-60).

The APF is usually carried out as a one-stage procedure in which submarginal scalloped incisions and full thickness flaps are followed by bone recontouring to recreate the space for adequate supracrestal tissue attachment. Incision design and the amount of bone recontouring are usually guided by the presurgical assessment of the CEJ either through transgingival probing or by radiographic examination when no restorative work is needed after the CL procedure. However, when restorative work is planned, an acrylic *mock-up* is fabricated which is useful not only for patient acceptance, but also to design the first incision according to the restorative plan (Fig. 39-61, Fig. 39-62)

The final position of the gingival margin after healing, however, is not always predictable (Christiaens *et al*. 2018) and may result in unfavorable outcomes, such as marginal tissue rebound or gingival recession. Factors such as the position of the gingival margin relative to the bone crest (Lanning *et al*. 2003; Deas *et al*. 2014), the extent of ostectomy performed (Deas *et al*. 2004), the patient's periodontal phenotype, the healing time (Pontoriero & Carnevale 2001), and the experience of the surgeon (Herrero *et al*. 1995) may influence the result.

When performing the two stage APF crown lengthening procedure, once the scallop incision has been designed and the full thickness flaps have been raised, it is important to calculate the space available for the supracrestal connective tissue attachment. When no further restorative work is planned, the distance between the CEJ and the bone crest should be at least 3 mm. When using a mock-up of the restorative plan, the distance between the restoration and the bone crest should be used as a reference. Ostectomy should be carried out using rotary instruments and bone chisels. Care should be taken not to eliminate root surface to avoid subsequent dentin hypersensitivity. Flaps should be then positioned over the bone crest using suspensory sutures to avoid any bone or connective tissue exposure (Fig. 39-62).

To overcome some of these limitations, an alternative CL surgical approach in two stages was proposed (Sonick 1997). This surgical approach involves two staged surgical interventions. In the first surgical phase, after raising a full thickness flap following intrasulcular incisions, the space for supracrestal tissue attachment is recreated by ostectomy and osteoplasty by direct visualization of the CEJ anatomy, and then the flap is repositioned and sutured. Three to four months later, once the supracrestal tissue attachment is re-established, a second minimally invasive surgical intervention is carried out, if needed, by only minor gingival recontouring to attain the ideal gingival margin contours. This approach is expected to reduce the risk associated with the initial removal of

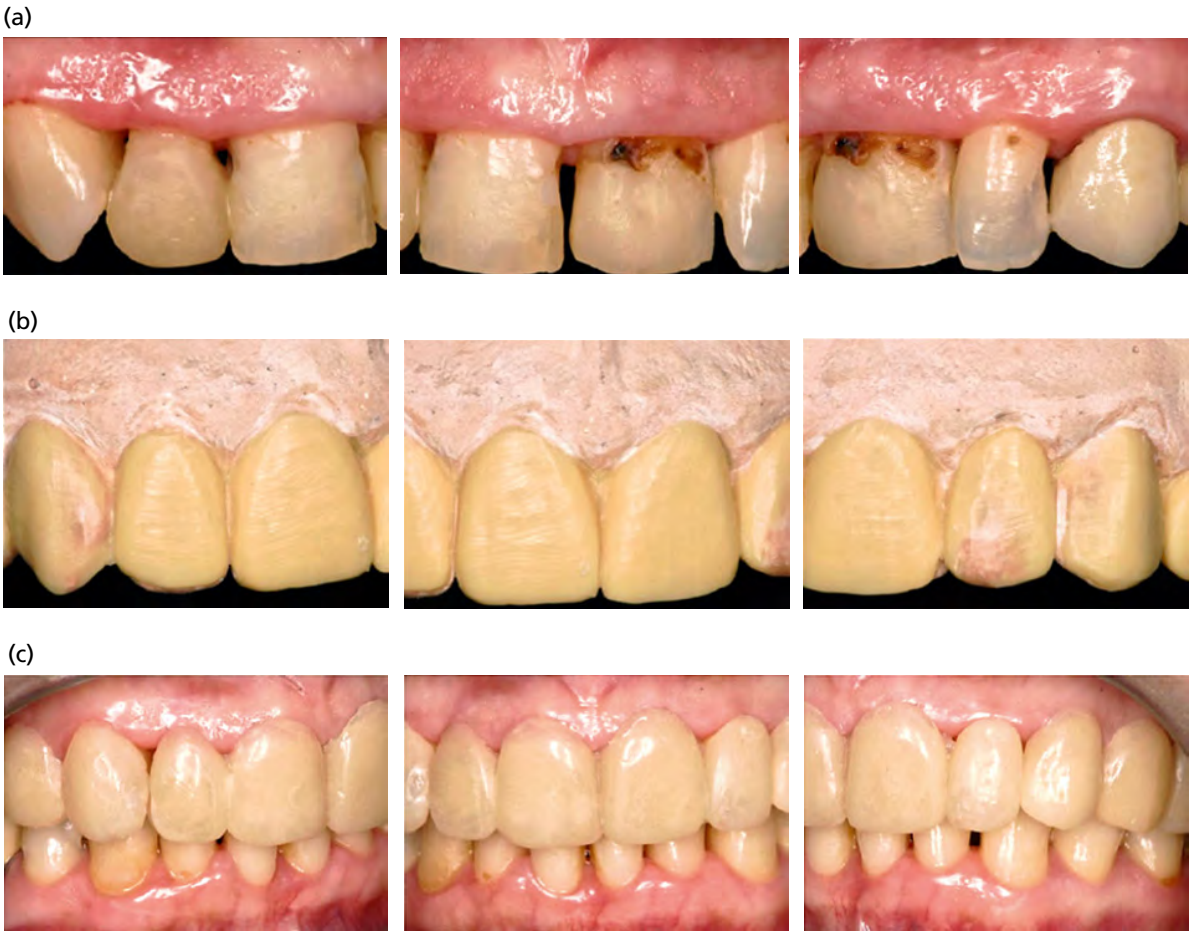

Fig. 39-61 (a) Patient's gummy smile and clear restorative needs. (b) Wax up of the ideal size and shape of the teeth before the crown lengthening procedure. (c) Acrylic mock-up in place with the ideal planned restorations.

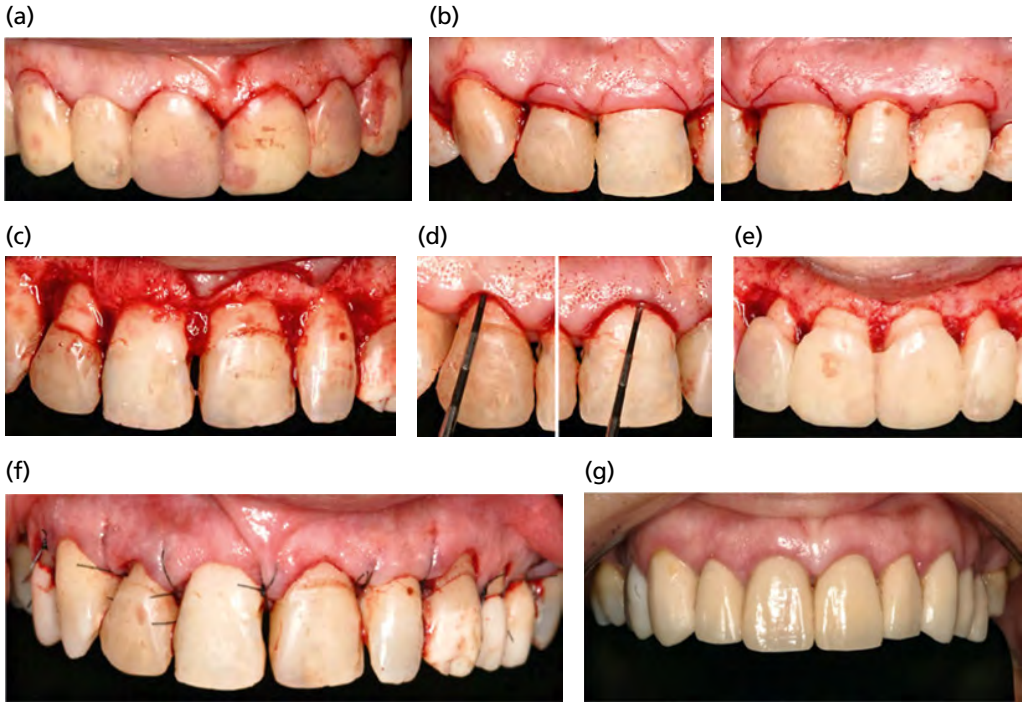

Fig. 39-62 (a) Scalloped first incision is done following the contour of the ideal planned crown (mock-up). (b) Scalloped first incision after removing the mock-up. (c) Available space for supracrestal tissue attachment. (d) Evaluation of the distance between the cementoenamel juntion and the bone crest. (e) Ostectomy to create the ideal space between the mock-up and the bone crest. (f) Suture to adapt the flap to the bone crest. (g) Final result 1 year after the crown lengthening procedure.

soft tissue based on anatomic landmarks that may be difficult to determine with precision, such as the CEJ or the bone crest (Fig. 39-63).

A recent randomized clinical trial comparing the one- versus two-stage CL procedures for esthetic restorative indications reported similar outcomes in terms of the final desired position of the gingival margins, although the two-stage procedure was preferred by the patients and only one third required the secondary minimally invasive procedure (González-Martín *et al*. 2020).

Forced tooth eruption

An alternative technique for gaining clinical crown height by means of orthodontic forced eruption in combination with gingival fiberotomy was described by Pontoriero *et al*. (1987). Fiberotomy is used during the forced tooth eruption procedure when the objective is to retain the crestal bone and the gingival margin at their pretreatment locations. Fiberotomy is usually performed using a scalpel at 7–10-day intervals during the forced eruption to sever the supracrestal connective tissue fibers, thereby preventing the crestal bone from following the root in a coronal direction. If fiberotomy is not carried out and moderate eruptive forces are used, the entire attachment apparatus will move in unison with the tooth. In these situations, once the tooth has reached the intended position and has been stabilized, a full-thickness flap should be elevated and bone recontouring performed to expose sound root structure. For esthetic reasons it is important that the bone and soft tissue levels at adjacent teeth remain unchanged (Fig. 39-64).

Forced tooth eruption can also be used to level and align gingival margins and the crowns of teeth to obtain esthetic harmony. Instead of using surgical procedures to position the gingival margins of unaffected normal teeth apically to the level of a tooth with recession or orthodontic malalignment, the tooth that is malpositioned or has sustained recession is erupted to the level of the normally positioned teeth. The entire attachment apparatus and dentogingival junction will follow the root of the tooth as it is moved coronally.

The forced eruption technique can also be used as a method for reducing pocket depth at sites with angular bony defects (Brown 1973; Ingber 1974, 1976).

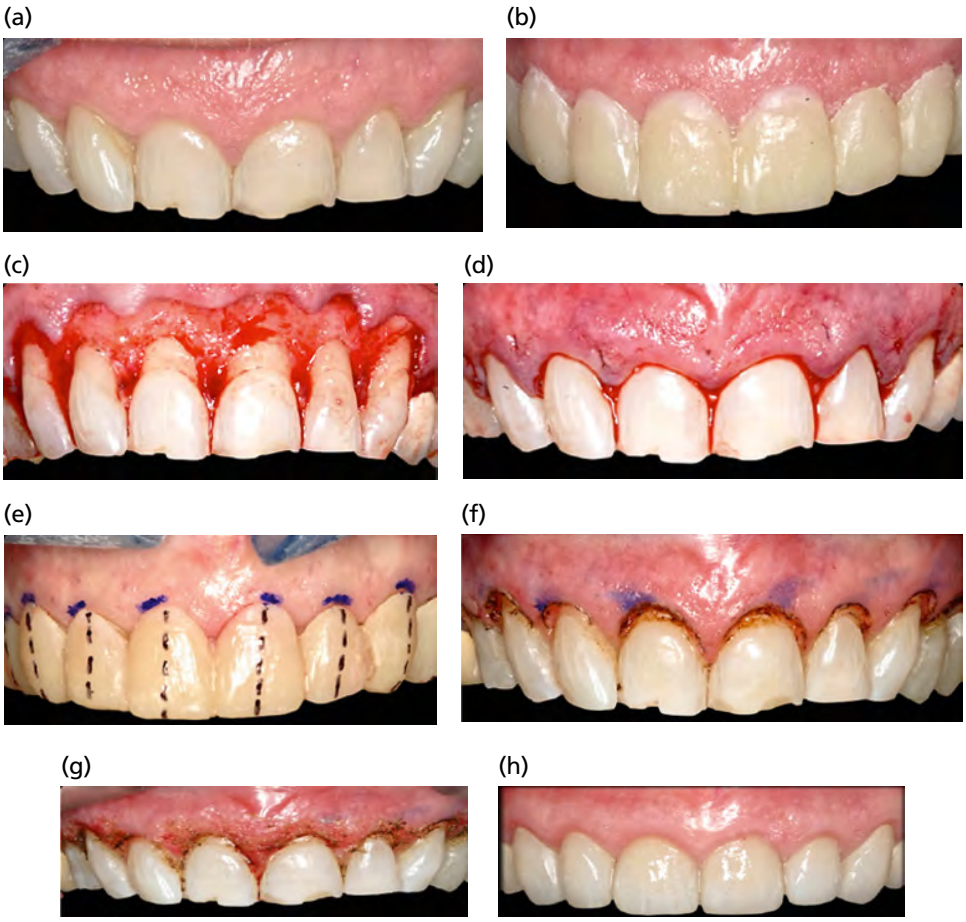

Fig. 39-63 *Two stage crown lengthening procedure*. (a) Preoperative view. (b) Mock-up depicting the contours of the ideal planned crowns. (c) First incision is performed intrasurgically and after raising a full thickness flap the ostectomy is carried out to obtain the ideal supracrestal tissue attachment space. (d) Flaps are repositioned to the same level as presurgery. (e) Six-month postoperatively the mock-up is used to identify whether a gingivectomy should be done to achieve the ideal tooth size and shape. (f) Internal bevel gingivectomy. (g) Gingivoplasty. (h) Final result with the new restoration in place.

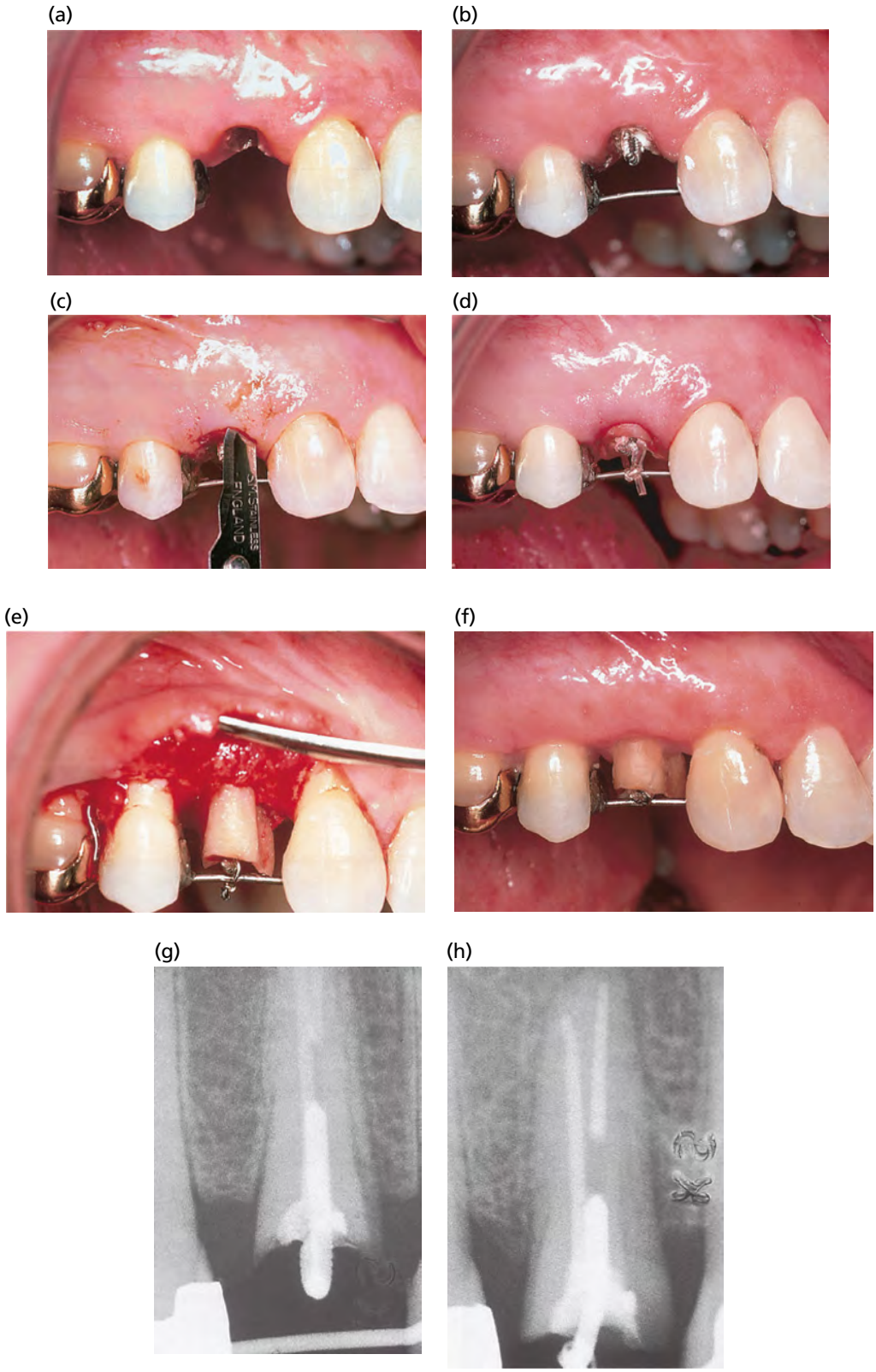

Fig. 39-64 Forced tooth eruption in conjunction with fiberotomy. (a) Buccal view, the fracture on the first premolar extended subgingivally. (b) Soft tooth structure was excavated and a twisted wire with an occlusal hook was temporarily cemented in the root canal. A bar was placed into the amalgam restoration on the premolar and bonded to the lingual surface of the canine. (c, d) Sulcular fiber resection was performed at the mesial half of the tooth to the level of the bone crest. The distal half remained as a control surface. The fiber resection was repeated once a week during the 3-week eruption phase. (e) Tooth was stabilized for 6 weeks, and at that time a full-thickness flap was raised. The bone crest had a "positive" angulation at the distal surface and remained unchanged at the "test" mesial surface. Osseous resection was used to level the bony septum on the distal surface. (f) Ample crown lengthening was obtained, and the gingival margins healed to their former shape and location. (g) Pretreatment radiograph enlarged to show the normal shape of the crests of the interdental septae. (h) Enlargement of the post-eruption radiograph (3 weeks of rapid eruption and 6 weeks of stabilization) to show the "positive" angular crest on the "control" distal side and the unchanged crest on the mesial "test" side. (Source: Courtesy of R. Pontoriero.)

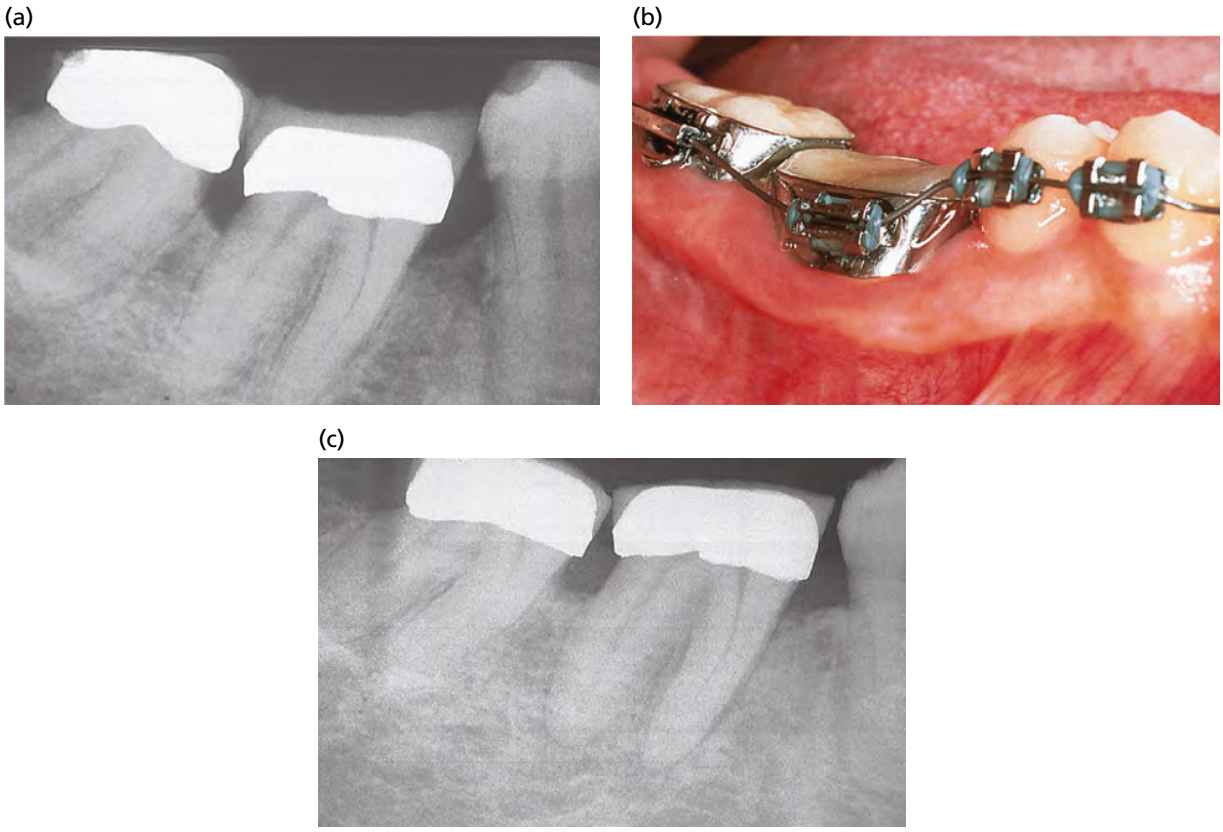

Fig. 39-65 Slow tooth eruption procedure used to level cementoenamel junctions and angular bone crests. (a) Pretreatment radiograph. (b) Nitol wire was used to erupt the molar. (c) Radiograph taken 8 months after the start of treatment. The angular bone defects were leveled.

The angular bony defect at the problem tooth can be reduced, while the attachment level at the adjacent tooth surface remains unchanged (Fig. 39-65).

Forced eruption has the advantage over crown lengthening procedures in that root exposure can be performed without the need for a flap procedure in combination with osseous surgery, which would possibly affect the periodontal tissues of a neighbouring tooth. However, this technique cannot be applied in all situations which require lengthening of the clinical crown, such as prosthetic reconstruction in dentitions with severe attrition.

Gingival preservation at ectopic tooth eruption

Surgical interventions are often indicated for preserving the gingival tissues around teeth erupting ectopically, that is with an eruption position facial to the alveolar process (Fig. 39-66). To create a satisfactory

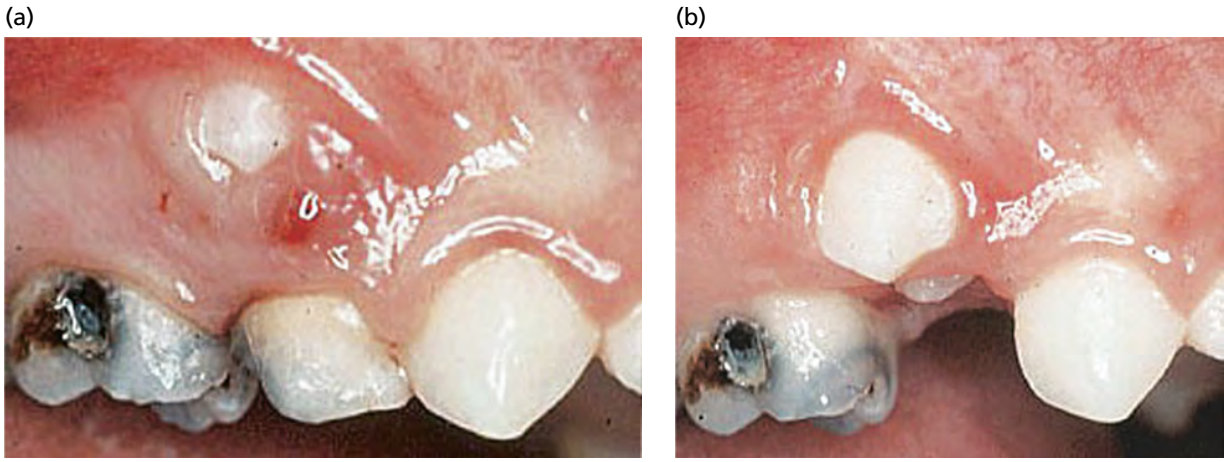

Fig. 39-66 (a, b) Ectopic tooth eruption. The permanent tooth is erupting close to the mucogingival junction. (Source: Courtesy of Professor Giampaolo Pini Prato.)

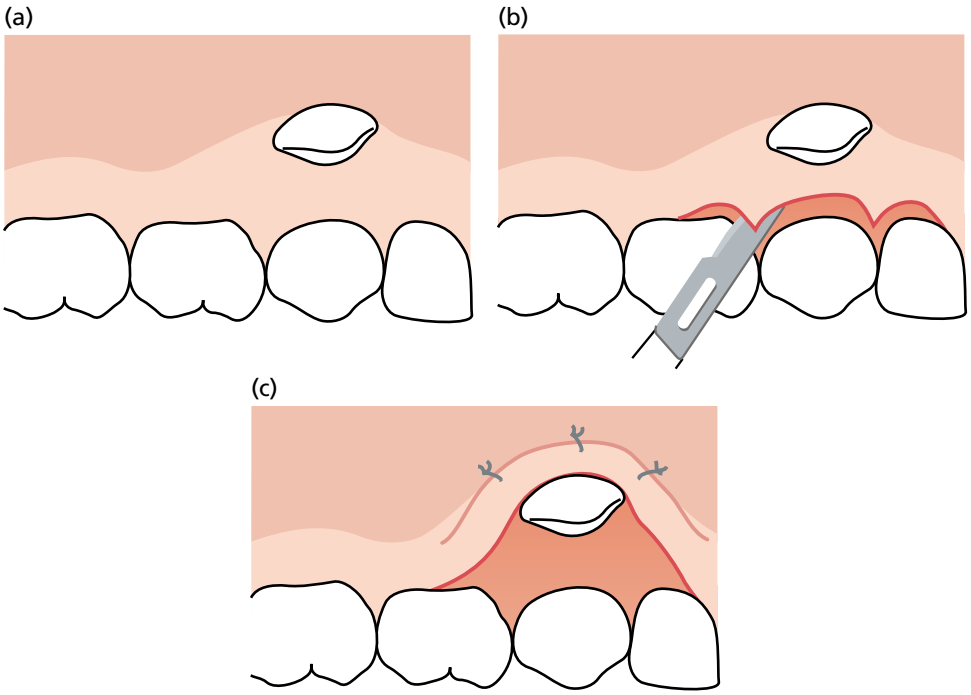

Fig. 39-67 (a–c) Ectopically erupting tooth: double pedicle graft (see text for explanation).

width of the gingiva for the permanent tooth, the tissue entrapped between the erupting tooth and the deciduous tooth is usually utilized as donor tissue (Agudio *et al*. 1985; Pini Prato *et al*. 2000b).

Three different techniques have been described for the interceptive mucogingival treatment of buccally erupting teeth, depending on the distance from the donor site (entrapped gingiva) to the recipient site (area located facially–apically to the erupting permanent tooth) (Agudio *et al*. 1985; Pini Prato *et al*. 2000b):

- *Double pedicle graft* (Fig. 39-67). This flap procedure is indicated when the permanent tooth erupts within the zone of keratinized tissue but close to the mucogingival junction. An intrasulcular incision is performed at the deciduous tooth and extended laterally to the gingival crevice of the adjacent teeth and apically to the erupting permanent tooth. By mobilization of the flap apical to the mucogingival line, the entrapped gingiva can be elevated and transposed for positioning apically to the erupting tooth. Sutures may be placed to secure the position of the gingival tissue facial to the erupting tooth.
- *Apically positioned flap* (Fig. 39-68). When the permanent tooth is erupting apical to the mucogingival junction, vertical releasing incisions have to be placed to allow for apical positioning of the keratinized tissue. Two lateral releasing incisions are made and extended apically beyond the mucogingival junction. An intrasulcular incision is performed at the deciduous tooth and a partial-thickness flap is elevated beyond the ectopically erupting tooth. The mobilized gingival flap is

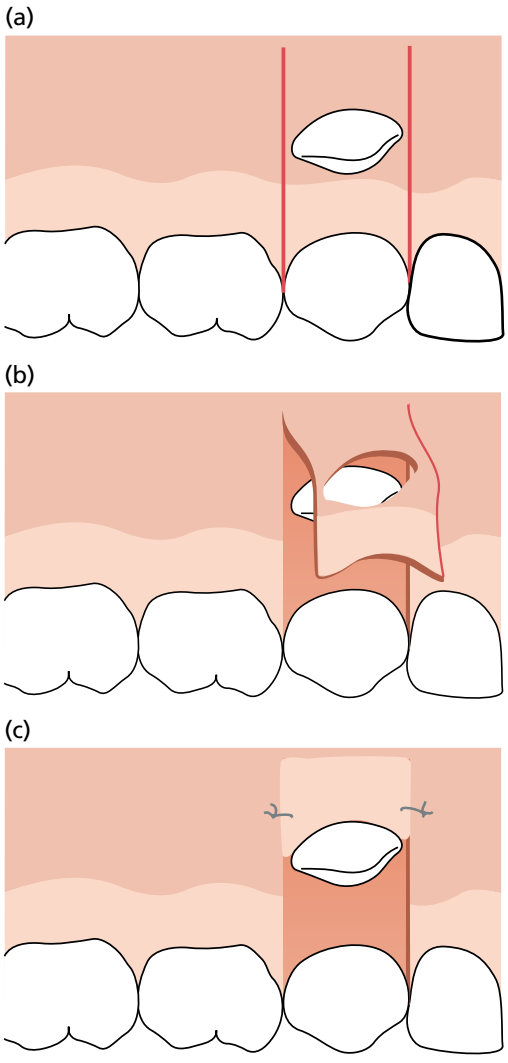

Fig. 39-68 (a–c) Ectopically erupting tooth: apically positioned flap (see text for explanation).

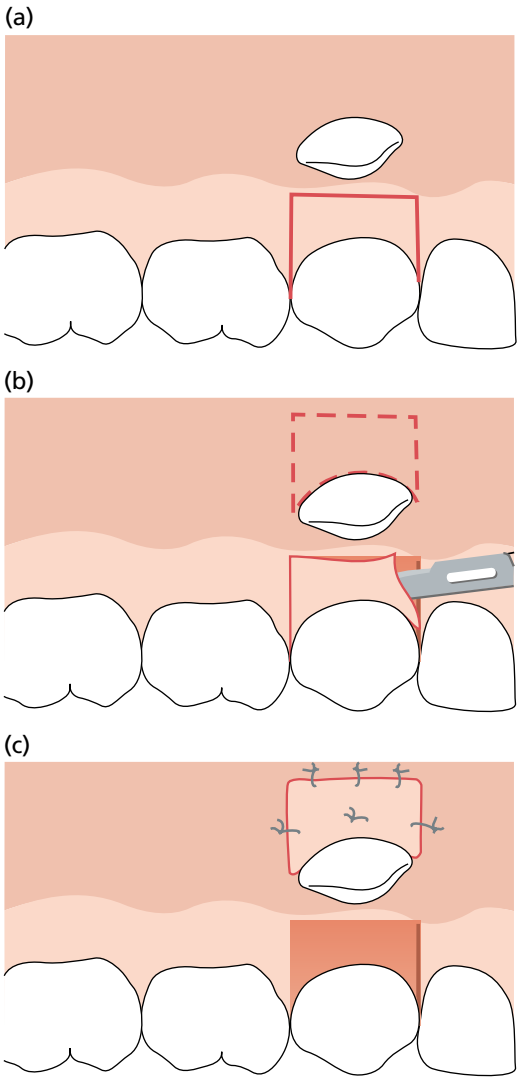

Fig. 39-69 (a–c) Ectopically erupting tooth: free gingival graft (see text for explanation).

moved apical to the erupting tooth and secured in position by sutures.

- *Free gingival graft* (Fig. 39-69). If the tooth is erupting within the alveolar mucosa distant to the mucogingival junction, a free gingival graft procedure may be selected. The entrapped gingiva is removed by a split incision and used as an epithelialized CTG. The free gingival graft is placed at a prepared recipient site facial/apical of the erupting tooth. Careful suturing is performed to secure close adaptation of the graft to the underlying connective tissue bed.

All these procedures have been proven to be effective in establishing a facial zone of gingiva following the alignment of teeth erupting in an ectopic position (Pini Prato *et al*. 2000b, c).

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Part 14: Surgery for Implant Installation

Chapter 40

Timing of Implant Placement

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Introduction

Restorative therapy performed on implant(s) placed in a fully healed and non-compromised alveolar process has high clinical success and survival rates (Pjetursson *et al*. 2004; Jung *et al*. 2012; Pjetursson *et al*. 2014). Currently, however, implants are also being placed in (1) sites with ridge defects of various dimensions, (2) fresh extraction sockets, (3) the area of the maxillary sinus, etc. Although some of these clinical procedures were first described many years ago, their application has only relatively recently become common. Accordingly, one issue of primary interest in current clinical and animal research in implant dentistry includes the study of tissue alterations that occur following tooth loss and the proper timing thereafter for implant placement.

In the optimal case, the clinician will have time to plan for the restorative therapy (including the use of implants) prior to the extraction of one or several teeth. In this planning, a decision must be made whether the implant(s) should be placed immediately after the tooth extraction(s) or if a certain number of weeks (or months) of healing of the soft and hard tissues of the alveolar process should be allowed prior to implant installation. The decision regarding the timing for implant placement, in relation to tooth extraction, must be based on a proper understanding of the structural changes that occur in the alveolar process following the loss of the tooth (teeth). Such adaptive processes are described in Chapter 3.

The removal of single or multiple teeth will result in a series of alterations within the edentulous segment of the alveolar process. Hence, during socket healing, the hard tissue walls of the alveolus will resorb, the center of the socket will become filled with cancellous bone, and the overall volume of the site will become markedly reduced. In particular, the buccal wall of the edentulous site will be diminished not only in the buccolingual/palatal direction but also with respect to its apico-coronal dimension (Pietrokovski & Massler 1967; Schropp *et al*. 2003). In addition to hard tissue alterations, the soft tissue in the extraction site will undergo marked adaptive changes. Immediately following tooth extraction, there is a lack of mucosa and the socket entrance is thus open. During the first weeks following the removal of a tooth, cell proliferation within the mucosa will result in an increase of its connective tissue volume. Eventually, the soft tissue wound will become epithelialized and a keratinized

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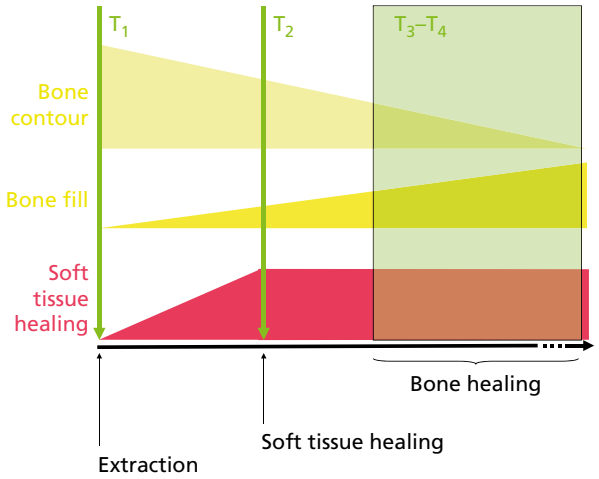

Fig. 40-1 Schematic drawing depicting the changes in the soft and hard tissues following tooth extraction over time. T_1, T_2, T_3, and T_4 represent the four different time points for implant placement.

mucosa will cover the extraction site. The contour of the mucosa will subsequently adapt to follow the changes that occur in the external profile of the hard tissue of the alveolar process. Thus, the contraction of the ridge is the net result of bone loss as well as loss of connective tissue. Figure 40-1 illustrates the tissue alterations described above. It is obvious that no ideal time point exists following the removal of a tooth, when the extraction site has (1) maximum bone fill in the socket and (2) voluminous mature covering mucosa. More recent studies have found an influence of tooth type, intact or deficient buccal bone plates, and the thickness of the buccal bone plate on the degree of ridge alterations following tooth extraction (Chen & Darby 2017; for review see Avila-Ortiz *et al*. 2019). Incisors showed more volume loss than canines and premolars. Intact buccal bone plates showed less volume loss than dehisced and fenestrated bone plates. Finally, thick bone plates were associated with less bone loss than thin bone plates.

A consensus report was published in 2004 describing issues related to the timing of implant placement in extraction sockets (Hammerle *et al*. 2004). Attempts had previously been made to identify the advantages and disadvantages of early, delayed, and late implant placements. Hämmerle and co-workers considered it necessary, however, to develop a new concept (classification) that incorporated the growing knowledge in this field of implant dentistry. This new classification took into consideration data describing structural alterations that occur following tooth extraction as well as knowledge derived from clinical observations.

The classification presented in Table 40-1 was introduced in the consensus report. Important aspects included:

- In clinical practice, the decision to place an implant following tooth extraction is usually determined by some soft and hard tissue characteristics of the healing socket. Healing does not necessarily follow rigid time frames, and may vary according to site and patient factors.
- To avoid temporal-based descriptions, this new classification used numerical descriptors – types 1, 2, 3, and 4 – that reflect the conditions of the hard and soft tissues:
  - Type 1 placement: the implant is placed immediately following the extraction of a tooth
  - Type 2 placement: the implant is placed in a site where the soft tissues have healed and a mucosa is covering the socket entrance
  - Type 3 placement: the implant is placed in an extraction site at which substantial amounts of new bone have formed in the socket
  - Type 4 placement: the implant is placed in a fully healed ridge.
- It was further recognized that there is a clear separation between hard tissue healing and soft tissue healing within and around the extraction socket.

This classification has since been refined (Chen *et al*. 2009).

Advantages and disadvantages of the various timings are shown in Table 40-1.

Two methods for flap closure at implant sites have been described. One approach requires primary wound closure, whereas the other one allows for a transmucosal position of the implant or the healing cap. No differences regarding survival rates and interproximal bone levels were found when these two methods were compared in a split-mouth design (Ericsson *et al*. 1997; Astrand *et al*. 2002; Cecchinato *et al*. 2004; Guarnieri *et al*. 2019). These studies did not, however, analyze in detail the differences between submerged or transmucosal healing in sites of high esthetic importance. Hence, not only the width of the gap but also the width of the alveolar process is a parameter to be considered during treatment planning.

A review analyzed the clinical outcomes of implants placed according to the timing scheme described above (Chen & Buser 2009). Based on the analysis of 91 studies, it was found that bone augmentation procedures were more effective in type 1, 2, and 3 placements than in type 4 placement. Furthermore, it appeared that recession of the facial mucosal margin was more frequent when implants were placed according to the type 1 timing.

Type 1 placement as part of the same surgical procedure as and immediately following tooth extraction

Ridge alterations in conjunction with implant placement

It has become common practice to insert implants immediately after the removal of teeth that were

Table 40-1 Classification of types 1–4 implant placements, and advantages and disadvantages of each type.

Classification	Definition	Advantages	Disadvantages
Type 1	Implant placement as part of the same surgical procedure as and immediately following tooth extraction	Reduced number of surgical procedures Reduced overall treatment time Optimal availability of existing bone	Site morphology may complicate optimal placement and anchorage Thin tissue phenotype may compromise optimal outcome Potential lack of keratinized mucosa for flap adaptation Adjunctive surgical procedures may be required Technique-sensitive procedure
Type 2	Complete soft tissue coverage of the socket (typically 4–8 weeks)	Increased soft tissue area and volume facilitates soft tissue flap management Allows resolution of local pathology to be assessed	Site morphology may complicate optimal placement and anchorage Increased treatment time Varying amounts of resorption of the socket walls Adjunctive surgical procedures may be required Technique-sensitive procedure
Type 3	Substantial clinical and/or radiographic bone fill of the socket (typically 12–16 weeks)	Substantial bone fill of the socket facilitates implant placement Mature soft tissues facilitate flap management	Increased treatment time Adjunctive surgical procedures may be required Varying amounts of resorption of the socket walls
Type 4	Healed site (typically >16 weeks)	Clinically healed ridge Mature soft tissues facilitate flap management	Increased treatment time Adjunctive surgical procedures may be required Large variation in available bone volume

scheduled for extraction for various reasons. Over the years, many claims have been made regarding the advantages of immediate implant placement (Chen *et al*. 2004). These advantages include easier definition of the implant position, reduced number of visits to the dental office, reduced overall treatment time and costs, preservation of bone at the site of implantation, optimal soft tissue esthetics, and enhanced patient acceptance (Werbitt & Goldberg 1992; Barzilay 1993; Schwartz-Arad & Chaushu 1997b; Mayfield 1999; Hammerle *et al*. 2004).

It was proposed that placement of an implant in a fresh extraction socket may stimulate bone tissue formation and osseointegration, and hence counteract the adaptive alterations that occur following tooth extraction. In other words, type 1 implant installation may allow the preservation of bone tissue of the socket and the surrounding jaw. It was in fact recommended (e.g. Denissen *et al*. 1993; Watzek *et al*. 1995; for review see Chen *et al*. 2004) that implant installation should be performed directly following tooth extraction as a means to avoid bone atrophy.

Clinical studies in humans (Botticelli *et al*. 2004; Covani *et al*. 2004) and experiments in dogs (Araújo & Lindhe 2005; Araújo *et al*. 2006a, b) have examined the influence of implant installation in the fresh extraction socket on bone modeling and remodeling in the surgical site.

Botticelli *et al*. (2004) examined hard tissue alterations that occurred in the alveolar process during a 4-month period of healing following implant placement in fresh extraction sockets. Eighteen subjects (21 extraction sites) with moderate chronic periodontitis were studied. The treatment planning of all 18 subjects called for extraction of single teeth, and restoration by means of implants in the incisor, canine, and premolar regions of the dentition. Following sulcus incisions, full-thickness mucosal flaps were raised and the tooth was carefully mobilized and removed with forceps. The site was prepared for implant installation with pilot and twist drills. The apical portion of the socket was pretapped. A non-cutting solid-screw implant with a medium rough surface topography was installed. The implant was positioned in such a way that the marginal level of its rough surface portion was located apical to the marginal level of the buccal and lingual/palatal walls of the socket (Fig. 40-2a). After implant installation (1) the distance between the implant and the inner and outer surface of the buccal and/or lingual bone plates and (2) the width of the marginal gap that was present between the implant and the buccal, lingual, mesial, and distal bone walls were determined with the use of sliding calipers. The soft tissue flaps were replaced and the implants were "semi-submerged" during healing (Fig. 40-2b). After 4 months of healing, a surgical

re-entry procedure was performed (Fig. 40-2c). The clinical measurements were repeated so that alterations that had occurred during healing regarding (1) the thickness and height of the buccal and lingual/palatal socket walls and (2) the width of the marginal gap could be calculated.

Figure 40-3a shows an extraction socket immediately after the removal of a maxillary canine tooth. At re-entry it was realized that the marginal gap had completely resolved. Furthermore, the thickness of the buccal as well as the palatal bone walls had markedly reduced (Fig. 40-3c, d). In Fig. 40-3d, the implant surface can be seen through the very thin remaining buccal bone wall.

Another site from this clinical study is shown in Fig. 40-4. The first maxillary premolar (tooth 14) was removed (Fig. 40-4a) and one implant was placed in the palatal socket of the fresh extraction site. A second implant was placed in the healed edentulous ridge and in position 15 (Fig. 40-4b). At re-entry, it was observed that (1) the marginal gap had completely resolved and (2) the distance between the implant and the outer surface of the buccal bone plate had markedly reduced (Fig. 40-4c).

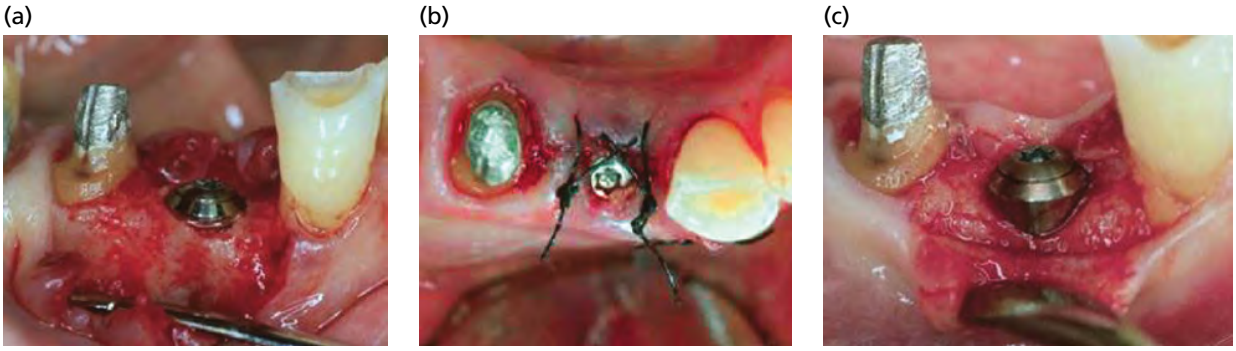

Fig. 40-2 (a) Implant position in the fresh extraction socket. (b) Flaps replaced and sutured. (c) Implant site after 4 months of healing (buccal view).

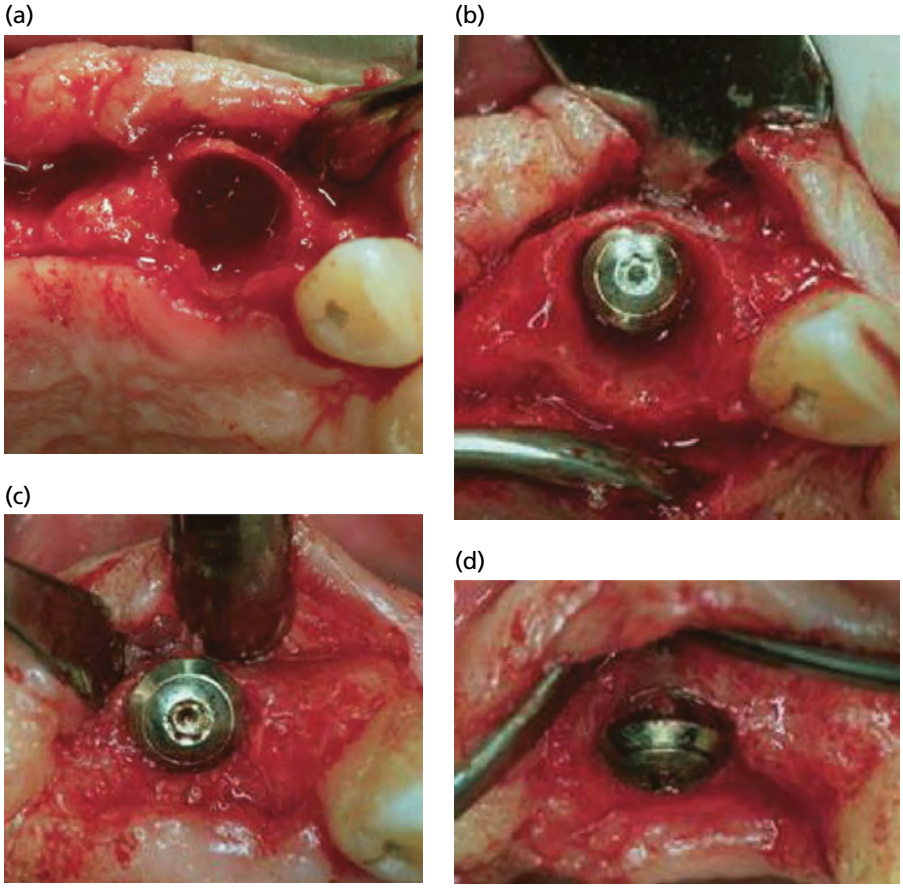

Fig. 40-3 (a) Alveolar socket of a maxillary canine. (b) Implant position in the fresh extraction socket. (c) Implant site after 4 months of healing (occlusal view). (d) Implant site after 4 months of healing (buccal view). Note the very thin bone covering the buccal aspect.

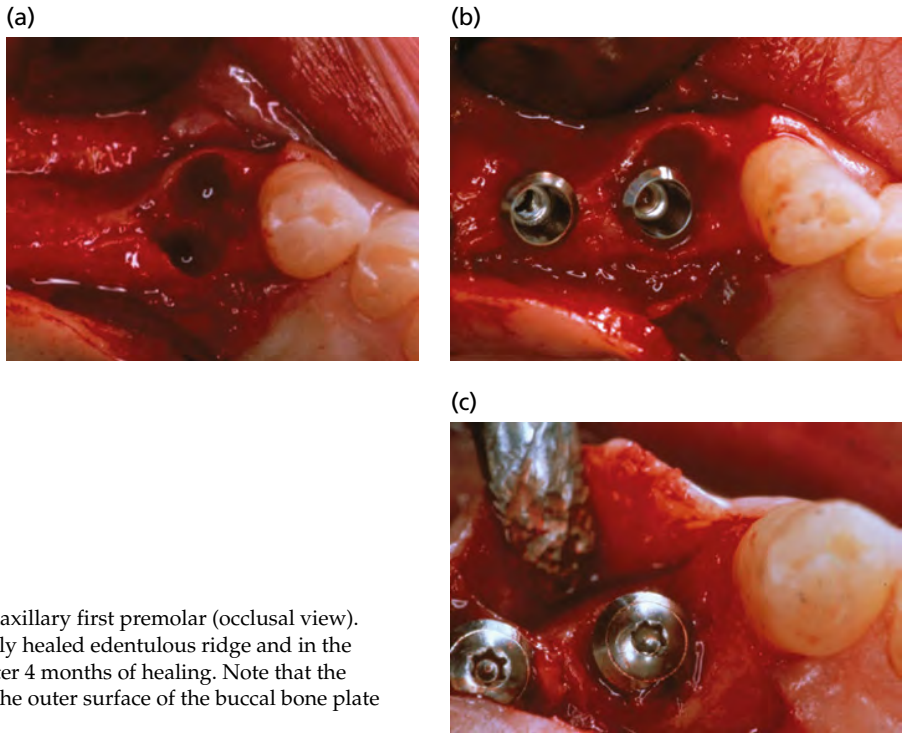

Fig. 40-4 (a) Alveolar socket of a maxillary first premolar (occlusal view). (b) Implants placed in the previously healed edentulous ridge and in the alveolar socket. (c) Implant sites after 4 months of healing. Note that the distance between the implant and the outer surface of the buccal bone plate was markedly reduced.

Botticelli *et al*. (2004) reported that during the 4 months of healing following tooth extraction and implant installation practically all marginal gaps had resolved. At the time of implant placement, the mean distance (18 subjects, 21 sites) between the implant and the outer surface of the buccal bone wall was 3.4 mm, while the matching dimension on the lingual/palatal aspect was 3.0 mm. At re-entry after 4 months, the corresponding dimensions were 1.5 mm (buccal) and 2.2 mm (lingual). In other words, the reduction of the buccal dimension was 1.9 mm (56%), while the equivalent reduction of the lingual dimension was 0.8 mm (27%). The findings by Botticelli *et al*. (2004) strongly indicate that implant placement in a fresh extraction socket may, in fact, not prevent the physiologic modeling/remodeling that occurs in the ridge following tooth removal.

In a randomized controlled clinical study, parallel-walled and conical implants exhibiting modified medium rough surfaces were placed immediately into 93 extraction sockets of maxillary non-molar teeth (Sanz *et al*. 2010). Detailed clinical measurements taken at implant placement and 16 weeks thereafter assessed the changes in the relationship between the bone of the socket and the implant surface. A pronounced reduction of the buccal bone dimension occurred over this time period. A smaller reduction of external bone dimension was observed at the lingual aspect. No differences were found between the parallel-walled and conical implants with respect to reduction of the ridge contour. In contrast to the reduction of the external dimensions of the ridge, the gaps between the walls of the socket and the implant surface at the time of placement had partially been filled with newly formed bone at the 16-week follow-up examination (Huynh-Ba *et al*. 2010; Sanz *et al*. 2010).

In a subsequent paper analyzing the same patient groups, it was found that the bone fill of the gap between the implant and the bone walls of the socket as well as the maintenance of the buccal bone height were more favorable at premolar as compared with canine and incisor sites (Ferrus *et al*. 2010; Tomasi *et al*. 2010). Furthermore, the thickness of the buccal bone wall and the dimension of the gap described above favorably influenced the amount of bone fill during the 4-month healing period. A 3-year follow-up examination reported minimal implant failures and stable soft and hard tissue conditions in both groups of implants (Sanz *et al*. 2014).

In order to study the bone modeling/remodeling that occurs in the fresh extraction site following implant placement in more detail, Araújo and Lindhe (2005) used histologic means to determine the magnitude of the dimensional alterations that occurred in the alveolar process following the placement of implants in fresh extraction sockets in the Beagle dog. Buccal and lingual full-thickness flaps were elevated in both quadrants of the mandible. The distal roots of the third and fourth premolars were removed (Fig. 40-5a). In the right jaw quadrants, implants with a medium rough surface were placed in the sockets so that the marginal border of the rough surface was below the buccal and lingual bone margin (Fig. 40-5b). The flaps were replaced to allow a "semi-submerged" healing (Fig. 40-5c). In the left jaws, the corresponding sockets were left without implantation and the extraction sockets

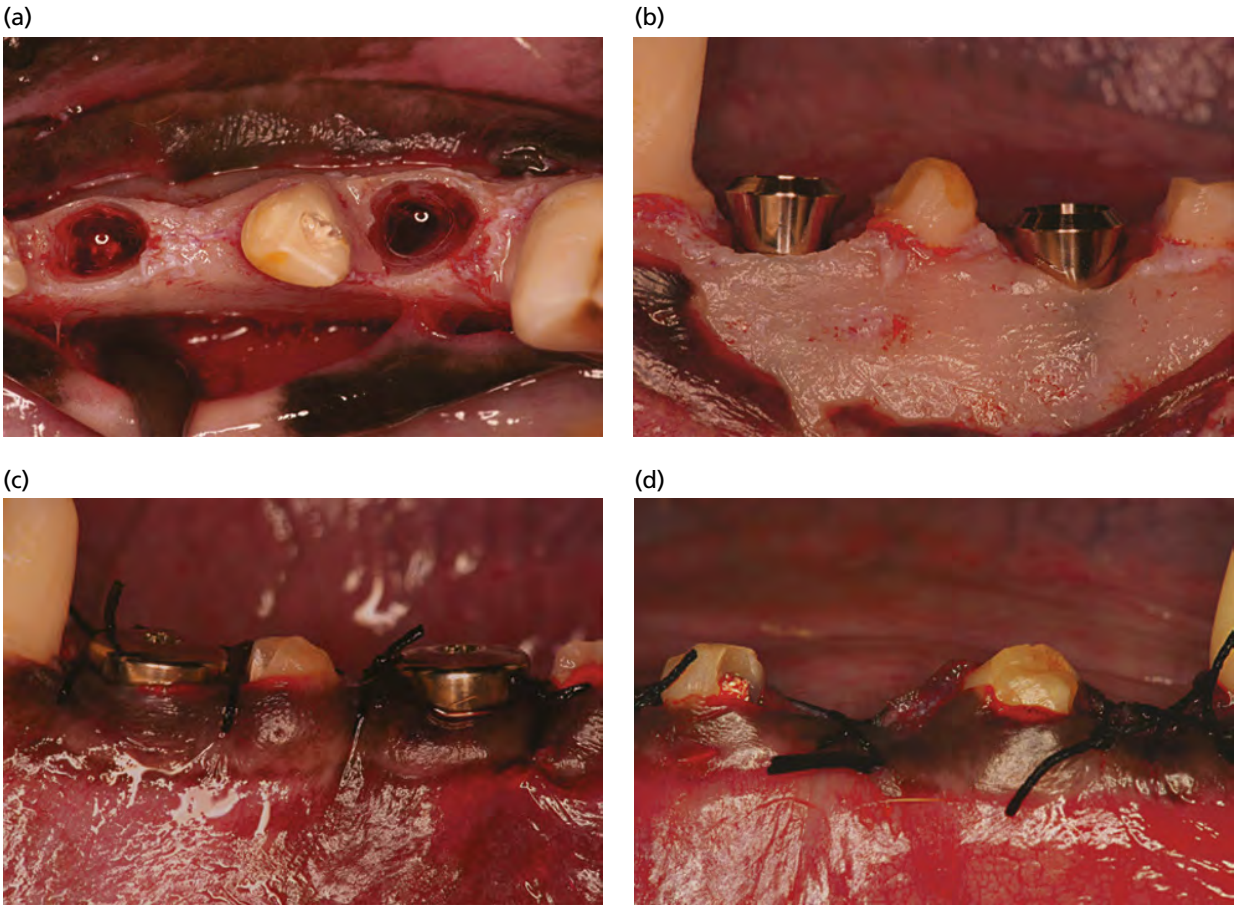

Fig. 40-5 (a) Mandibular premolar site (in a dog experiment) from which the distal root of the fourth premolar was removed. (b) In the test side of the mandible, the implant was placed in the socket in such a way that the rough surface marginal limit was flush with the bone crest. (c) Mucosal, full-thickness flaps were replaced and sutured to allow a "semi-submerged" healing. (d) On the contralateral side of the mandible, the sockets were left without implantation.

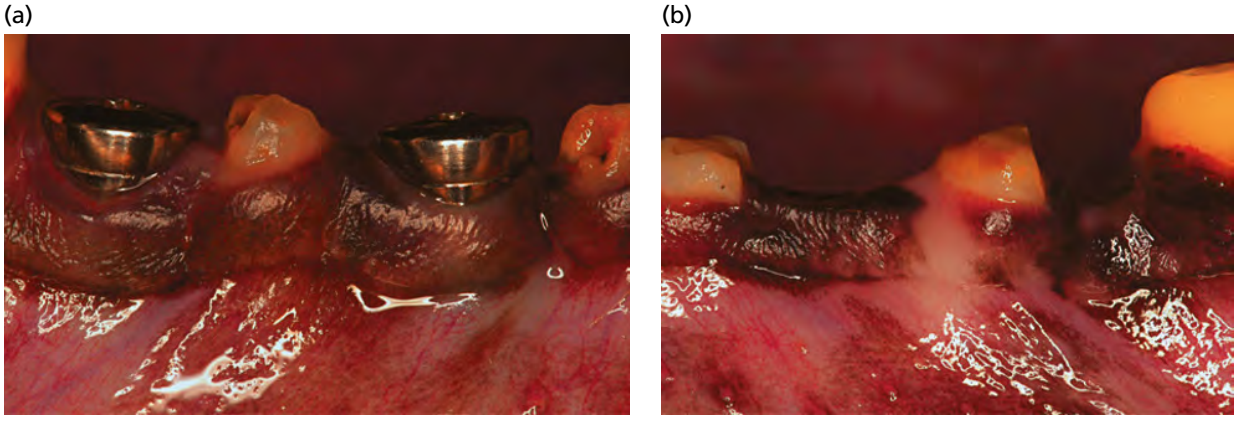

Fig. 40-6 (a) Implant and (b) edentulous sites after 6 months of healing.

were fully submerged under the mobilized flaps (Fig. 40-5d). After 3 months, the mucosa at the experimental sites in the right and left jaw quadrants appeared to be properly healed (Fig. 40-6). The animals were euthanized and tissue blocks containing the implant sites and the edentulous socket sites were dissected and prepared for histologic examination. Figure 40-7 shows a buccolingual section of one edentulous site after 3 months of healing. Newly formed bone covers the entrance of the socket. The lamellar bone of the buccal cortical plate is located about 2.2 mm apical to its lingual counterpart. Figure 40-8a presents a similar section from an implant site in the same dog. The marginal termination of the buccal bone plate is located about 2.4 mm apical to the lingual crest. In other words, the placement of an implant in the fresh extraction socket failed to influence the process of modeling that occurred in the hard tissue walls of the socket following tooth removal. Thus, after 3 months of

healing the amount of reduction of the height of the buccal bone wall (in comparison to the lingual bone alteration) was similar at the implant sites and the edentulous sites. At 3 months, the vertical discrepancy between the buccal and lingual bone margins was >2 mm in both categories of sites (edentulous sites 2.2 mm, implant sites 2.4 mm).

In a follow-up experiment in the dog, Araújo *et al*. (2006a) studied whether osseointegration, once established following implant placement in a fresh extraction socket, could be lost as a result of continued tissue modeling of the bone walls during healing. As was the case in their previous study (Araújo & Lindhe 2005), the distal roots of the third and fourth premolars in both quadrants of the mandible were removed following flap elevation. Implants were installed in the fresh extraction sockets, and initial stability of all implants was secured. The flaps were replaced and "semi-submerged" healing of the implant sites was allowed. Immediately following flap closure, biopsies were obtained from two dogs, while in five dogs healing periods of 1 month and 3 months were permitted prior to biopsy. Figure 40-9a shows a buccolingual aspect of an extraction site immediately after implant installation. Contact was established between the pitch on the surface of the implant body and the walls of the socket. A coagulum resided in the void between the contact regions (Fig. 40-9b) and also in the marginal gap. In sections taken after 4 weeks of healing, it was observed that this void had become filled with woven bone that made contact with the rough surface part of the implant (Fig. 40-10). In this 4-week interval, (1) the buccal and lingual bone walls

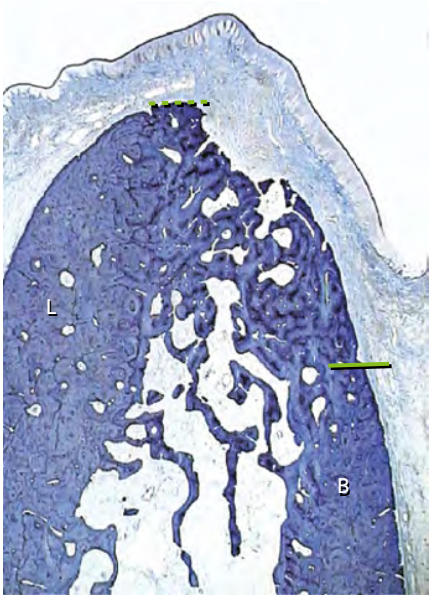

Fig. 40-7 Buccolingual section of the edentulous site. Note that the remaining buccal crest (continuous line) is located far below the lingual counterpart (dotted line). B, buccal aspect; L, lingual aspect.

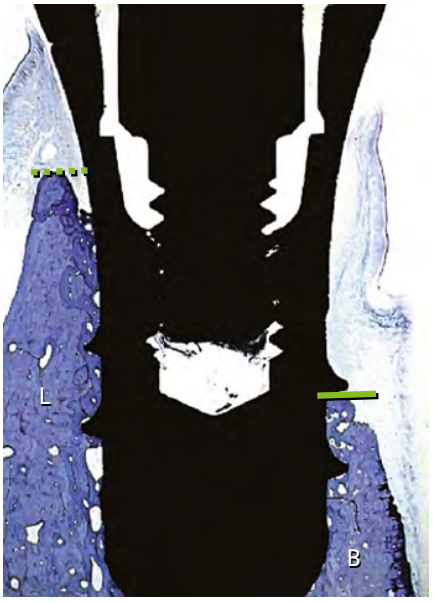

Fig. 40-8 Buccolingual section of the implant site. Note that the remaining buccal crest (continuous line) is located far below the lingual counterpart (dotted line). B, buccal aspect; L, lingual aspect.

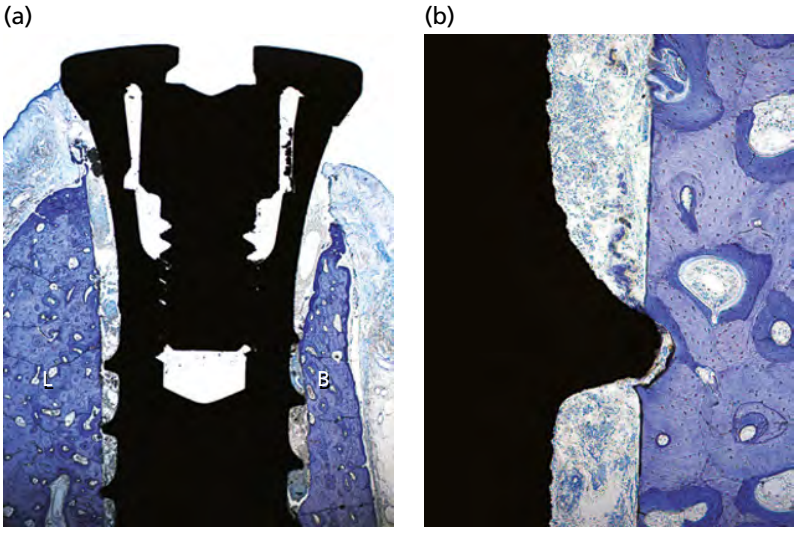

Fig. 40-9 (a) Buccolingual section of an extraction site immediately after implant installation. (b) Contact was established between the pitch on the surface of the implant body and the walls of the socket. B, buccal aspect; L, lingual aspect.

had undergone marked surface resorption, and (2) the height of the thin buccal hard tissue wall had been reduced. In the interval between 4 weeks and 12 weeks of healing, the buccal bone crest shifted further in an apical direction (Fig. 40-11). The woven bone at the buccal aspect that in the 4-week sample made contact with the implant in the marginal gap region had modeled and only fragments of this bone remained (Fig. 40-11c). At the end of the study, the buccal bone crest was located >2 mm apical to the marginal border of the rough implant surface.

These findings demonstrate that the bone (woven bone)-to-implant contact that was established during the early phase of socket healing following implant installation was in part lost when the buccal bone wall underwent continued atrophy. It is obvious, therefore, that the alveolar process following tooth extraction (loss) will adapt to the altered functional demands by atrophy and that an implant, in this respect, is unable to substitute for the tooth. The clinical problem with type 1 placement is that the bone loss will frequently cause the buccal portion of the implant to gradually lose its hard tissue coverage, and that the metal surface may become visible through a thin peri-implant mucosa and cause esthetic concerns (Fig. 40-12).

The question now arises whether it is possible to overcome this problem. This issue was studied in a Beagle dog experiment by Araújo *et al*. (2006b). The

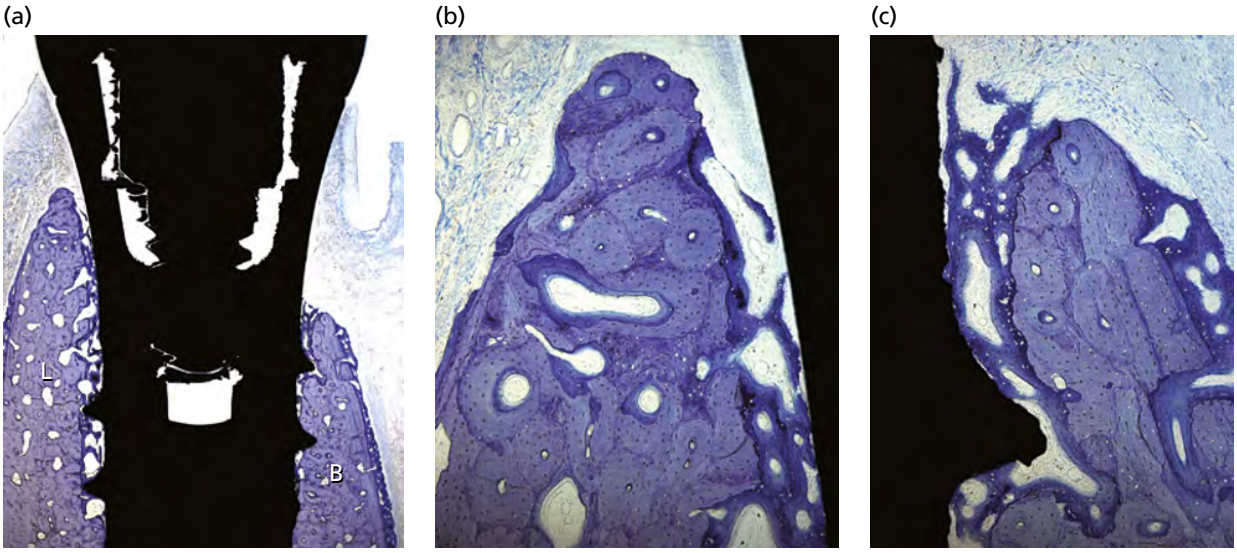

Fig. 40-10 (a) Buccolingual section 4 weeks after implant installation. The void between the implant surface and the bone wall was completely filled with newly formed bone in both lingual (b) and buccal (c) aspects. B, buccal aspect; L, lingual aspect.

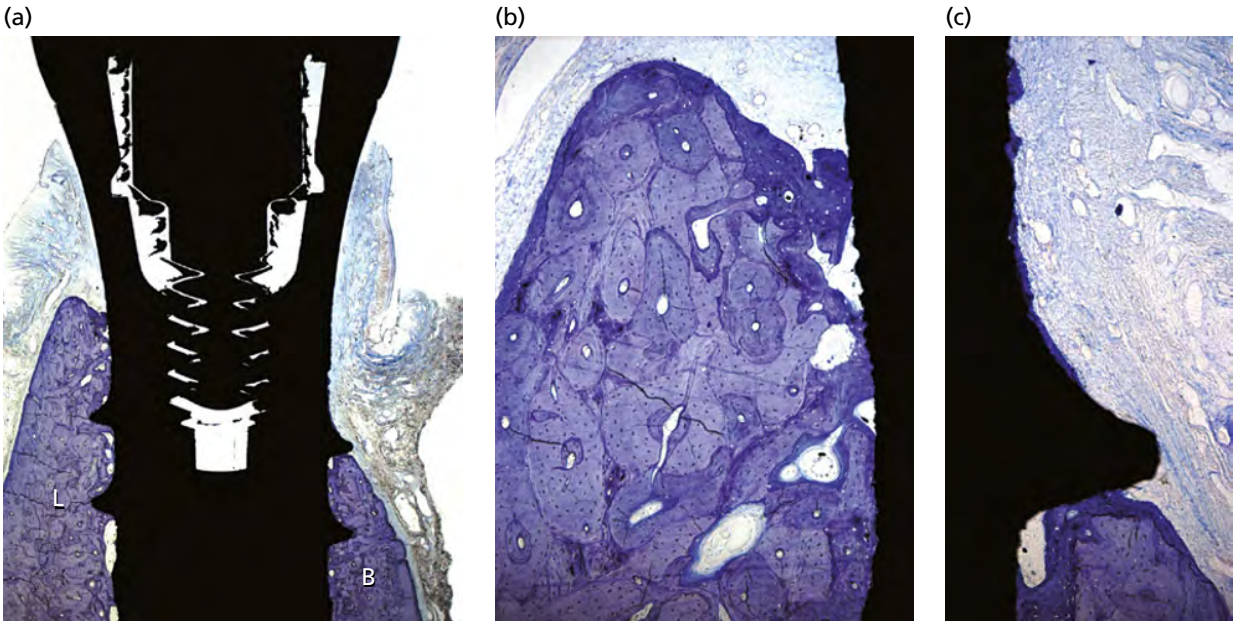

Fig. 40-11 (a) Buccolingual section 12 weeks after implant installation. Note that the buccal bone crest shifted in an apical direction and fragments of it can be seen on the denuded implant surface (c). The lingual bone crest, however, remained stable (b). B, buccal aspect; L, lingual aspect.

distal root of the third mandibular premolar and the distal root of the first mandibular molar were removed and implants placed in the fresh extraction sockets. The third premolar socket in this dog model is comparatively small, and hence the implant inserted exhibiting a diameter of 4.1 mm occupied most of the hard tissue wound (Fig. 40-13). During healing, resorption of the buccal bone wall occurred (Fig. 40-14) and >2 mm of the marginal portion of the implant became exposed to peri-implant mucosa.

The molar socket, on the other hand, is very large (Fig. 40-15) and hence after placement of an implant with a diameter of 4.1 mm, a >1-mm wide marginal gap occurred between the metal body and the bone walls (Fig. 40-16b). Primary stability of the implant was achieved through contacts between the metal body and the bone in the apical (periapical) portions of the socket. During the early phase of healing, this gap in the molar site became filled with woven bone. In the interval during which the buccal bone wall underwent programmed atrophy, the newly formed bone in the gap region maintained osseointegration and continued to cover all surfaces of the implant (Fig. 40-16a, b).

Conclusion: The data reported illustrate an important biologic principle. Atrophy of the edentulous ridge will occur following tooth loss. This contraction of the ridge cannot be prevented by placing an implant in the fresh extraction socket. The atrophy includes a marked reduction of the width and height of both the buccal and lingual bone plates; in particular, the buccal bone plate will undergo marked change. To some extent the problem with buccal bone resorption can be overcome by placing the implant deeper into the fresh socket and in the lingual/palatal portion of the socket.

As a consequence of the above-described healing, bone regeneration procedures may be required to improve or retain bone volume and the buccal contour at a fresh extraction site. Such bone augmentation is sometimes mandatory in the esthetic area.

Stability of implant

Another issue with type 1 (and also type 2) placement is the anchorage of the implant to obtain primary stability in a position in the jaw that will enable

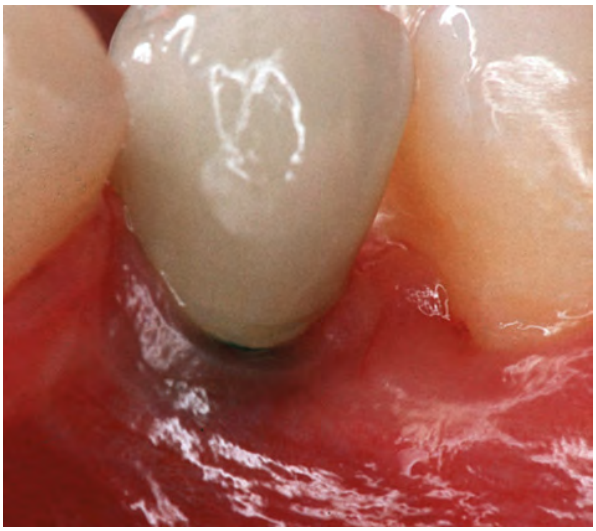

Fig. 40-12 An implant lacking the buccal bone. Note that the metal surface had become visible through the thin mucosa.

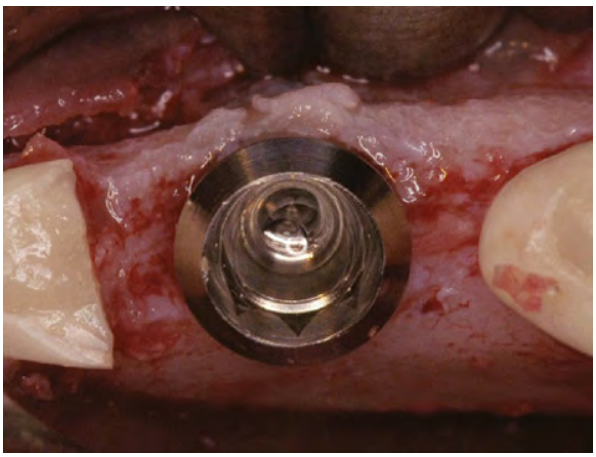

Fig. 40-13 Implant installation in the narrow, third premolar alveolar socket.

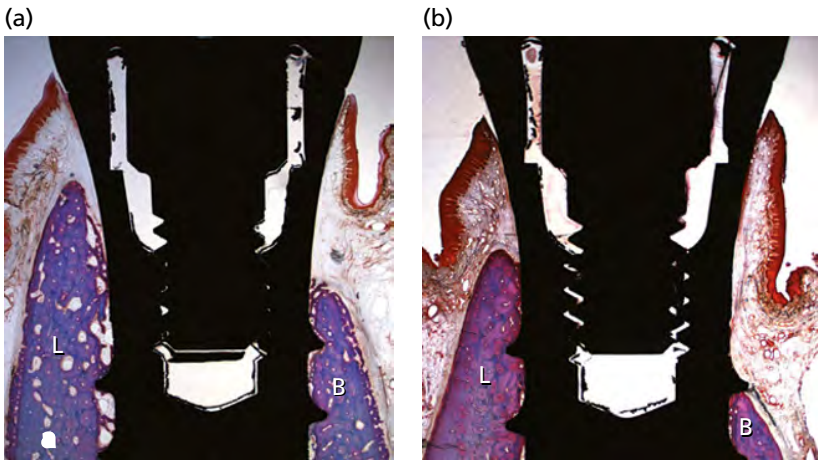

Fig. 40-14 Buccolingual section of the healed premolar sites (a) 4 and (b) 12 weeks after implant installation. B, buccal aspect; L, lingual aspect.

the subsequent restoration to meet high demands regarding esthetics and function. In most cases of type 1 placement, the implants are fixed in native bone apical to the alveolus (Fig. 40-17). Additional retention may be achieved by anchoring the implant in the bony structures of the alveolar walls or interradicular septa.

Another critical issue with type 1 placement is related to how to deal with the presence of periapical pathology at the tooth to be extracted. In a controlled clinical trial, it was observed that primary stability of some implants in a type 1 procedure could not be achieved (Siegenthaler *et al*. 2007). In this study, implants were inserted to replace teeth either exhibiting periapical pathology (test) or presenting healthy periapical conditions (control) (Siegenthaler *et al*. 2007). Apart from the finding that in four implant sites in the test group and one in the control group no implants could be placed due to an unfavorable bone morphology that precluded primary implant stability, no differences were found between the test and the control groups. At 5-year follow-up of the same group of patients, 100% implant survival was recorded in both groups (Jung *et al*. 2013). Furthermore, low levels of marginal bone loss and favorable clinical parameters with no statistically significant difference between the implants in the test and control groups were observed. Focusing on anterior and premolar sites in the maxilla similarly favorable outcomes were earlier reported (Lindeboom *et al*. 2006). In this study sites showing radiographic signs of periapical pathology were randomized into two groups of 25 each. These sites received implants placed either immediately or 3 months after tooth extraction. During the insertion procedure a minimum torque of 25 Nm was required as an inclusion criterion. In contrast to the above study the survival rate in the immediate group reached 92%, whereas it reached 100% in the control group at the 1-year follow-up examination. No differences were found in the other clinical and radiographic parameters assessed except for a more pronounced recession of the midfacial mucosa in the immediate placement group (Lindeboom *et al*. 2006).

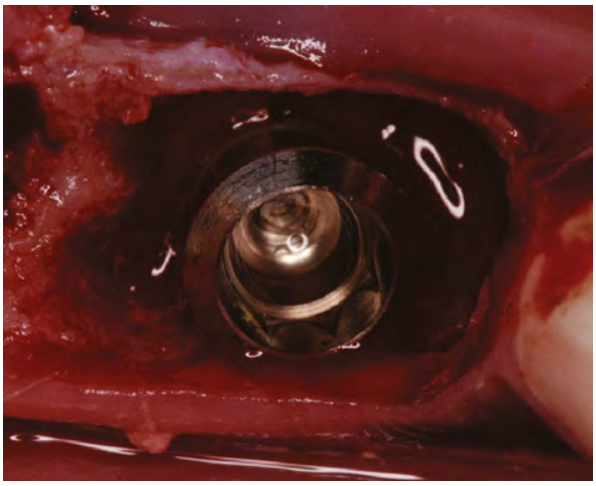

Fig. 40-15 Implant installation in the wide, first molar alveolar socket.

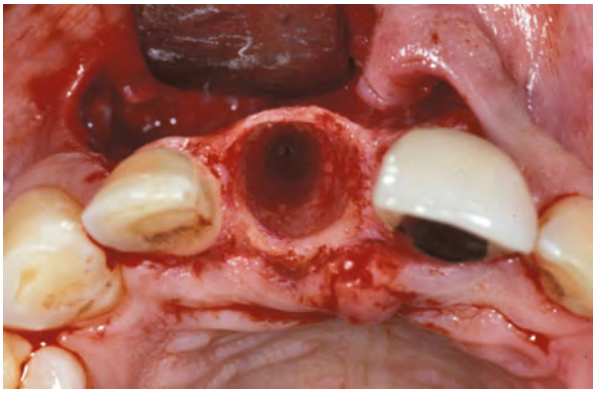

Fig. 40-17 Type 1 implant placement provides optimal availability of existing bone contours. Note the presence of a thin buccal bone plate. Anchorage of an implant can be achieved by engaging the bone apical to the apex of the extracted tooth and the palatal wall of the socket.

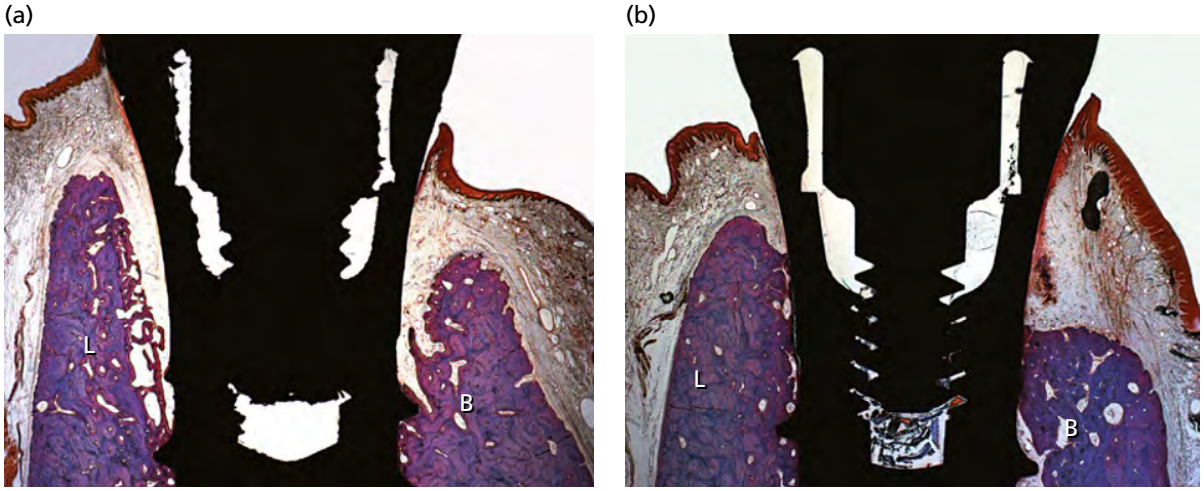

Fig. 40-16 Buccolingual section of the healed molars sites (a) 4 and (b) 12 weeks after implant installation. B, buccal aspect; L, lingual aspect.

Data from a recent study analyzing 418 sites where implants were immediately placed into extraction sockets with periapical pathology revealed 97.8% survival after a mean follow-up of >5 years (Fugazzotto 2012).

A systematic review analyzed data from eight human trials with implants immediately placed into extraction sockets in the presence of periapical pathology (Waasdorp *et al*. 2010). Treatment regimens consistently included thorough debridement of the site prior to implant placement. Bone defects present were normally treated with guided bone regeneration procedures. In the majority of cases, an antibiotic regimen was prescribed. Clinical and radiographic results revealed survival and success rates similar to those for implants placed in non-infected sites. In contrast, studies have reported a higher occurrence of periapical lesions at implants, when the tooth replaced by the implant had exhibited periapical pathology, or when the tooth next to the implant site exhibited periapical pathology (Lefever *et al*. 2013).

Hence, it appears that the presence of periapical pathology at the tooth to be extracted may represent a higher risk for periapical problems at implants immediately placed into the extraction socket. An important body of evidence, however, suggests that by applying a meticulous treatment regimen, implants placed into the site where teeth with periapical pathology have been extracted, can be maintained with high survival and success rates over time.

How to deal with teeth exhibiting marginal periodontal pathology is another important clinical question regarding type 1 implant placement. In a recent study, implants were immediately placed to replace two groups of teeth (Crespi *et al*. 2010). In one group, the marginal periodontium showed signs of infection, but in the other group the marginal periodontium was clinically healthy. Four years after implant placement, no significant differences between the two groups were found regarding implant survival, marginal bone levels, and peri-implant soft tissue parameters. Hence, properly performed immediate implant placement may lead to successful outcomes when replacing teeth affected by marginal periodontitis.

When compared with delayed implant placement in the context of controlled studies, immediate implant placement resulted in an implant survival rate reduced by 4% (94% versus 98%) as reported in a recent systematic review (Cosyn *et al*. 2019). In a recent multicenter, parallel armed, randomized study, implants were placed immediately after extraction of anterior and premolar teeth in 62 patients and 12 weeks after tooth extraction in another 62 patients (Tonetti *et al*. 2017). The results showed similar survival rates in both groups. In the immediate placement group the need for bone augmentation was higher than in the delayed placement group (72% versus 43.9%). In the immediate group probing depths were higher whereas marginal bone levels and esthetics scores were lower in the immediate group compared with the delayed group. Interestingly patient reported outcomes showed no difference between the groups. Collectively, these data indicate a higher probability for the desired treatment outcomes when placing implants in a delayed compared with an immediate placement protocol.

When focusing on posterior sites (molars and premolars) in both the maxilla and the mandible, a recent study reported no difference between implants placed immediately after tooth extraction or following a 4-month healing period (Cucchi *et al*. 2017). The investigators had randomized 92 patients into two groups and analyzed clinical and radiographic parameters for an average observation period of 2 years after initiation of prosthetic loading. No differences were reported between the two groups with respect to implant survival, marginal bone level changes, width of the buccal keratinized mucosa, and biologic or prosthetic complications. Overall, the study results indicated both procedures to be successful in posterior sites of both jaws.

Type 2 placement: completed soft tissue coverage of the tooth socket

There are several reasons why the type 2 approach is often recommended. At this stage of healing, the socket entrance is covered with a mucosa. The soft tissue is (1) comparatively mature, (2) has proper volume, and (3) can be easily managed during flap elevation and replacement procedures. Furthermore, the type 2 timing permits an assessment of the resolution of periapical lesions that may have been associated with the extracted tooth. The disadvantages inherent in the type 2 approach include (1) resorption of the socket walls and (2) an extended treatment time (see Table 40-1).

Following tooth extraction, the socket becomes filled with a coagulum that is then replaced with granulation tissue within a few weeks. In the normal case, it takes about 4–8 weeks before the soft tissue (granulation tissue, provisional connective tissue; see Chapter 3) fills the socket and its surface becomes covered with epithelium (Amler 1969; Zitzmann *et al*. 1999; Hammerle & Lang 2001; Nemcovsky & Artzi 2002). The maturation of the soft tissue (further deposition and orientation of collagen fibers) that can facilitate flap management may require an even longer healing time.

The larger amount of soft tissue that is present at the site of implant placement when the type 2 approach is used allows for precise management of the mucosal flap and hence optimal soft tissue healing (Fig. 40-18). This advantage with the type 2 timing must be matched against the hard tissue reduction and the change of the ridge contour that results from

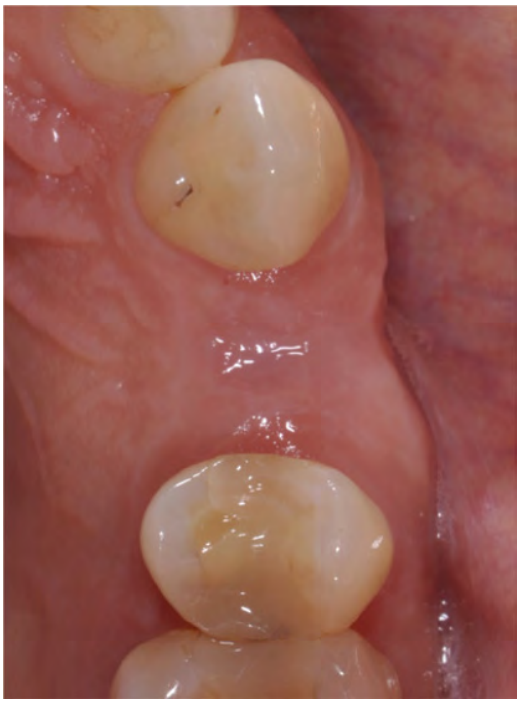

Fig. 40-18 Soft tissues have completely healed over the extraction socket 8 weeks after tooth removal and a small loss of ridge contour is visible buccally (type 2).

the resorption of the socket walls and of the buccal bone plate. It must be noted that at some extraction sites the mucosa may remain adherent via scar tissue to the underlying bone or to the provisional connective tissue of the socket. In such cases, it may be difficult to separate the soft tissue from the bone and to mobilize the flap. In such a situation, the trauma caused in conjunction with flap elevation may rupture the soft tissue and compromise healing. This in turn may result in soft tissue dehiscence, local infection, and inflammation (Zitzmann *et al*. 1997).

As shown in Fig. 40-1, the initial gain in mucosa (area and volume) is later followed by an overall loss of soft tissue volume. This is evidenced by the fact that the volume of the alveolar process – including the bone as well as the mucosal compartments – markedly decreases during the first 12 months following tooth extraction (Schropp *et al*. 2003).

During the 4–8 weeks between tooth extraction and type 2 implant placement, only small amounts of new bone (woven bone) will form in the socket. This means that the risk of not achieving primary implant stability is similar in type 1 and type 2 approaches. Thus, in sites where the available bone height apical to the tip of the root is <3 mm, it is frequently impossible to obtain primary implant stability in the bone beyond the apex of the extracted tooth. When, in addition, a wide alveolus is precluding the engagement of its bony walls, the type 3 approach may be favored.

Whereas the potential clinical advantages of type 2 implant placement are listed above, there is a paucity of well-controlled clinical trials comparing type 2 placement to immediate or late implant placement with respect to these factors in anterior areas (for review see Graziani *et al*. 2019). There are, however, a few controlled studies and case series of up to 10-year duration demonstrating high survival rates, low biological complication rates, and pleasing esthetic outcomes (for review see Graziani *et al*. 2019).

Currently, the paucity of data from well-controlled clinical studies precludes clear statements regarding the effect of the different types of implant placement on the stability and the height of the soft tissues at the implant sites.

Type 3 placement: substantial bone fill has occurred in the extraction socket

The type 3 time frame is chosen for implant installation at sites where, for various reasons, bone fill is required within the extraction socket. Newly formed woven bone will occupy the socket area after healing periods extending from 10 to 16 weeks (Evian *et al*. 1982). In this period, however, the walls of the socket are frequently completely resorbed and replaced with woven bone. The entrance to the socket is closed with a cap of woven bone that is in the process of remodeling. The mucosa that covers the extraction site is (1) residing on a mineralized ridge, and (2) mature and easier to manage during surgical flap elevation and replacement procedures.

The type 3 approach often allows the clinician to place the implant in a position that facilitates the prosthetic phase of the treatment. The disadvantages with this approach encompass (1) a prolonged treatment time, (2) additional resorption and diminution of the ridge, including a substantial change of its contour, and (3) a concomitant loss of soft tissue volume.

Type 4 placement: alveolar process is healed following tooth loss

In the type 4 approach, the implant is placed in a fully healed ridge. Such a ridge can be found after 6–12 months of healing following tooth extraction (loss). The clinician may now find a ridge that is lined by a mature, often well-keratinized mucosa that resides on dense cortical bone. Beneath the cortical bone plate, cancellous bone occupies a varying portion of the alveolar process (see Chapter 3).

The advantage of type 4 installation is that healing is more or less complete and only minor additional change of the ridge may occur. It must be realized, however, that additional loss of ridge volume may at times occur and require bone augmentation procedures (Fig. 40-19).

Clinical concepts

When implants are to be placed in the edentulous portion of the ridge, factors in addition to the tissue

changes over time must be considered. Thus, in the treatment planning phase, aspects such as the (1) overall objective of the treatment, (2) location of the tooth within the oral cavity – in the esthetic or non-esthetic zone, and (3) anatomy of the bone and the soft tissue at the site(s) to be treated, must be evaluated.

Aim of therapy

Dental implants are most commonly used to restore health and function. During the surgical phase of therapy, therefore, ideal conditions must be established for successful bone and soft tissue integration with the implant. In a growing number of cases, however, treatment must also satisfy patient demands regarding the esthetic outcome. In such cases, the overall surgical and prosthetic treatment protocol may become more demanding, since factors other than osseointegration and soft tissue integration may play an important role.

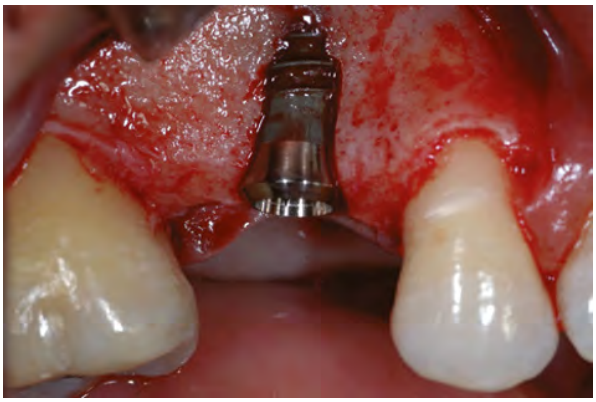

Fig. 40-19 Buccal dehiscence defect is present at an implant placed into a ridge, which has undergone substantial buccal bone resorption since tooth extraction several months ago (type 4).

Restoration of health and function

In cases where the restoration of health and function constitutes the primary goal of the treatment, the location and volume of available hard and soft tissues are the important factors to consider. In such cases, the type 1 approach is usually selected (Wichmann 1990).

The replacement of a single-rooted tooth with an implant in a fully healed ridge will, in most cases, ensure proper primary stability with the implant in a prosthetically correct position. In addition, the soft tissues are sufficient in volume and area. The mucosal flap can be adapted to the neck (or the healing cap) of the implant (one-stage protocol). When primary wound closure is intended (two-stage protocol), mobilization of the soft tissue will allow tension-free adaptation and connection of the flap margins.

When an implant is placed in the unhealed site of a multirooted tooth, the surgical procedure becomes more demanding. Often, the ideal position for the implant is in the area of the inter-radicular septum. If the septa are delicate, anchorage for primary implant stability may be difficult to achieve (Fig. 40-20). In addition, in molar sites there is often only a small amount of soft tissue present. This may create a problem with respect to wound closure with a mobilized, tension-free flap. In some molar sites, primary wound closure may not be possible following implant installation.

The presence of marginal defects (gaps) between the implant and the fully healed ridge following type 4 placement was regarded in the past as a significant problem that could compromise osseointegration. However, studies in humans and animals have demonstrated that in such a horizontal marginal defect (gap) of ≤2 mm, new bone formation as well as defect resolution and osseointegration of the implant (with a rough titanium surface) will occur (Wilson *et al*. 1998; Botticelli *et al*. 2004; Cornelini *et al*. 2005).

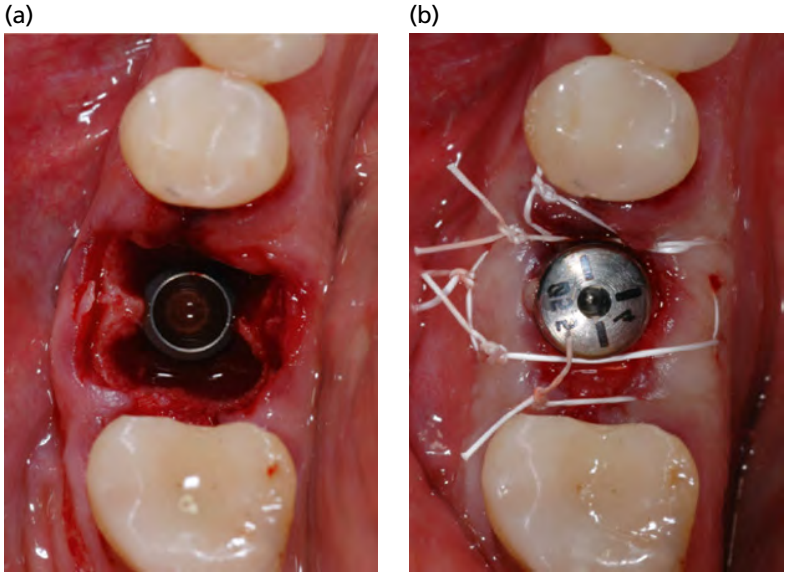

Fig. 40-20 (a) Immediate implant placement (type 1) in a mandibular premolar extraction socket. Note the buccal bone deficiency, where bone will be augmented by guided bone regeneration. (b) Same site as in (a) following adaptation of the flap around the neck of the implant, obtaining a transmucosal mode of healing.

Esthetic importance and tissue phenotype

The replacement of missing teeth with implants in the esthetic zone is a demanding procedure. Deficiencies in the bone architecture and in the soft tissue volume and architecture may compromise the esthetic outcome of treatment (Grunder 2000). Hence, when an implant is to be placed in the esthetic zone, not only the anatomy of the hard tissues but also the texture and the appearance of the soft tissues must be considered.

In a recent systematic review including patients with intact facial bone walls and a thick soft tissue phenotype, a limited risk for advanced mid-facial soft tissue recession was reported (Cosyn *et al*. 2012). Furthermore, it was stated that the literature was scarce regarding the effect of different parameters on mid-facial soft tissue recession, such as thin or thick tissue phenotype, flapless or flap surgery, and immediate or late provisionalization. In another study of a specific treatment protocol that included type 1 implant placement, flapless surgery, and immediate provisionalization, Cabello *et al*. (2013) reported good esthetic outcomes with only small changes in the height of the interproximal papillae and the level of the mid-facial mucosal margin.

Type 2 or 3 installations are often preferred when implants are placed in the esthetic zone (Fig. 40-21). The key advantage of type 2 (as opposed to type 1) installation is the increased amount of soft tissue that will have formed during the first weeks of healing following tooth extraction. Randomized controlled studies comparing the treatment outcomes in type 1 or type 3 placements have reported slightly higher implant survival rates and improved esthetic outcomes (Lindeboom *et al*. 2006; Cucchi *et al*. 2017; Tonetti *et al*. 2017). Non-controlled studies have reported high survival rates for type 2 placement of implants combined with early and conventional loading compared with type 1 placement (for review see Gallucci *et al*. 2018).

Apart from obtaining soft tissue coverage of the previous entrance to the alveolus, type 2 installation has also been claimed to reduce facial soft tissue recession compared with type 1 implant placement. In a comparative study assessing esthetic outcomes of immediate and conventional implant placement, no treatment was favored over any other with respect to overall esthetic results (Raes *et al*. 2011). Interestingly, conventional implant placement was associated with more mid-facial recession than immediate implant placement. In a clinical study of implants placed in fresh extraction sockets (Botticelli *et al*. 2004), during healing, they became clinically osseointegrated within the borders of the previous extraction socket. However, significant loss of buccal bone height (contour) also occurred. In esthetically critical situations, this loss of contour may lead to a compromised outcome. Hence, tissue augmentation procedures must frequently be performed in the esthetic zone.

In this context, it is important to realize that when a two-stage implant placement protocol is used, the labial mucosa will recede following abutment connection surgery. Mean values of recession between 0.5 mm and 1.5 mm, but with large variations, have been reported in several clinical studies (Grunder 2000; Oates *et al*. 2002; Ekfeldt *et al*. 2003). These findings additionally stress the necessity for a careful treatment approach when implants are placed in the esthetic zone. The phenotype (see Chapter 4) of the soft and hard tissues may play a role in the esthetic outcome of implant therapy. Characteristics of soft and hard tissues at teeth were described and classified into two phenotypes: the flat thick or the pronounced scalloped, thin phenotype (Olsson & Lindhe 1991; Olsson *et al*. 1993; Weisgold *et al*. 1997). The thin tissues in the latter type include a thin free gingiva, a narrow zone of attached mucosa, and a pronounced "scalloped" contour of the gingival margin. In addition, the scalloped thin phenotype is associated with a delicate bone housing. In a recent study it was found that buccal tissue recession at single-tooth

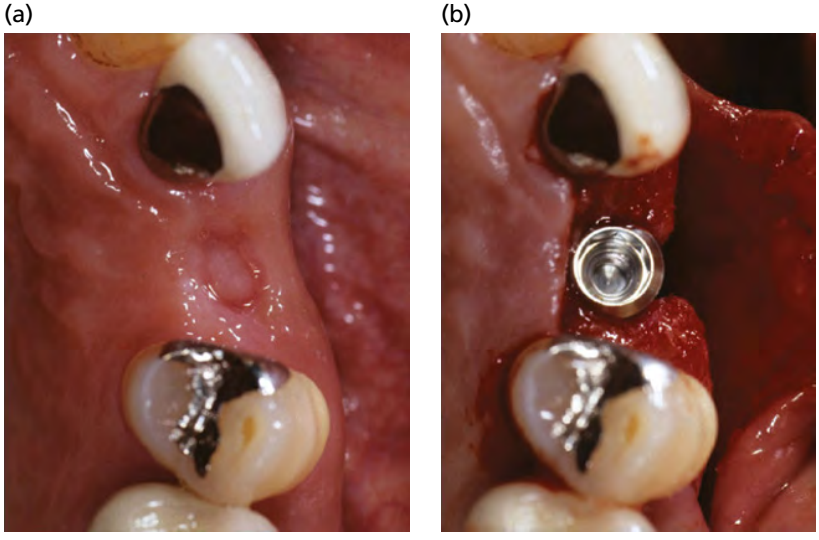

Fig. 40-21 (a) Single-tooth gap 8 weeks following tooth extraction. The soft tissues have completely healed over the extraction socket. (b) Same site as in (a). An implant has been placed in the edentulous gap. The resulting buccal dehiscence defect will be augmented with bone by applying guided bone regeneration.

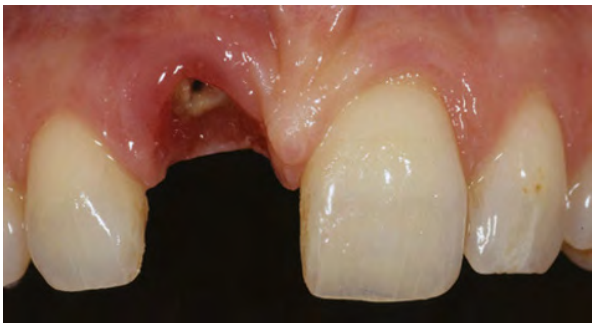

Fig. 40-22 Patient exhibiting a thin tissue phenotype as characterized by a thin free gingiva, a narrow zone of keratinized and attached mucosa, shallow probing depths, and a pronounced "scalloped" contour of the gingival margin, including recessions at some maxillary anterior teeth. Tooth 11 is scheduled for extraction and replacement by an implant using a type 2 or 3 approach.

implants was more pronounced in patients exhibiting a thin phenotype compared with patients with a thick phenotype (Evans & Chen 2008). Based on these findings and on clinical experience, it was proposed that patients exhibiting a pronounced scalloped phenotype should be treated with a type 2, 3, or 4 rather than a type 1 implant installation approach (Fig. 40-22).

Success of treatment and long-term outcomes

Numerous clinical studies have demonstrated that type 1 implant placement is a successful and predictable clinical method (Lang *et al*. 1994; Schwartz-Arad & Chaushu 1997a; Hammerle *et al*. 1998; Covani *et al*. 2004). In addition, success and survival rates for type 1 implants have been reported to be of the same magnitude as those for implants placed in healed ridges (Gelb 1993; Grunder 2000; Gomez-Roman *et al*. 2001; Gotfredsen 2004; Schwartz-Arad *et al*. 2004). Histologic studies in animals confirmed the viability of type 1 placement. Unloaded titanium implants placed in extraction sockets showed a high degree of osseointegration (Anneroth *et al*. 1985) that is similar to that for implants placed in healed sites. Furthermore, a few studies analyzing survival rates for type 2 and 3 placements have shown survival rates similar to those reported for type 1 and 4 placements (Watzek *et al*. 1995; Nir-Hadar *et al*. 1998; Polizzi *et al*. 2000).

Conclusion

In situations where teeth are to be replaced with implants, various factors govern the decision regarding the optimal time point for implantation following tooth extraction. Of special importance are the overall objective of the treatment, the location of the tooth within the oral cavity, the anatomy of the bone and the soft tissue at the site, and the adaptive changes of the alveolar process following tooth extraction. The decision regarding the timing for implant placement needs to be based on a thorough understanding of the structural changes that occur in the alveolar process following tooth extraction, with and without implant placement, as presented in this chapter.

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Part 15: Reconstructive Ridge Therapy

Chapter 41

Ridge Augmentation Procedures

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Introduction: principles of alveolar bone regeneration

The alveolar process is sensitive to a variety of environmental and physiologic factors that influence its ability to function and maintain its integrity. Before implant therapy became available, the physiology and healing patterns of the edentulous ridge after a tooth was extracted were often neglected or not dealt with properly (Amler *et al*. 1960; Amler 1969). Today, implant placement in severe cases of alveolar resorption is a well-understood and recognized challenge that significantly impacts the success of implant therapy. Although alveolar bone loss can be congenital, the result of chronic/acute infections, trauma, pathology, or the consequence of periodontitis, the loss of mechanical function following a tooth extraction is most often the cause of this clinical deficiency. In fact, after tooth extraction, approximately 25% of the bone volume is lost during the first year and over time, may progress to a 40–60% loss of alveolar volume after 3 years of the extraction. The resulting ridge deficiency is primarily the result of a rapid loss of bone height and gradual loss of the horizontal dimension (Carlsson *et al*. 1967). In light of these changes, clinicians have suggested protocols to minimize the resorption of the ridge or to correct these clinically unfavourable deficiencies (Tarnow & Eskow 1995; Sclar 2004; Seo *et al*. 2004) (Fig. 41-1).

Successful ridge augmentation procedures utilize bone biological and physical principles to

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

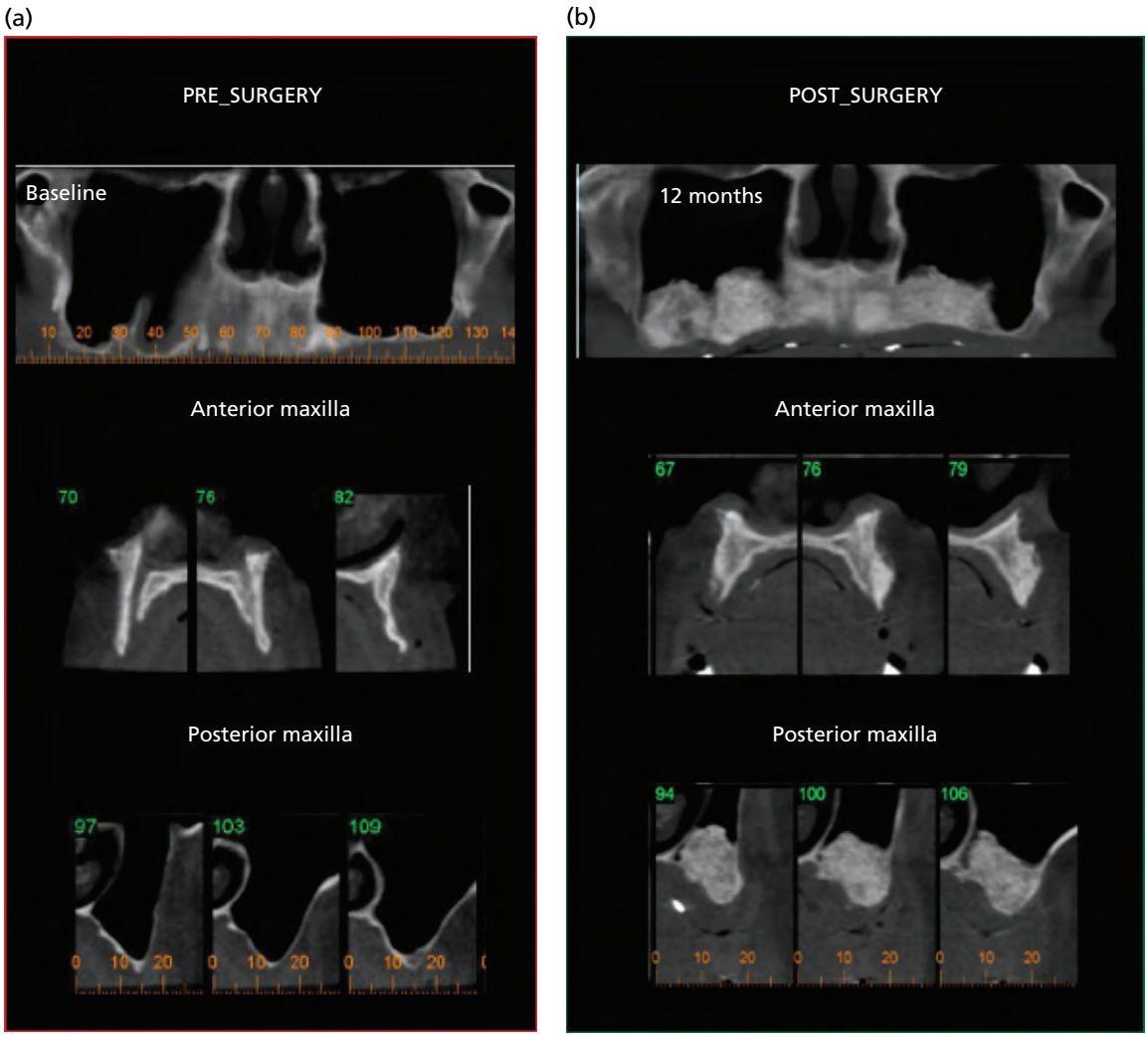

Fig. 41-1 (a) Preoperative and (b) postoperative cone-beam computer tomography images of an adequately corrected anterior and posterior ridge deficiency. Advanced bone grafting protocols have evolved to allow predictable implant placement in severe ridge deficiencies that would have otherwise prevented implant therapy.

enhance its regenerative potential. The placement of bone grafting materials to enhance the healing of osseous defects or to augment atrophic edentulous ridges has allowed the successful placement of dental implants. These regenerative interventions have become a standard procedure in implant dentistry and their efficacy has been evaluated in a number of experimental and clinical studies (Fig. 41-2).

The surgical principles that favour bone regenerative therapies should be based on sound biological factors that encourage adequate healing (Wang & Boyapati 2006). The molecular wound healing events following tooth extraction occur through an orderly sequence of expression of osteogenic factors associated with angiogenesis, cell survival, matrix synthesis, and maturation (Lin *et al*. 2011). These events require an appropriate environment, influenced by local as well as systemic factors, to maximize the osteogenic potential and the eventual reconstruction of the residual ridge. When these environmental conditions are not met (for example in the presence of bacterial contamination and local inflammation) the incorporation of the bone graft in the recipient site may be partially or completely impaired, resulting in bone resorption and bone loss associated with the donor grafting material. Some of the factors that are critical to attaining adequate wound management are discussed below.

Promoting primary wound closure

Primary closure is primordial for bone regeneration because it provides an undisturbed environment for healing (Gelb 1993; Becker & Becker 1996; Fugazzotto 1999; Goldstein *et al*. 2002). Ideal flap closure should be relatively passive and tension-free. In this way, the risk of exposure of the regenerative materials, wound contraction, ingrowth of connective tissue, re-epithelialization, and the associated patient morbidity are decreased. To assure primary closure, the presence of adequate soft tissue volume should be a pre-requisite before bone regenerative surgery. In cases of soft tissue deficiency, it may be advisable to augment the soft tissues prior to bone augmentation.

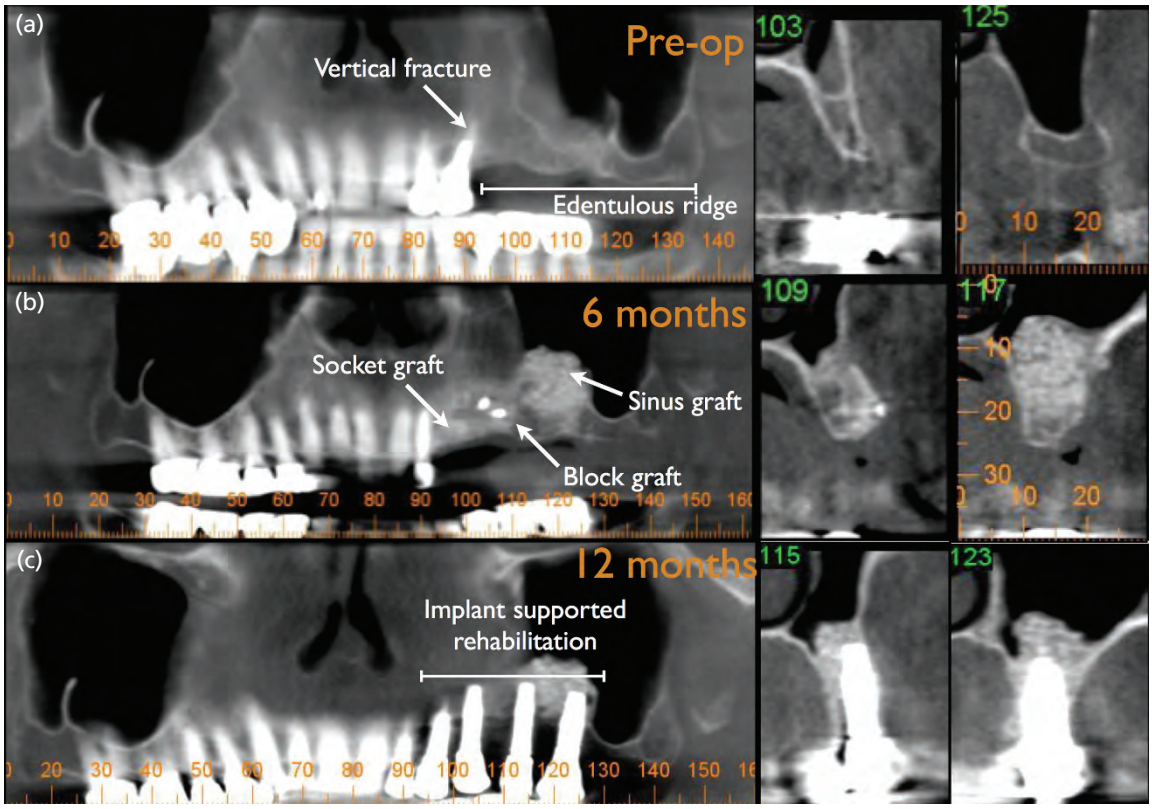

Fig. 41-2 Availability of diverse bone grafting materials. This has significantly contributed to the development of successful ridge augmentation techniques. (a) Baseline radiographic image highlights the edentulous deficient ridge. (b) Six months after the required grafting procedures. (c) Twelve months after surgery and implant supported rehabilitation.

Enhancing cell proliferation and differentiation

Proper enhancement of cell proliferation and differentiation not only provides angiogenic and osteogenic cells, but also acts as a source of blood, oxygen, and nutrients to the tissues. Sources of undifferentiated pluripotent mesenchymal cells and osteogenic cells include the periosteum and the endosteum (the walls of the defect). Bone marrow is an excellent source of mesenchymal cells, which will differentiate into osteoblasts with the appropriate molecular signalling. To increase the access of bone marrow to the healing site, perforations of the cortical plate have been recommended (Buser *et al*. 1995) because they act as a mechanical or non-infective stimulus that increases blood perfusion to the healing site and the release of growth factors that will improve the normal unperturbed regeneration process (Frost 1983; Shih & Norrdin 1985). This is a process referred to in the literature as the regional acceleratory phenomenon (RAP).

To enhance cell proliferation and differentiation, by increasing the bone anabolic signalling processes, a number of biologically active products are available and have been tested in preclinical and clinical investigations.

Protecting initial wound stability and integrity

One factor that affects wound healing is the stability of the blood clot (Wang *et al*. 2004). This is important because the clot contains a plethora of cytokines (e.g. interleukin [IL]-1, IL-8, tumor necrosis factor), growth factors (e.g. platelet-derived growth factor [PDGF], insulin-like growth factor 1 [IGF-1], fibroblast growth factor 2 [FGF-2]), and signalling molecules that aid in recruiting cells to promote neoangiogenesis and wound healing. Moreover, the blood clot is important, since it is eventually transformed into granulation tissue, which will be the framework of the subsequent bone formation (Schenk *et al*. 1994).

Since the jaw bones are usually convex or flat, they do not lend themselves for space provision, and therefore, a physical space is necessary to allow for the regenerative events leading to bone augmentation of the alveolar process (Oh *et al*. 2003). This is typically achieved through the use of bone replacement grafts that serve as a scaffold to allow the biological events leading to bone formation. Furthermore, the epithelial and connective tissue cells from the mucosa must be excluded from ingrowing into this space to allow for the osteogenic cells and the ensuing new bone formation. This is usually accomplished by the placement of barrier membranes, which usually serve a dual function of maintaining the soft tissues excluded from the healing of the bone defect and also supporting the stabilization of the blood clot. Different types of barrier membranes have been tested: those serving only as tissue barriers (bioabsorbable membranes) and others also providing space maintenance properties (titanium reinforced non-bioabsorbable membranes) (Jovanovic *et al*. 1995; Oh *et al*. 2003).

This chapter discusses the growing evidence in the area of bone augmentation procedures that are frequently employed by clinicians to augment the deficient residual ridges prior to implant therapy.

Treatment objectives

The rationale behind any crestal bone augmentation procedure is to establish sufficient bone availability for safe and predictable dental implant therapy, as well as for attaining adequate bone thickness around the installed implant. Spray *et al*. (2000) evaluated the influence of bone thickness on the marginal bone response at second-stage implant uncovering surgeries, and reported that as the bone thickness approached 1.8–2 mm, the occurrence of bone loss (i.e. implant dehiscence) decreased significantly. Although the "adequate" bone thickness may vary depending on the macroscopic and microscopic implant configurations, as well as the clinical indication, it is generally agreed that at least 2 mm of bone on the buccal side of the implant are recommended to increase the probability of long-term stability of peri-implant health and to attain good aesthetics.

This rationale is further justified by the growing bulk of evidence for biologic complications around functional implants. The prevalence of peri-implantitis, characterized by inflammation and implant-supporting bone loss was reported by Zitzmann and Lindhe ranging between 28% and 56% of patients and between 12% and 43% of implants (Zitzmann & Berglundh 2008). Most recently, a meta-analyses estimated weighted mean prevalence of peri-implant mucositis and peri-implantitis of 43% (CI [confidence interval]: 32–54%) and 22% (CI: 14–30%), respectively (Derks & Tomasi 2015). Among the potential risk factors for peri-implantitis, rough implant surfaces exposed to the oral environment are at a higher risk of accumulating bacterial plaque biofilms and hence the development of mucosal inflammation (Renvert *et al*. 2011). Schwarz *et al*. (2012) evaluated the influence of residual marginal dehiscence bone defects after guided bone regeneration (GBR) on the long-term stability of peri-implant health, and reported that implants exhibiting residual defect heights of >1 mm were at higher risk of presenting mucosal clinical attachment loss, marginal recession, and deepened probing pocket depths 4 years after treatment. Hence, any clinician placing dental implants should ensure that there is enough available bone covering the implant surface and in case there is limited availability, to carry out a bone augmentation procedure.

Diagnosis and treatment planning

Patient

In general, there are no specific contraindications for ridge augmentation procedures provided the patient can withstand a conventional oral surgical procedure. For bone augmentation procedures as well as for other types of oral implant operations, there are some relative contraindications that need to be taken into consideration, mainly medical conditions that might impair normal bone healing. For example, in patients with diabetes, there is evidence that implant success rates are similar to those in healthy patients, provided there is appropriate glycaemic control. Experimental studies, however, have provided histologic evidence of impaired healing in implants placed in diabetic animals when compared with healthy controls, although osseointegration was achieved in both groups (Colombo *et al*. 2011; Schlegel *et al*. 2013). The effect of experimental diabetes and metabolic control on the potential for *de novo* bone formation following GBR has been investigated in the rat mandible (Retzepi *et al*. 2010). These authors did not observe statistically significant differences in the amount of vertical bone regeneration when uncontrolled diabetic, insulin-controlled diabetic, and healthy animals were compared. The uncontrolled diabetes group, however, showed an increased rate of infectious complications and a less predictable outcome. When metabolic control of the systemic condition was achieved, the detrimental effects on healing were reversed.

Smoking has also been found to negatively affect the long-term prognosis of osseointegration (Bain & Moy 1993). Clinical studies have reported that smokers present not only higher rates of implant failure when compared with non-smokers (De Bruyn & Collaert 1994; Lambert *et al*. 2000), but also a greater number of complications around successfully integrated implants (Roos-Jansaker *et al*. 2006), such as a higher incidence of peri-implant mucositis and peri-implantitis (Heitz-Mayfield 2008). Although there is ample evidence on the negative effects of tobacco smoking on the clinical outcomes of periodontal regenerative therapies, such as guided tissue regeneration (GTR) (Patel *et al*. 2012), few studies have directly evaluated its effect on GBR. A meta-analysis, based on six studies, evaluated the effects of smoking on dental implants placed on augmented bone and reported an odds ratio (OR) of 3.61 (95% CI 2.26–5.77) for implant failures (Strietzel *et al*. 2007). In this systematic review, the impact of smoking on the outcomes of different bone regeneration techniques (lateral and/or vertical augmentation) was assessed in four retrospective studies: three studies reported more failures and complications in smokers compared with non-smokers. Moreover, the amount of bone augmentation in smokers was inferior when compared with that in non-smokers. Similarly, a clinical case series evaluated the outcomes of a GBR procedure combining autogenous bone and an expanded polytetrafluoroethylene (ePTFE) membrane (Lindfors *et al*. 2010). In the group of non-smokers, the augmentation procedure was successful in 95% of the cases, whereas in smokers it was successful in only 63% of the cases. Moreover, signs of soft tissue inflammation were present in 10 (37%) of the augmentation sites, and this occurred more often in smokers (75%) than in non-smokers (21%).

These patient-related factors are not absolute contraindications for bone augmentation procedures, but they should be taken into consideration during diagnosis and treatment planning. When a bone augmentation procedure is indicated, the patient's systemic status should be optimal.

Defect classification

Bone availability is the main prerequisite for safe and predictable implant placement. There are, however, many clinical situations where bone quantity is limited and therefore, bone augmentation procedures are indicated. In order to decide on the appropriate bone augmentation strategy, the available bone crest must be carefully evaluated with careful clinical examination and three-dimensional (3D) radiographical diagnosis (see Figs. 41-1, Fig 41-2).

According to Seibert (1983), alveolar crest defects are classified into three categories (Fig. 41-3):

- Class 1 defects: when the bone deficiency is predominantly in the horizontal dimension
- Class 2 defects: when the bone deficiency is predominantly in the vertical dimension
- Class 3 defects: when the bone deficiency affects both the vertical and horizontal dimensions.

Depending on the amount of available bone and the defect type, the treatment strategy may consider implant placement and a concomitant bone augmentation procedure (simultaneous implant-GBR procedure) or bone augmentation and delayed implant placement once the bone volume has been augmented (staged-GBR procedure). The simultaneous procedure is indicated in class 1 defects when there is enough vertical bone for placing an implant with appropriate primary stability and the bone regenerative procedure is intended for lateral bone augmentation. In class 2 and 3 defects, depending on the amount of vertical augmentation needed, the staged approach is usually indicated (Fig. 41-4).

Bone augmentation procedures could also be considered when placing implants in fresh extraction sockets. In most of these clinical situations, the morphology of the socket does not match the implant diameter and, depending on the resulting bone defect, a different bone augmentation procedure might be indicated.

Benić and Hämmerle (2014) (Fig. 41-3) have classified these defects as:

- Class 0 Site with a ridge contour deficit and sufficient bone volume for standard implant placement
- Class 1 Intra-alveolar defect between the implant surface and intact bone walls

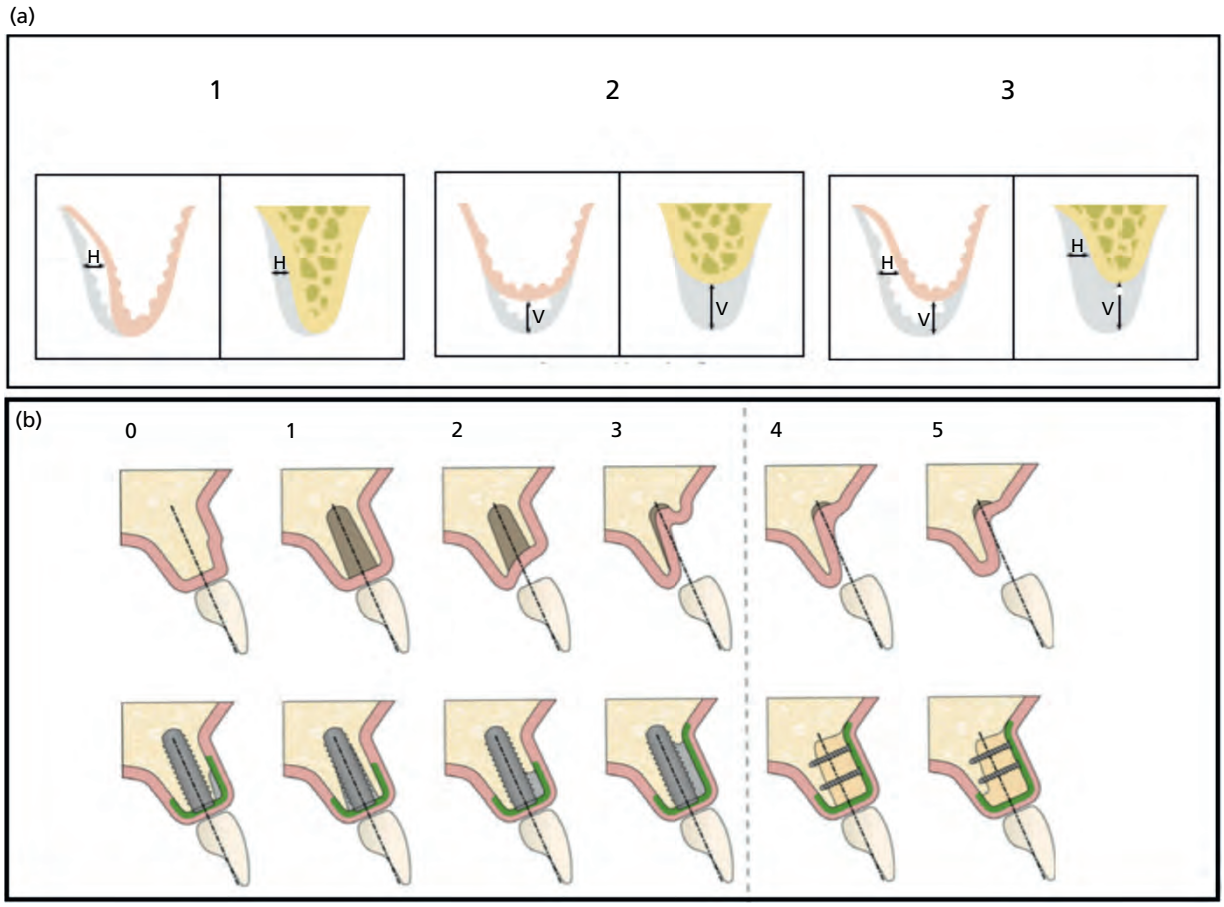

Fig. 41-3 (a) Alveolar crest defects, Seibert classification. (b) Extraction sockets defect, Benic and Hammerle classification.

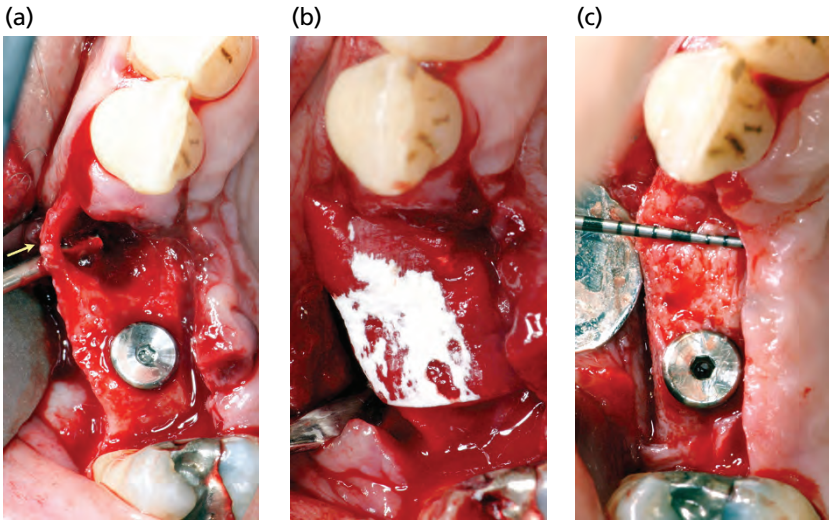

Fig. 41-4 (a, b) Socket preservation (deproteinized bovine bone mineral + non-cross-linked collagen membrane) in position 13 due to fenestration (arrow) of the buccal bone wall of the socket (class II defect, Hämmerle & Jung) and immediate implant (no graft) in position 14. (c) Re-entry surgery at 4 months. Outcome of the socket preservation procedure. Note the bone remodeling at the implant site.

- Class 2 Peri-implant dehiscence, in which the volume stability of the area to be augmented is provided by the adjacent bone walls
- Class 3 Peri-implant dehiscence, in which the volume stability of the area to be augmented is not provided by the adjacent bone walls
- Class 4 Horizontal ridge defect requiring bone augmentation before implant placement
- Class 5 Vertical ridge defect requiring bone augmentation before implant placement

A one-step GBR procedure is usually indicated for class 0–3 defects, while in larger horizontal and vertical bone defects the delayed approach should be indicated.

When placing implants in extraction sockets, timing of the bone augmentation procedure is also very important since, depending on the time elapsed from tooth extraction, different soft tissue conditions may be encountered. For details regarding the different implant treatment strategies in extraction sockets, see Chapter 40.

Bone augmentation therapies

In the mid-1980s, the GTR principle was applied in periodontal regeneration, based on the early studies of Melcher (1976), who developed the concept of using barrier membranes to "guide" the biologic process of wound healing. These early experimental studies demonstrated that the exclusion of soft tissue invasion of the defect by means of a barrier membrane, allowed the cells with regenerative potential to migrate to the site (derived from the periodontal ligament or bone marrow) and promoted periodontal regeneration (Nyman *et al*. 1982). Based on the same biologic principle, the GBR treatment concept aimed for mechanical exclusion of the soft tissues from filling the osseous defect, thus allowing the cells with osteogenic cells to colonize the wound (Dahlin *et al*. 1988). The key prognostic factor in GBR was to have enough space under the barrier membrane to allow for bone regeneration of the crestal defect. Depending on the morphology of the defect, this space can only be maintained with the use of a bone replacement graft, either particulated or as a block. Different biomaterials, natural and/or synthetic, have been used and investigated in their capacity to be used as bone replacement grafts in bone augmentation procedures of the jaws (Haugen et al. 2019).

The following sections describe the biologic principles of GBR and the efficacy of the biomaterials used as bone replacement grafts and barrier membranes.

Biologic principles of guided bone regeneration

Seibert and Nyman (1990) demonstrated successful reconstruction of surgically created, buccolingual defects in the edentulous ridge of dogs after 90 days of healing, with newly formed bone filling the space created beneath e-PTFE (Gore-Tex®) non-resorbable barrier membranes. Furthermore, Smukler *et al*. (1995) reported that the application of barrier membranes in class III ridge defects led to a mean vertical augmentation of 3.31 mm (Buser *et al*. 1995) and demonstrated that this regenerated bone could successfully integrate dental implants when these were placed 6 months after the GBR procedure.

The sequence and pattern of bone regeneration in GBR procedures has been investigated in experimental studies. Schenk *et al*. (1994) investigated surgically created, membrane-protected defects in the edentulous ridge in dogs. The sequence of events assessed histologically, started with the organization of a blood clot that filled the space protected under the membrane. Then a connective tissue matrix, rich in new vascular structures, replaced this blood clot and subsequently, woven bone started to deposit from the surrounding bony walls and concentrically filled the defect. This woven bone was later replaced by parallel-fibered lamellar

bone, resulting in a new cortical structure at the periphery of the defects. This pattern of intramembranous bone growth shown in GBR was described also in the healing of an alveolar sockets after tooth extraction (Cardaropoli *et al*. 2003). Dahlin *et al*. (1989) were the first to provide evidence to support the effectiveness of GBR around implants. e-PTFE membranes were applied around exposed implant threads inserted in rabbit tibiae and peri-implant bone formation was observed provided enough space was secured under the membrane. Becker *et al*. (1990) also assessed the potential of GBR in treating exposed threads of implants placed in dog mandibles. They reported a mean increase of 1.37 mm in bone height for the GBR-treated test sites, versus 0.23 mm for the sham-operated controls.

Vertical bone augmentation using this principle was also demonstrated by Jovanovic *et al*. (1995) who reported regeneration of the mandibular process when applying e-PTFE membranes around supracrestally placed implants in dogs. The new bone formed supracrestally amounted to 1.82 mm (SD 1.04) and 1.9 mm (SD 0.3) when using titanium-reinforced and standard e-PTFE membranes, respectively. GBR was also studied histologically in monkeys with e-PTFE membranes placed around dental implants inserted immediately into fresh extraction sockets (Warrer *et al*. 1991): bone regeneration was observed around the implant circumference in GBR-treated sites, compared with a lack of bone contact in non-GBR-treated control sites. Similar experimental studies in dogs also showed successful bone regeneration using e-PTFE membranes in implants immediately placed in fresh extraction sockets (Becker *et al*. 1991; Gotfredsen *et al*. 1993).

Regenerative materials

Barrier membranes

Different types of barrier membranes have been tested for GBR. These membranes must fulfil specific criteria for promoting bone regeneration of the edentulous ridge, such as biocompatibility, cell occlusion properties, integration by the host tissue, and space-making capacity. Their specific composition falls into two broad categories: non-resorbable (PTFE and e-PTFE) and resorbable. e-PTFE has been the most frequently investigated material for *non-resorbable membranes* in both periodontal and bone regeneration clinical applications. e-PTFE membranes are flexible with an external porous structure allowing for tissue integration and an internal occlusive layer providing the barrier mechanism. They are composed of a chemically stable and biologically inert polymer that resists microbiologic and enzymatic degradation and do not elicit any immunologic reactions. To enhance the space-making capacity of these devices, a titanium scaffold is applied between the two e-PTFE layers, adding stiffness and reinforcing the membrane structure. These non-degradable barrier membranes require a second surgical intervention to remove them. This disadvantage, together with the high occurrence of postoperative complications, mainly early membrane exposure, has limited their clinical use and has led to the development and broader use of resorbable membranes.

Bioresorbable membranes must ensure that the tissue reactions during the process of membrane resorption or biodegradation are minimal and do not affect the outcome of bone regeneration (Hardwick *et al*. 1995). Several bioresorbable materials have been tested with varying success in bone regeneration applications. Bioresorbable membranes are either natural (xenogeneic collagen type I or III) or made of synthetic polymers, including polyurethane, polyglactin 910, polylactic acid, polyglycolic acid, polyorthoester, polyethylene glycol, and different combinations of polylactic and polyglycolic acid (Sandberg *et al*. 1993; Zellin *et al*. 1995; Brunel *et al*. 1998; Jung *et al*. 2006). When inserted into an aqueous environment, such as a biologic system, the biodegradable polymers undergo enzymatic degradation by hydrolysis. The natural collagen membranes undergo resorption by enzymatic degradation. This membrane degradation process depends on many factors, such as membrane composition, pH, temperature, degree of polymer crystallization, cross-linking in collagen membranes, and membrane volume (Warrer *et al*. 1992; Hämmerle & Jung 2003). The duration of the barrier function is, therefore, variable and the resorption process may interfere with the wound healing and bone regenerative outcome.

Several experimental studies have compared the potential of these barrier membranes for promoting bone regeneration. When non-resorbable e-PTFE membranes were compared with synthetic bioresorbable membranes made of poly d,l-lactide-co-trimethylencarbonate, significantly more bone was formed around implants covered with e-PTFE membranes, although both test and control implants exhibited new direct bone-to-implant contact (Hurzeler *et al*. 1997). These differences are mainly due to the lack of stiffness and space-making capacity of bioresorbable membranes, which when placed directly over the implant threads, tend to collapse and occlude the space available for bone regeneration. This problem is usually overcome by using a scaffold or graft material under the membrane that provides the space for tissue ingrowth and subsequent bone formation. Experimental studies comparing non-resorbable and collagen resorbable membranes, with and without the use of a scaffold, have shown similar bone regenerative outcomes for the non-resorbable membranes and the collagen resorbable membranes used with a scaffold (Hurzeler *et al*. 1998).

For collagen membranes, the biodegradation and concomitant tissue integration depends on the degree of collagen cross-linking. A comparative study evaluated different collagen membranes: (1) BioGide

(BG) (non–cross-linked porcine type I and III collagens, bilayered) (Geistlich Biomaterials, Wolhusen, Switzerland); (2) BioMend (BM) (glutaraldehyde cross-linked bovine type I collagen) (Sulzer Medica, Colla-Tec Inc., Plainsboro, NJ, USA); (3) BioMendExtend (BME) (glutaraldehyde cross-linked bovine type I collagen) (Sulzer Medica); (4) Ossix (OS) (enzymatic cross-linked bovine type I collagen) (3i, Colbar R&D Ltd, Ramat Hush-aron, Israel); (5) TutoDents (TD) (non-cross-linked bovine type I collagen, bilayered) (Tutogen, Carlsbad, CA, USA); (6) VN(1); (7) VN(2); and (8) VN(3) (1, 3, 4 × chemical cross-linked porcine type I and III collagens, bilayered, respectively) (Geistlich Biomaterials) (Rothamel *et al*. 2004). The non-cross-linked porcine-derived collagen types I and III exhibited good tissue integration (without observable foreign body reactions), rapid neo-angiogenesis, and almost complete biodegradation 4 weeks after implantation. The vascularization and biodegradation of chemical and enzymatically cross-linked collagen membranes, however, were slower and the resorption rate was directly related to the degree of cross-linking.

The choice of membrane material usually depends on the amount of bone regeneration needed, mainly in the vertical dimension. e-PTFE barrier membranes have demonstrated more favourable results when compared with resorbable devices, mainly due to their better space-making capacity, longer barrier function, and lack of a resorption process that may negatively affect bone formation (Hämmerle & Jung 2003). Nevertheless, a high rate of soft tissue dehiscence was observed with the use of e-PTFE membranes. When this complication occurs, early contamination of the exposed membrane usually jeopardizes the regenerative outcome. A meta-analysis evaluating the influence of membrane exposure on the outcomes of regenerative procedures reported that new bone formation was six-fold greater when no soft tissue dehiscence occurred (Machtei 2001).

As already mentioned, these frequent complications and the need for a second surgery to remove the membrane with non-resorbable membranes make resorbable membranes the current gold standard, provided they are used with an adequate space-making graft material. The choice of non-cross-linked resorbable collagen membranes should be based on their advantages in terms of earlier neo-angiogenesis, lack of inflammatory response, and fast biodegradation/integration within the host tissue.

Bone grafts and bone and soft tissue substitutes

Bone grafts

Autogenous bone grafts (autografts) have historically been the gold standard in bone regeneration therapies since they have well-documented osteoinductive, osteoconductive, and osteogenic properties (Yukna 1993). In alveolar bone augmentation surgeries, autogenous bone is used either as a particulate or a block graft. Particulate bone grafts are normally harvested from intraoral sites and used in combination with barrier membranes following the principles of GBR. These bone chips have the disadvantages that their availability is limited within the oral cavity and, as they lack a rigid and supportive structure, they do not provide the space-making capacity necessary for the treatment of class II and III defects. In these cases, rigid titanium-reinforced ePTFE barrier membranes or other space maintenance strategies, such as tenting screws or micro-implants, have been used in conjunction with particulate bone autografts. Another drawback with the use of autografts is their fast resorption rate, which requires early implant placement to assure functional loading to the regenerated bone, thus preventing its resorption.

Monocortical block autografts may be harvested from intra- or extra-oral sites. Common intraoral donor sites are the mandibular chin or the ascending ramus area, whereas common extraoral donor sites are the iliac crest or the calvarial bone. They may be used in combination with barrier membranes or alone and they require fixation to the recipient crestal site with mini-screws to avoid micro-movements during healing. These grafts, due to their excellent space maintenance capacity, are indicated in large crestal defects in which there is a need for vertical bone augmentation. Their main disadvantage is the morbidity associated with their harvesting, mainly from the chin area. As with particulate autografts, their resorption rate is high, although when combined with a barrier membrane or with bone particulate xenografts, resorption is slowed.

Bone substitutes

In order to avoid the morbidity associated with the harvesting of autogenous bone grafts, allografts, xenografts, and alloplasts have been indicated and tested.

Allografts are bone grafts harvested from cadaver donors and processed by freezing or demineralizing and freezing. These grafts are then sterilized and supplied by specially licensed tissue banks as bone particles or large blocks. Demineralized freeze-dried bone allografts (DFDBA) have shown osteoconductive as well as osteoinductive properties due to the release of bone morphogenetic proteins (BMP) during the demineralization process. There is some concern, however, regarding their absolute non-infectivity, although there have been no reported cases of disease transmission from DFDBA used for dental purposes among over 1 million cases over 25 years (Yukna 1993). These allografts are usually used in combination with barrier membranes following the principles of GBR.

Xenografts are graft biomaterials of animal origin, mainly bovine and equine. These graft materials are deproteinized in order to completely remove the organic component and thus avoid any immunogenic reaction. This chemical or low heat process preserves the original bone architecture and the inorganic mineral composition, which assures the osteoconductive properties of the biomaterial. Inorganic bovine bone grafts are usually particulate and utilized according to the principles of GBR in combination with resorbable collagen membranes. Different preclinical and clinical studies have demonstrated their safety and efficacy as bone substitutes for both periodontal and peri-implant augmentation procedures (Baldini *et al*. 2011). Recently, highly purified porcine collagen type I has been added to xenografts to enhance their clinical handling by improving the cohesion between the mineral granules.

Alloplasts are synthetic bone substitutes that include different combinations of calcium phosphates fabricated under different sintering conditions, which yields different physical properties and resorption rates. The combination of hydroxyapatite and beta-tricalcium phosphate (β-TCP) provides a scaffolding function (hydroxyapatite) as well as osteoconductive properties (β-TCP). These biomaterials are usually resorbable and delivered as granules. They should be always used in combination with barrier membranes.

Soft tissue substitutes

Soft tissue substitutes have been introduced in periodontal plastic surgery as alternative materials to the use of soft tissue autografts. Their use in bone augmentation is limited to alveolar ridge preservation techniques and to bone augmentation at immediate implant sites. Based on their origin, these scaffold materials may be xenogeneic or allogeneic (for details see Chapter 39). The scaffolds tested so far in pre-clinical and clinical research are of xenogeneic porcine origin and aim at clot stabilization, cell invasion/guidance, and tissue integration.

Choice of the material

This choice should be based on the clinical indication. For small bone defects requiring mainly horizontal bone augmentation, the use of xenografts and alloplasts has demonstrated excellent results. When the objective is to preserve the socket walls after tooth extraction, experimental studies have evaluated the histologic healing when the sockets are filled with different graft materials. The use of autogenous bone chips alone does not counteract the physiologic process of bone remodeling that occurs at the socket bone walls after tooth extraction (Araújo & Lindhe 2011). Indeed, the healing process at these sites filled with autografts showed characteristics similar to those of the sockets without any filling. In contrast, the use of xenografts with a much slower resorption rate demonstrated significantly better preservation of the socket walls than the non-grafted sites. Histologically, these xenograft granules were integrated and fully surrounded by newly formed bone (Araújo & Lindhe 2009). In a similar experimental model, a β-TCP alloplast demonstrated limited bone promotion properties, with the graft particles being encapsulated with connective tissue (Araújo *et al*. 2010). In fresh extractions sockets, the use of collagen matrices of porcine origin has been introduced to seal the socket orifice (Jung *et al*. 2013) in alveolar ridge procedures or in combination with bone augmentation at immediate implant sites (Frizzera *et al*. 2019; Sanz-Martin *et al*. 2019).

In peri-implant dehiscence type defects, requiring simultaneous lateral augmentation, particulated bone grafts should be utilized in combination with barrier membranes. One experimental study testing different graft materials (biphasic hydroxyapatite + beta tricalcium phosphate β[β- TCP] [BCG]) or collagen-coated deproteinized bovine bone mineral (BOC) showed that both biomaterials increased bone fill and the percentage of osseointegrated bone–graft particles (Schwarz *et al*. 2007). Similarly, one experimental study testing (1) synthetic bone substitute covered by a cross-linked collagen membrane and (2) deproteinized bovine bone mineral covered by a natural collagen membrane, showed that both combinations of biomaterials increased horizontal bone augmentation compared with the control group. The synthetic bone substitute achieved better histological outcomes in terms of linear horizontal bone gain and tissue thickness (Jung *et al*. 2017). Therefore, it may be concluded that both synthetic and xenogeneic biomaterials may provide an osteoconductive scaffold to support GBR procedures at dehiscence-type defects.

For the treatment of horizontally deficient alveolar ridges that require a staged lateral bone augmentation, the GBR concept using a native collagen membrane with a combination of 1:1 ratio of particulate DBBM and autogenous bone has been tested, demonstrating the efficacy of this technique both in terms of average amount of horizontal bone gain and implant survival rates (Urban *et al*. 2013).

In large crestal defects for which the aim is both lateral and vertical bone augmentation, the GBR concept with titanium reinforced non-resorbable membranes, and a combination of particulate DBBM and autogenous bone (Urban *et al*. 2014), or the use of monocortical autogenous corticocancellous block grafts, may be recommended. In experimental studies comparing the use of these block grafts with and without a barrier membrane, a significant resorption and limited bone augmentation were demonstrated in the non-membrane protected group, thus demonstrating the clear indication for always protecting the block graft with a resorbable barrier device (von Arx *et al*. 2001).

Evidence-based results for ridge augmentation procedures

These procedures have been used in five main clinical applications: alveolar ridge preservation; bone regeneration in fresh extraction sockets; horizontal bone augmentation; ridge splitting/expansion; and vertical ridge augmentation.

Alveolar ridge preservation

Important structural changes of the edentulous ridge take place after tooth extraction and eventually lead to dimensional changes of the alveolar crest. A classic systematic review assessed the hard and soft tissue changes occurring 6 months after tooth extraction in humans and demonstrated a horizontal bone loss of 29–63% and vertical bone loss of 11–22% from the dimensions of the alveolar bone crest at the time of extraction (Tan *et al*. 2012). With the goal of preventing these physiologic hard and soft tissue changes, different bone augmentation techniques have been proposed to preserve the alveolar architecture after tooth extraction. In general, these ridge preservation techniques have been defined as: "Any therapeutic approach carried out immediately after tooth extraction aimed to preserve the alveolar socket architecture and to provide the maximum bone availability for implant placement" (Vignoletti *et al*. 2012).

These ridge preservation approaches have utilized GBR principles using the following regenerative technologies:

- Resorbable and non-resorbable barrier membranes alone
- Resorbable and non-resorbable barrier membranes in combination with bone substitutes
- Bone substitutes alone
- Bone substitutes in combination with soft tissue autografts
- Bone substitutes in combination with soft tissue substitutes.

From a surgical standpoint, either flapped and flapless approaches have been proposed. The flapped approach allows a primary intention healing due to coronal positioning of the buccal flap. Within the flapless approach, the "socket seal" technique has been introduced allowing a secondary soft tissue closure (Jung *et al*. 2004). The sealing of the socket orifice may be achieved by using either an autogenous or an exogenous barrier material. The purpose of both techniques is to protect the underlying bone compartment and assist soft tissue healing (Tonetti *et al*. 2019).

The efficacy of alveolar ridge preservation has been widely investigated through several systematic reviews and metanalyses (Avila-Ortiz *et al*. 2019). The effect of this procedure should be analyzed at the alveolar ridge dimension, implant, and patient level.

There is robust evidence that alveolar ridge procedures reduce the bone dimensional changes that occur after tooth extraction, although some degree of vertical and horizontal bone loss can still be expected (Ten Heggeler *et al*. 2011). Furthermore, all studies agree that the effect is more pronounced in the horizontal, rather than the vertical dimension. Results from a pooled quantitative analysis in a recent systematic review (Avila-Ortiz *et al*. 2019) demonstrated that alveolar ridge preservation prevented horizontal (M = 1.99 mm; 95% CI 1.54–2.44; P <0.00001), vertical mid-buccal (M = 1.72 mm; 95% CI 0.96–2.48; P <0.00001), and vertical mid-lingual (M = 1.16 mm; 95% CI 0.81–1.52; P <0.00001) bone resorption, as compared with spontaneous healing of the fresh extraction socket.

At the implant level, results from two systematic reviews highlighted less need of ancillary grafting at the time of implant placement (Mardas *et al*. 2015; Avila-Ortiz *et al*. 2019). Nevertheless, although the feasibility of implant placement was higher in sites that received alveolar ridge preservation, additional bone augmentation at the time of implant placement may still be required. Furthermore, when evaluating implant loss and implant success after a minimum of 12 months of functional loading with the final prosthesis, sites that received alveolar ridge procedures exhibited no differences compared with sites that underwent unassisted socket healing.

At the patient level, patient-related outcomes have been rarely reported. In two studies involving the use of autologous blood-derived products (Alissa *et al*. 2010; Temmerman *et al*. 2016), discomfort, perceived benefit, and quality-of-life scores were marginally in favor of alveolar ridge preservation therapies.

There are several factors that may influence the outcomes of therapy. These may be organized into three main categories: (1) the patient, (2) the fresh extraction socket, and (3) the surgical protocol. At the patient level, age, history of periodontal disease, systemic diseases, or smoking habits are all factors that may have an impact on the effect of therapy. Nevertheless, none of these systemic factors have been shown to be significant. When looking at the sites, reason for extraction, socket anatomy (single- or multi-rooted), integrity of extraction site, and buccal bone thickness have been explored as potential influencing factors. Buccal bone thickness has been highlighted as a crucial factor during the early spontaneous healing of the socket (Chappuis *et al*. 2015). In this 3D radiographic evaluation, the authors demonstrated that sockets presenting a thin (<1 mm) buccal bone at baseline demonstrated, after 8 weeks, seven times more mid-vertical buccal bone resorption as compared with sockets presenting a thick buccal bone wall. Taking this into consideration, when applying alveolar ridge preservation, no correlation between the initial thickness of the buccal bone and the final alveolar bone dimension was observed (Cardaropoli *et al*. 2014). This indicates that alveolar

ridge preservation masks the negative influence of a thin buccal bone. Indeed, the magnitude of effect of the application of alveolar ridge preservation-socket grafting is higher and more beneficial in sites exhibiting thin buccal bone (Avila-Ortiz *et al*. 2019).

When looking at the surgical protocol, several aspects have been explored, such as biomaterials utilized, modality of socket seal, flap elevation, primary or secondary closure, healing period. In an attempt to explore which of these factors mostly influenced the outcomes, a subgroup analysis with meta-regression was performed as part of a systematic review and meta-analysis (Vignoletti *et al*. 2012). The conclusions from the subgroup analysis demonstrated that: (1) the use of membranes; (2) primary intention healing; and (3) flapped surgical procedures were associated with less horizontal bone resorption. Similarly, the application of a xenogeneic or allogeneic bone grafting material and the necessity of sealing the socket orifice, has been strongly recommended in the consensus report of working group 3 on the management of the extraction socket of the XV European Workshop in Periodontology. This highlights the importance of achieving primary intention healing throughout the 3–4 months of recommended healing (Tonetti *et al*. 2019).

Bone regeneration at implants into fresh extraction sockets

According to the classification proposed at the Third ITI Consensus Conference (Hämmerle *et al*. 2004), immediate and early implant placement (type 1, 2) protocols have been indicated as the most suitable for implant placement following tooth extraction. The type 1 protocol (immediate implant placement) was first presented in 1976 by Schulte and Heimke (1976). The several advantages inherent to placing the implant immediately after tooth extraction have led to a growth in popularity of this protocol in the last decades and this has attracted the interest of clinicians and investigators (Fig. 41-5). Nevertheless, immediate implant placement has to be considered as a challenging procedure for the clinician. The osteotomy has to be performed in the palatal/lingual apical part of the socket to allow the ideal three-dimensional buccolingual and apicocoronal position together with adequate primary implant stability. It must also be kept in mind that most of the studies in the literature report on single unit, ideal, strictly selected cases with intact bony walls.

Based on preclinical and human studies, it is well accepted that implant placement into a fresh extraction socket does not counteract the physiologic bone modeling of the alveolar bone crest. Results from human trials have demonstrated that both vertical and horizontal dimensional changes of the alveolar crest may be expected. Botticelli *et al*. (2004) demonstrated a horizontal resorption of approximately 56% and 30% of the original dimension of the buccal and lingual bone walls of the sockets, respectively, when placing single-tooth immediate implants in the anterior region of the maxilla. These results are consistent with data from a similar study demonstrating 36% and 14% bone resorption at the buccal and palatal bone walls, respectively. Furthermore, the vertical bone resorption of the buccal bone crest was also investigated and amounted to a mean value of 1 mm (SD 2) (Sanz *et al*. 2010). These changes in the horizontal and vertical dimension were mainly influenced by the thickness of the buccal bone plate (>1 mm) and the gap that occurred between the implant surface and the buccal socket wall. Hence, implants placed into sockets with a ≤1-mm buccal thickness/gap are at higher risk of presenting a dehiscence defect that exposes the implant surface to the oral environment and a greater overall horizontal resorption of the alveolar crest.

To counteract these horizontal and vertical dimensional changes, the application of graft and/or barrier membranes and/or an autogenous or exogenous soft tissue graft (Fig. 41-6), in combination with either flapped or flapless surgery and the application of immediate provisionalization, have been proposed and investigated in combination with immediate implant placement.

It is widely accepted that the application of a graft material within the gap or in combination with a barrier membrane reduce in part the horizontal bone resorption that occurs after tooth extraction.

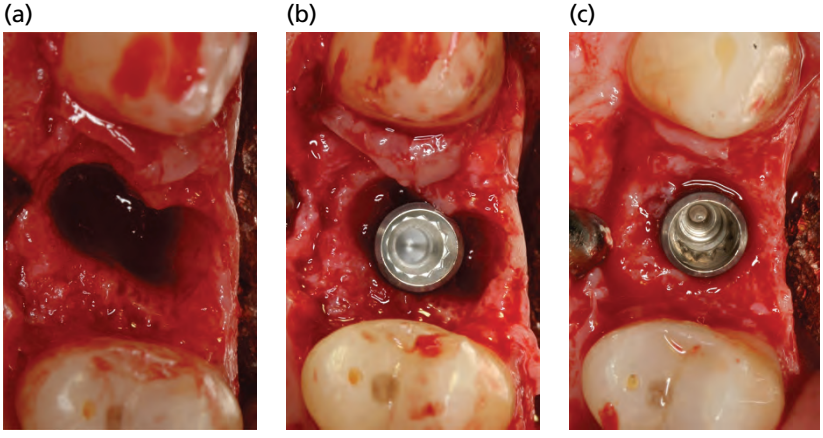

Fig. 41-5 (a) Class I defect (Hämmerle & Jung). Extraction of tooth 14. (b) Immediate implant placement and (c) re-entry procedure after 4 months of healing. Note the overall contraction of the maxillary ridge.

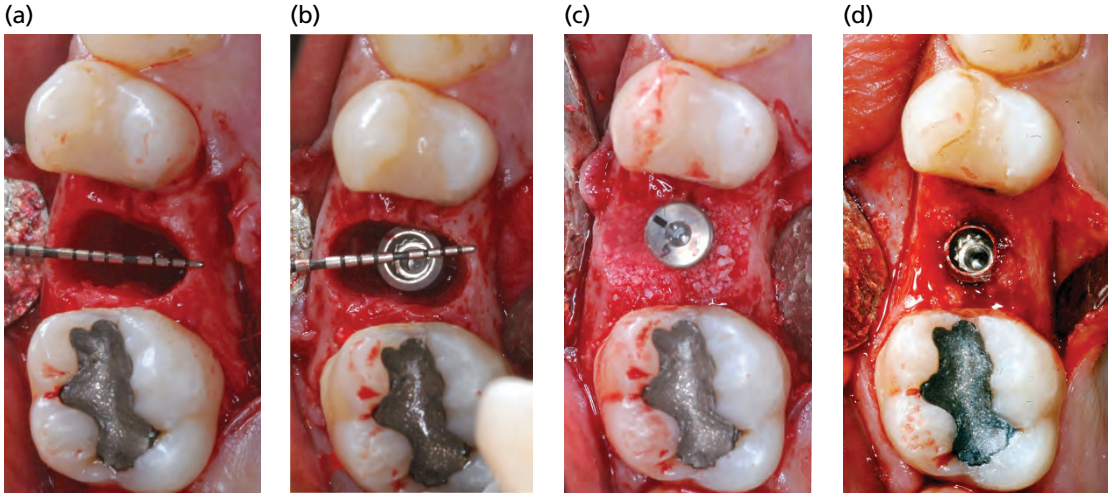

Fig. 41-6 (a) Class I defect (Hämmerle & Jung). Extraction of tooth 15. (b, c) Immediate implant placement with deproteinized bovine bone and porcine collagen fibers. (d) Re-entry surgery at 4 months. Outcome of the grafting procedure.

Several studies investigated the use of graft and/or barrier membranes in combination with immediate implants, assessing their effect on bone dimensional changes. Chen *et al*. (2007) compared three groups of treatment: (1) Immediate implants with a xenogeneic graft material alone, (2) immediate implants with a combination of graft material and a resorbable barrier membrane, and (3) immediate implants as control treatment. The horizontal bone resorption observed at the end of the study was 15%, 20%, and 48%, respectively. Differences were statistically significant between the two test treatments and the control group. Similarly, Sanz *et al*. (2016) observed 28.8% as compared with 37.8% buccal bone resorption, when using a xenogeneic bone graft within the gap as compared with immediate implant alone.

As this surgical protocol mostly applies to the maxillary highly aesthetic area, growing attention has been played to soft tissues. The introduction of volumetric analyses into clinical research allows for detailed evaluation of soft tissue vertical and horizontal changes that occur after immediate implant placement. Hence, a combination of hard tissue, soft tissue grafting and immediate provisionalization has been proposed recently.

Sanz-Martin *et al*. (2019) observed a mean 0.67 (SD 0.65) linear horizontal soft tissue reduction compared with baseline, after flapless immediate implant placement in combination with a buccally inserted xenogeneic bovine bone graft, a xenogeneic porcine collagen matrix, and immediate provisionalization (Fig. 41.7). Similarly, Van Nimwegen *et al*. (2018) observed a 0.68 mm (SD 0.59) linear horizontal reduction after flapless immediate implant placement in combination with a mixture of autologous bone and a xenogeneic bovine bone graft, a buccally inserted connective tissue graft, and immediate provisionalization. However, results from these combinations of treatment lack long-term follow-up data and definite conclusions cannot be drawn.

When evaluating survival and success rates, a systematic review estimated the prevalence of biologic, technical, and esthetic complications, and the magnitude of soft and hard tissue changes following implant placement immediately into fresh extraction sockets (Lang *et al*. 2012). On the basis of 46 included clinical trials, the 2-year survival rate of implants placed into extraction sockets was 98.4% (97.3–99%). Unfortunately, only limited long-term data were available for the occurrence of biologic complications. In terms of esthetic results, it was reported that about 20% of patients who underwent immediate implant placement suffered from suboptimal aesthetic outcomes due to buccal soft tissue dehiscence in studies with observation periods of 3 years or more. Important risk factors for unpredictable esthetic outcomes were the limited thickness of the buccal bone plate, thin gingival phenotype, and buccal positioning of the implant.

However, it must be taken into consideration that, although high survival rates for type 1 immediate implants have been reported in the literature, results from a recent systematic review and meta-analysis demonstrated higher early implant loss (94.9 % vs 98.9 %) compared with delayed implant placement, whereas similar outcomes were observed for marginal bone levels, probing pocket depths, and pink aesthetic scores (Cosyn et al. 2019).

To overcome some of these surgical/clinical limitations, the type 2 or early implant placement protocol has been advocated. This surgical protocol consists of performing the extraction and thoroughly cleaning the extraction socket, then waiting 4–6 weeks before placing the implant, which allows for soft tissue coverage and full healing of the extraction wound. The rationale for this surgical approach lies in the elimination of any infectious tissue, mostly in situations where the reason for the extraction was periapical or very deep periodontal pathology, and at the same time having enough soft tissue to allow

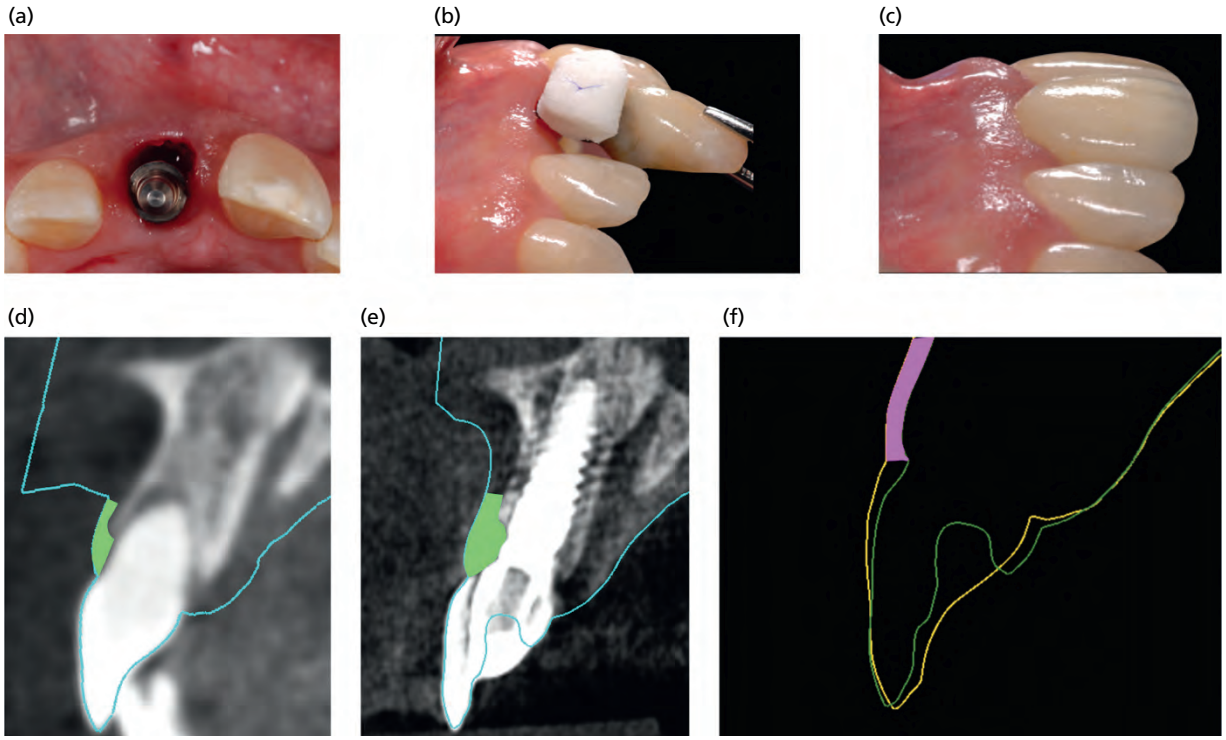

Fig. 41-7 (a) Immediate implant placement with a xenogeneic deproteinized bovine bone mineral. (b) Dimensions of the collagen matrix that is folded to increase its thickness. (c) Buccal view 6 months after surgery. (d, e) Baseline DICOM and STL files superimposed allowing for the evaluation of baseline soft tissue thickness (green area). An increase in soft tissue thickness may be appreciated between baseline and 6 months. (f) Reduction of the ridge profile (pink area) between implant placement (yellow line) and 6 months (green line). (Source: Adapted with permission from Sanz-Martin *et al*. 2019. Reproduced with permission from John Wiley & Sons, Inc.)

for primary intention healing during the implant therapy through a tension-free flap closure without altering the mucogingival line. This is particularly important because, in many clinical situations, the cause of extraction is deep periodontal or periapical pathology where the availability of bone is limited, and bone augmentation will be required in conjunction with the implant placement. The importance of early implant placement lies in the availability of the socket walls architecture, facilitating the placement of the implant and the required bone augmentation. Moreover, the evidence for a usually very thin (<1 mm) maxillary buccal bone wall (Huynh-Ba *et al*. 2010; Januario *et al*. 2011) makes the requirement for bone augmentation almost the norm whenever implants are placed in critically esthetic areas in the anterior maxilla, in spite of having enough vertical bone availability. The type 2 implant placement protocol may be considered in this indication. Not only is the bone height and width of the ridge mostly preserved, but there is also enough keratinized mucosa to allow for a successful bone augmentation procedure during the implant placement (Buser *et al*. 2008).

The efficacy of this surgical protocol has been studied in a systematic review comparing it to the standard type 3 (implant placement at least 3 months after tooth extraction). This reported the pooled mean difference between the type 2 versus type 3 protocols to be a 13.11% reduction of defect bone height and a 19.85% of reduction of defect bone width in favor of the type 2 protocol (Sanz *et al*. 2012). In terms of esthetic outcomes, based on two studies (Schropp *et al*. 2004; Schropp & Isidor 2008), at 2-year follow-up, patients were significantly more satisfied with the early placement protocol, both in terms of the appearance of the restoration and the overall experience with treatment. These differences, however, were lost at the 5-year follow-up. Nevertheless, although it appears from the literature that this protocol shows good performance both short and long term (Graziani *et al*. 2019), it has to be kept in mind that the evidence on type 2 implants is restricted to a limited number of experienced surgeons and patients and thus it is unclear if these data may be generalized (Tonetti *et al*. 2019).

Horizontal ridge augmentation

Horizontal ridge augmentation can be performed simultaneously with implant placement (one-stage) or in a two-stage or delayed approach. The use of particulate or block grafts with or without barrier membranes have been widely used and documented in lateral augmentation procedures (Fig. 41-8).

As far as the bone width availability allows for an ideal implant three-dimensional position and adequate primary stability, usually in class I bone defects, a one-stage horizontal ridge augmentation procedure should be considered. The use of particulate bone grafts together with barrier membrane

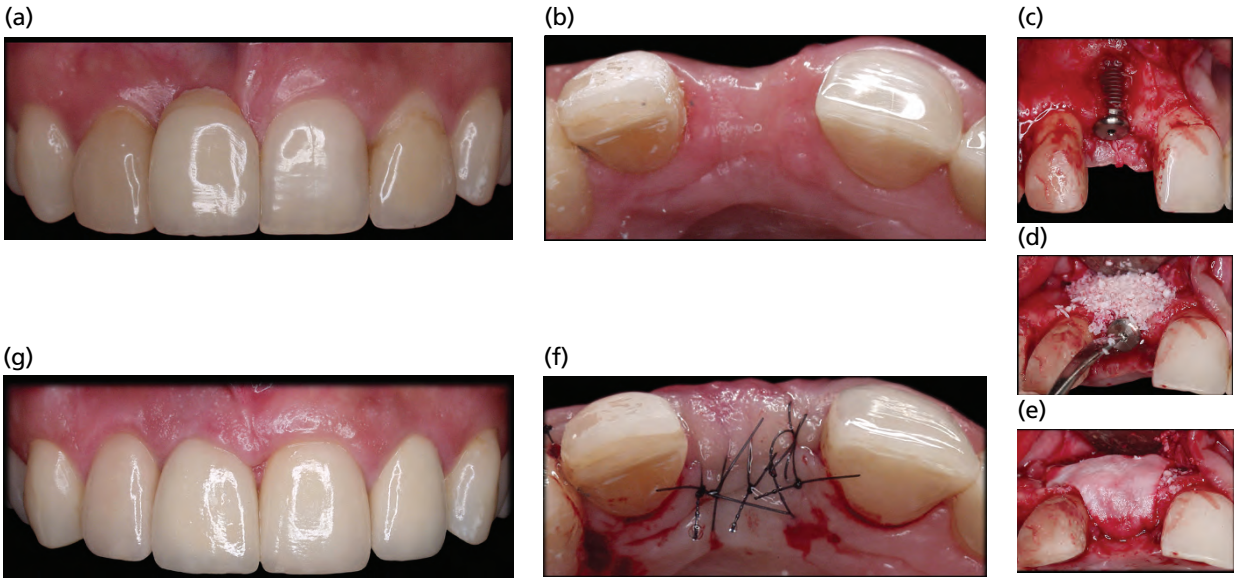

Fig. 41-8 (a, b) Class 2 defect (Seibert). (c–f) Implant placement and horizontal guided bone regeneration procedure with deproteinized bovine bone mineral + non-cross-linked collagen membrane. (g) Implant-supported prosthesis.

using the GBR principles is especially indicated in these types of clinical situations, being a well-established treatment modality. The efficacy of the procedure and the influence of various biomaterials on the outcomes have been recently investigated in a systematic review (Thoma *et al*. 2019). The most widely documented method for simultaneous lateral augmentation was the combination of a collagen membrane and a particulated xenogeneic grafting material. The overall mean vertical resolution of the defect was 81.3% (range 56.4–97.1) with a mean residual defect height of 0.9 mm (range 0.2–2.2) at re-entry. In terms of biomaterials, all barriers and biomaterial combinations yielded various degrees of defect resolution. Nevertheless, the bone augmentation was higher when a barrier membrane was used to cover the biomaterial (Thoma et al. 2019).

On the other hand, in severe class I defects, a delayed or staged ridge augmentation procedure is indicated. A block graft or a particulate bone graft in combination with a barrier membrane should be advocated to assure enough space maintenance to allow significant lateral augmentation. Both treatment strategies have been demonstrated to be successful and predictable treatment modalities to augment a horizontally deficient ridge and allow implant placement (Figs. 41-8, 41-9) (Fiorellini & Nevins 2003; Schwartz-Arad & Levin 2005; Schwartz-Arad *et al*. 2005; Sanz-Sanchez et al. 2015). Different authors have published several case series utilizing bone grafts for horizontal bone augmentation and have concluded that it is a reliable procedure. In 15 partially edentulous patients, 18 alveolar ridges were augmented with ramus or symphysis block grafts. The mean horizontal ridge augmentation was 6.5 ± 0.33 mm. At implant placement surgery, the graft had resorbed to 5.0 ± 0.23 mm, which is a reduction of 23.5%, but it was still sufficient for implant placement (Cordaro *et al*. 2002). Raghoebar *et al*. (2000) performed horizontal ridge augmentation on the edentulous mandibles of seven patients using autogenous block grafts. The bone width increased from 1.3 ± 0.3 mm to 5.6 ± 0.6 mm. Although after 3 months of healing, at implant placement, there had been a slight resorption of the bone width by 0.5 ± 0.3 mm, it was still sufficient for implant placement. In a controlled clinical study, 30 patients with inadequate bone width were assigned to two different groups: (1) GBR + e-PTFE + autograft and (2) autogenous onlay grafts only: 2.7 mm of horizontal bone gain was attained in the GBR group compared with 4.0 mm in the onlay graft group. The authors also found that the graft resorption was greater in the GBR group compared with the block graft group (40% vs 25%) (Chiapasco *et al*. 1999).

The use of autografts is currently somewhat limited due to the morbidity associated with their harvesting and their high resorption rate (mainly when used as bone chips). A recent systematic review reported an age dependent graft resorption. The authors indicated, based on the meta-analysis, that every additional year of age at the time of primary augmentation led to 0.05 mm more resorption of the augmented bone (Naenni *et al*. 2019). The use of bone substitutes, mainly of xenogeneic origin, together with resorbable membranes (collagen), has demonstrated good results in two-stage delayed horizontal bone augmentation techniques with minimal patient morbidity and few postoperative complications. Moreover, these xenogeneic grafts have a very slow resorption rate, which assure their long-term stability. A systematic review on the effectiveness of lateral bone augmentations indicated that the most frequently investigated therapy was the autologous block alone (Sanz-Sanchez *et al*. 2015). Results from the meta-analysis indicated that

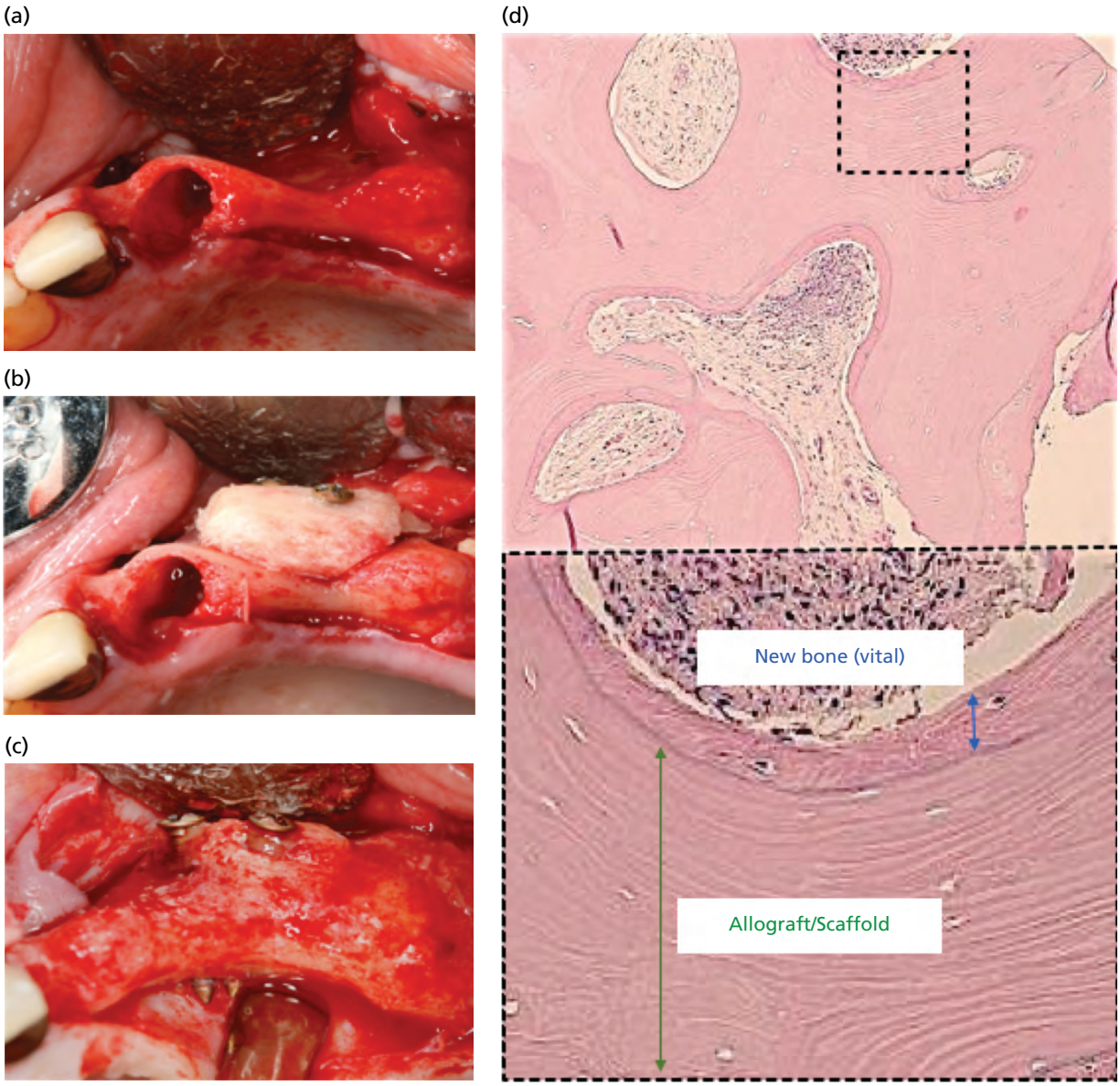

Fig. 41-9 (a, b) Use of an allograft block in the posterior maxilla. (c) Re-entry after 6 months. (d) Histologic evaluation of the regenerated bone shows significant osteoconductivity and incorporation of the allograft block particles with new/vital bone. Use of block grafts to overcome severe horizontal ridge deficiencies have proven very predictable.

the weighted mean gain for all studies on staged lateral augmentation was 3.90 mm (95% CI, 3.53, 4.28). The maximum bone width gain was reported for the combination of particulated xenograft plus autologous bone in combination with a resorbable membrane (5.68 mm; 95% CI, 5.00, 6.35), whereas the minimum was for the combination of particulated synthetic graft plus non-resorbable membrane (1.10; 95% CI, -0.33, 2.53).

According to Donos *et al*. (2008), the implant survival rate for staged GBR was 99–100%, while that for one-stage ridge augmentation was 87–95%, but this systematic review was hindered by a lack of randomized clinical controlled trials and heterogeneity of the available studies, thus restricting the number of studies included in the systematic review. These results are consistent with Sanz-Sanchez *et al*. (2015) who reported a mean high survival rate of 97.82% with a range in between 78.2% and 100%.

Ridge splitting/expansion

Another technique used in the maxilla to augment bone width through bone condensation is ridge splitting or ridge expansion osteotomy. Summers (1994a, b) first used this technique, osteocondensation, to augment bone width and elevate sinus floors in an attempt to avoid the lateral window sinus lift. This technique is preferably used in the maxilla because this bone is frequently type III or IV, which is more amendable to osteocondensation compared with type I or II bone. Chisels and osteotomes are used to produce longitudinal greenstick fractures in the bone and create osteotomy sites without the need for drilling. This preserves the compromised bone volume. The bone is compressed to the lateral surfaces with the use of osteotomes of increasing diameters, thus increasing its strength and density. The advantage of this technique is that it allows for the ideal

implant diameter to be placed in the restoratively driven position. In addition, the cancellous bone and marrow are exposed to grafting of the site, which improves revascularization and healing (Engelke *et al*. 1997). Summers (1994b) proposed the use of this technique if the alveolar bone is at least 3 mm wide on the basis of the assumption that this is the minimum width for cancellous bone found between the cortical plates. However, in a more recent study on cadavers, Katranji *et al*. (2007) found that the buccal plates in the edentulous maxilla and mandible had a mean cortical thickness of 1.0–2.1 mm. Therefore, it may be prudent to use this technique when the horizontal ridge width is 4–5 mm as at this width there is some cancellous bone between the cortical plates. This procedure is accompanied by simultaneous implant placement.

Ridge splitting and/or expansion are frequently described together because of their common treatment outcome: increase in horizontal bone width. Ridge splitting is essentially the fracture of the buccal cortical plate and its displacement laterally to accommodate implant placement. The spaces created between the cortical plates and the implants are subsequently filled with particulate bone graft materials (Scipioni *et al*. 1994; Engelke *et al*. 1997). Ridge expansion involves the creation of an osteotomy site with the initial implant drill and expansion of the site with osteotomes or the implant fixture. According to Chiapasco *et al*. (2006) and Kolerman *et al*. (2014), the reported bone widths gains were 3.5 mm (SD 0.93) and 3.9 mm (SD 0.8), respectively. In terms of implant survival rates, according to Donos *et al*. (2008), the implant survival rate ranged from 86.2% to 100%, while the success rate for the split osteotomy in achieving adequate ridge width for implant placement ranged from 87.5% to 97.8%.

Vertical ridge augmentation

In general, there is a lack of randomized controlled clinical trials evaluating the efficacy of these surgical techniques. Moreover, the available studies are very heterogeneous with relatively small sample sizes, which limits the ability to draw valid conclusions. From the limited information available, it appears that vertical augmentation is a highly technique-sensitive procedure which may give successful treatment outcomes, such as adequate gain in vertical bone height and successful implant placement (Fig. 41-10). Three treatment modalities have been proposed to treat vertical bone defects: GBR, onlay bone blocks, or distraction osteogenesis.

There are several published case series demonstrating the possibility of attaining a significant vertical bone augmentation, but also highlighting the technical difficulties and the high number of postoperative complications of this technique. In a small clinical study, six partially edentulous patients were recruited. Fourteen implants were placed, leaving the

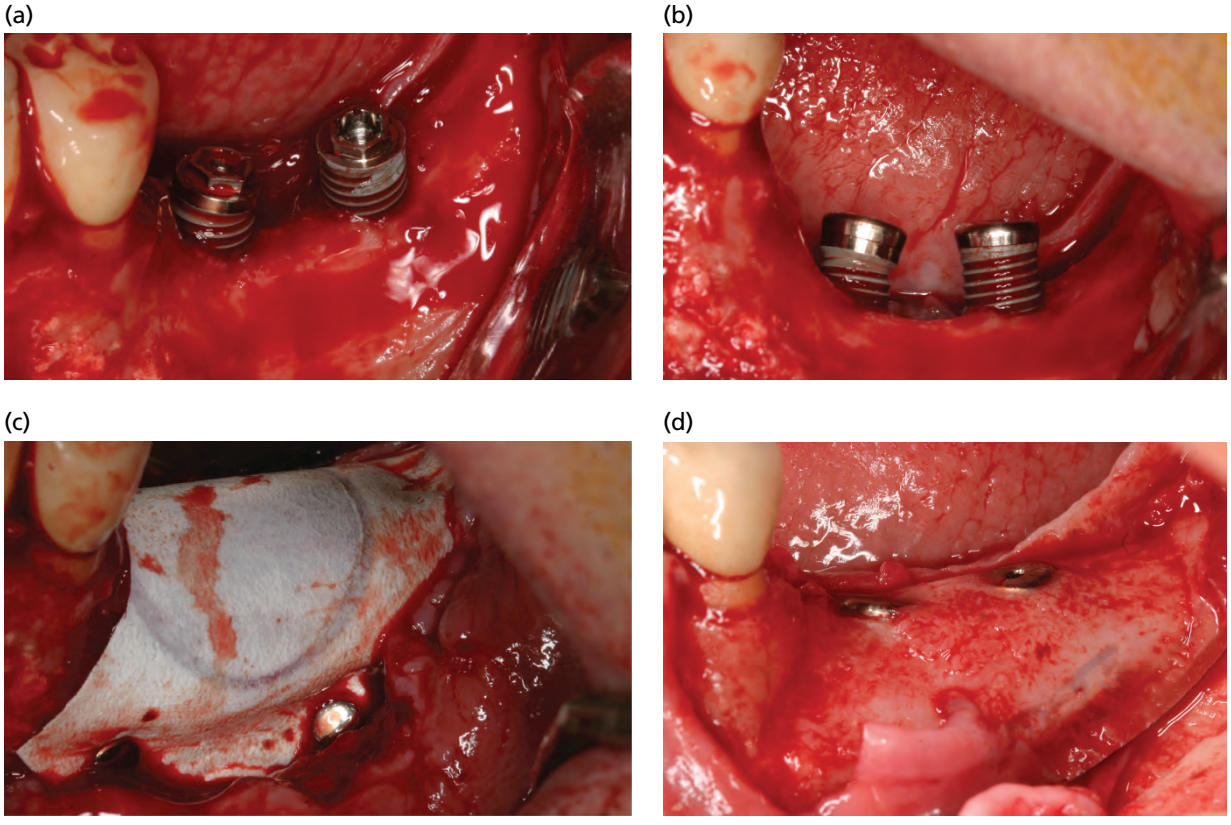

Fig. 41-10 (a–c) Class 3 defect (Seibert). Implant placement and vertical guided bone regeneration with an ePTFE membrane and autologous bone. (d) Re-entry surgery at 12 months. (Source: Courtesy of S. Morante.)

coronal third exposed circumferentially. Autogenous particulated bone grafts covered with titanium-reinforced e-PFTE membranes were used to cover the implants and the flaps were raised to allow for a submerged healing. An average of 4.95 mm of bone height was gained after 12 months in areas where the membranes were not exposed (Tinti *et al*. 1996). In a similar study, Simion *et al*. (1994) placed implants protruding 4–7 mm above the bone crest in five patients. e-PTFE membranes were used to cover the exposed implant threads. At 9 months, the histologic assessment showed bone formation up to 3–4 mm above the previous bone crest and the implant fixture was osseointegrated with the new bone. Most recently, a new titanium-reinforced non-resorbable membrane (high-density polytetrafluoroethylene), in combination with a mixture of anorganic bovine bone-derived mineral (ABBM) and autogenous particulated bone, was tested and used in vertical augmentation of deficient alveolar ridges, demonstrating successful results in terms of bone gain (Urban *et al*. 2014).

Onlay autologous bone blocks harvested from the chin or the mandibular retromolar area have been utilized for vertical ridge augmentation. Most recently, the split bone block technique has been introduced as a modification of the monocortical block autograft (Khoury & Hanser 2019) with the aim of accelerating bone regeneration and reducing graft resorption. The technique involves splitting the bone block into two bone laminae, which must then be reduced to a thickness of 1 mm each with a bone scraper. Once stabilized, the gap is filled with the autologous bone chips. In a case series with 146 treated patients, the authors demonstrated a mean vertical gain of 7.6 mm (SD 3.4). Similar results have been published by de Stavola and Tunkel (2013). In a 10 patient case series, the authors demonstrated a mean vertical gain of 6.50 mm (SD 1.43) with minimal bone graft resorption.

Distraction osteogenesis was initially used in orthopedics, and more recently adapted to augment deficient edentulous ridges. The technique involves three stages: (1) latency, (2) distraction, and (3) consolidation (Cano *et al*. 2006) (Fig. 41-11). In the latency phase, once the osteotomy has been performed, undisturbed healing takes place over 1 week. This is followed by the activation of the distractor, which is placed into the prepared site during surgery, with a daily controlled force that aims to separate the bone segments at a rate of 0.5–1 mm/day. Distraction is usually performed over a period of 30 days and significant bone gain can be attained (4–7 mm) (Gaggl *et al*. 2000). In the consolidation phase, a callus forms in the space between the bone segments and subsequently remodels into mature bone. This technique has the advantage of not requiring a donor site and the significant bone gain obtained can be in the vertical, horizontal, or both directions. However, distraction osteogenesis has frequent complications, sometimes of a severe nature, such as fracture of the mandible or the moveable segment. Increased patient discomfort during the activation of the device and the incorrect direction of the distractor leading to excessive bone on the lingual side are also frequent complications; the latter leads to inadequate bone formation (Saulacic *et al*. 2009).

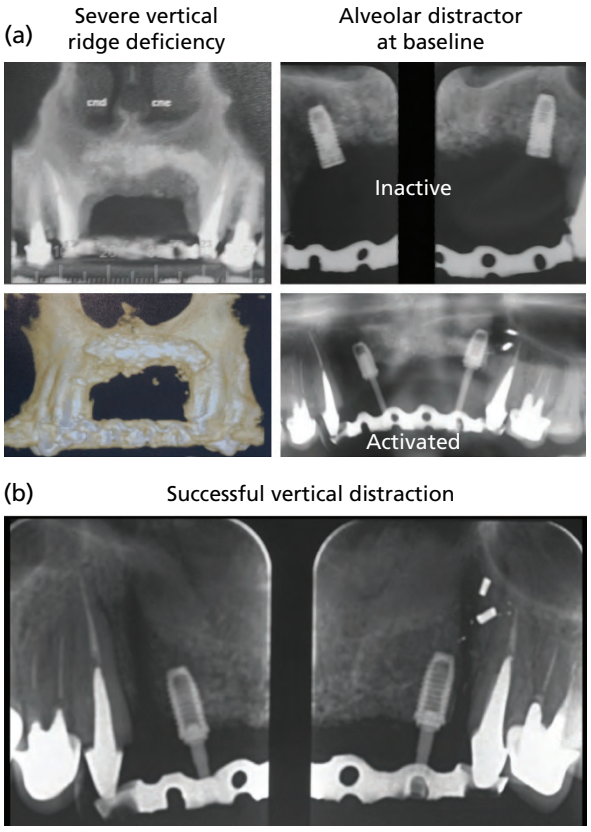

Fig. 41-11 Distraction osteogenesis. Stabilization of the ridge using a unidirectional vector distractor and successful vertical ridge compensation in the anterior maxilla. (Source: Courtesy of T. Valcanaia.)

According to a recent systematic review and meta-analysis (Urban *et al*. 2019), the most frequently investigated treatment modality was GBR. The weighted mean clinical vertical bone gain for all included studies was 4.16 (95% CI: 3.72–4.61 mm). Nevertheless, the clinical vertical bone gain varied among the different procedures. The weighted mean gains were 8.04 mm, 4.18 mm, and 3.46 mm for distraction osteogenesis (three studies), GBR (20 studies), and bone blocks (12 studies), respectively. The weighted mean complication rate was of 16.9% (95% CI: 12.5–21). This result is consistent with another systematic review (Rocchietta *et al*. 2008) that reported a broad range of technique-related complications. For GBR, the reported complication rates were 0–45.5% and complications were mainly related to membrane exposure. For distraction osteogenesis, complication rates were higher (10–75.7%), and complications included fractures or infection of the distractor, neurologic alterations, fractures of the distracted or basal bone, and lingual or palatal inclination of the distracted bone. Minor complications were reported after onlay block bone grafting and these were related to the morbidity from harvesting the block and graft shrinkage.

Taking into consideration the difficulties in performing these techniques, the common complications, and the heterogeneity and lack of quality of the available scientific evidence, their use should not be generalized, but rather limited to very experienced operators (Jepsen *et al*. 2019).

Emerging technologies

Growth factors

Tissue regeneration currently requires three main components: cells, scaffolds (matrices), and signaling molecules such as growth factors. Each of these components, together with sufficient vascularization, wound stability, and time, play an important role in regeneration. The introduction of growth factors has launched a new era in wound healing, and periodontal and bone regeneration in medicine and dentistry (Pilipchuk *et al*. 2018; Vaquette *et al*. 2018). The rationale behind the use of these natural biological mediators is to regulate crucial cellular events involved in tissue repair, including DNA synthesis, cell replication, chemotaxis, differentiation, matrix synthesis, and tissue vascularization (Larsson *et al*. 2016; Giannobile *et al*. 2019). Wound healing approaches using growth factors to increase bone volume have significantly advanced the fields of oral regenerative medicine reconstructive procedures. A major focus of oral regenerative research has been the impact of tissue growth factors on bone and tissue regeneration (Giannobile 1996; Anusaksathien & Giannobile 2002; Nakashima & Reddi 2003; Raja *et al*. 2009; Kaigler *et al*. 2011). Advances in molecular cloning have made available unlimited quantities of recombinant growth factors for applications in tissue engineering in the oral cavity. Recombinant growth factors known to promote skin and bone wound healing, such as PDGF (Rutherford *et al*. 1992; Giannobile *et al*. 1994; Camelo *et al*. 2003; Ojima *et al*. 2003; Nevins *et al*. 2005; Judith *et al*. 2010), IGF (Lynch *et al*. 1991; Giannobile *et al*. 1994, 1996; Howell *et al*. 1997), FGF (Murakami *et al*. 2003; Cochran *et al*. 2016; Aoki *et al*. 2021), and BMP (Sigurdsson *et al*. 1995; Giannobile *et al*. 1998; Wikesjo *et al*. 2004; Huang *et al*. 2005, Avila-Ortiz *et al*. 2016), have been used in preclinical and clinical trials for the treatment of large ridge and alveolar deficiencies (Jung *et al*. 2003; Fiorellini *et al*. 2005; Nevins *et al*. 2005; Nevins *et al*. 2013). Currently, there are two recombinant proteins clinically used to enhance and promote edentulous ridge augmentation and extraction socket healing, BMP-2 and PDGF-BB (Avila-Ortiz *et al*. 2016; Tavelli *et al*. 2020). Examples of studies using growth factors for regenerative approaches in teeth, implants, and alveolar ridge augmentation are shown in Table 41-1.

Table 41-1 Clinical studies of growth factors for periodontal, peri-implant and alveolar ridge regeneration.

Growth factors	Periodontal application	Implant-based application	Alveolar ridge construction/sinus augmentation
BMP-2	Off-label indications only	**Peri-implant bone regeneration** Rotenberg & Tatakis 2011	**Sinus augmentation** Boyne *et al*. 1997, 2005; Triplett *et al*. 2009; Lin *et al*. 2016 **Extraction socket augmentation** Howell *et al*. 1997a; Cochran *et al*. 2000; Bianchi *et al*. 2004; Fiorellini *et al*. 2005; Huh *et al*. 2011; Misch 2010, 2011; Coomes *et al*. 2014 **Alveolar ridge construction** Jung *et al*. 2003; de Freitas *et al*. 2013;
PDGF-BB	**Periodontal osseous defect** Howell *et al*. 1997b; Camelo *et al*. 2003; Nevins *et al*. 2003, 2005, 2013; Sarment *et al*. 2006; Ridgway *et al*. 2008; Jayakumar *et al*. 2011; Thakare & Deo 2012; Mishra *et al*. 2013; Maroo & Murthy 2014; Calin & Patrascu 2016; **Soft tissue augmentation** McGuire *et al*. 2009, 2014; Deshpande *et al*. 2014	Off-label indications only	**Alveolar bone reconstruction** Fagan *et al*. 2008; Simion *et al*. 2008; Nevins *et al*. 2014 **Maxillary sinus floor augmentation** Nevins *et al*. 2009 **Ridge preservation** Nevins *et al*. 2011; Wallace *et al*. 2013
FGF-2	**Periodontal osseous defect** Kitamura *et al*. 2011; Cochran *et al*. 2016	Off-label indications only	Off-label indications only
GDF-5	**Periodontal wound healing** Stavropoulos *et al*. 2011b; Windisch *et al*. 2012	Off-label indications only	**Maxillary sinus floor augmentation** Stavropoulos *et al*. 2011a
Teriparatide	**Osseous periodontal defect** Bashutski *et al*. 2010, 2012	**Osseointegration** Kuchler *et al*. 2011	Off-label indications only

(Adapted from Nevins *et al*. (2019). Reproduced with permission from John Wiley & Sons.)

Biologic and clinical effects of PDGF for ridge augmentation

PDGF is a member of a multifunctional polypeptide family that binds to two cell membrane tyrosine kinase receptors (PDGF-Rα and PDGF-Rβ) and subsequently exerts its biologic effects on cell proliferation, migration, extracellular matrix synthesis, and antiapoptosis (Heldin *et al*. 1989; Rosenkranz & Kazlauskas 1999). PDGF-α and -β receptors are expressed in regenerating periodontal soft and hard tissues (Parkar *et al*. 2001). In addition, PDGF initiates cell chemotaxis (Nishimura & Terranova 1996), mitogenesis (Oates *et al*. 1993), matrix synthesis (Haase *et al*. 1998), and attachment (Zaman *et al*. 1999). More importantly, *in vivo;* application of PDGF alone or in combination with (IGF-1 enhances mineralized tissue repair (Lynch *et al*. 1991; Rutherford *et al*. 1992; Giannobile *et al*. 1996). PDGF has been shown to have a significant regenerative impact on periodontal ligament cells as well as on osteoblasts (Matsuda *et al*. 1992; Oates *et al*. 1993; Marcopoulou *et al*. 2003; Ojima *et al*. 2003). Based on the available data from 63 human clinical studies as reported by Tavelli *et al*. (2020), the following conclusions can be drawn: (1) the utilization of rhPDGF is safe when used in combination with a variety of bone matrices, including allografts, xenografts, or alloplasts for GBR and alveolar ridge preservation; (2) the outcomes are consistent for PDGF for GBR and sinus augmentation procedures: this evidence is based on randomized controlled trials, and also case reports and case series; (3) the outcomes are also positive for PDGF for alveolar ridge preservation using histologic outcomes for vital bone and future randomized clinical trials should focus on the effects of PDGF in alveolar ridge preservation, GBR, and sinus floor augmentation procedures. Moreover, it is important to determine whether GBR with PDGF can be used with or without a barrier because the material may reduce the chemotactic potential of the growth factor.

Biological and clinical effects of BMPs for ridge augmentation

BMPs are multifunctional polypeptides belonging to the TGF-β superfamily of proteins (Wozney *et al*. 1988). The human genome encodes at least 20 BMP (Reddi 1998). BMPs bind to type I and II receptors that function as serine–threonine kinases. The type I receptor protein kinase phosphorylates intracellular signaling substrates called Smads (*Sma* gene in *Caenorhabditis elegans* and *Mad* gene in *Drosophila*). The phosphorylated BMP-signaling Smads enter the nucleus and initiate the production of other bone-related matrix proteins, leading to bone morphogenesis. The most remarkable feature of BMPs is their ability to induce ectopic bone formation (Urist 1965). BMPs are not only powerful regulators of cartilage and bone formation during embryonic development and regeneration in postnatal life, but also participate in the development and repair of other organs such as the brain, kidney, and nerves (Reddi 2001).

Studies have demonstrated the expression of BMP during tooth development and periodontal repair, including alveolar bone (Aberg *et al*. 1997; Amar *et al*. 1997). Investigations in animal models have shown the potential repair of alveolar bony defects using rhBMP-12 (Wikesjo *et al*. 2004) or rhBMP-2 (Lutolf *et al*. 2003; Wikesjo *et al*. 2003). In a clinical trial, rhBMP-2 delivered by a bioresorbable collagen sponge revealed significant bone formation in a human buccal wall defect model following tooth extraction when compared with the collagen sponge alone (Fiorellini *et al*. 2005). Furthermore, BMP-7, also known as osteogenic protein-1, has demonstrated the ability to stimulate bone regeneration around teeth, around endosseous dental implants, and in maxillary sinus floor augmentation procedures (Rutherford *et al*. 1992; Giannobile *et al*. 1998; van den Bergh *et al*. 2000).

In published randomized clinical trials on ridge augmentation procedures, most studies favored the use of rhBMP-2 (Lin *et al*. 2016). Augmentation of extraction sockets with severe dehiscence was also included in the systematic review and it was demonstrated that BMP can assist in regenerating lost buccal bone for ridge augmentation. Between 3 and 6 months of follow-up, all studies used computed tomography (CT) to measure the clinical outcome in terms of bone height and alveolar ridge width.

In summary, clinical applications of rhBMP-2 on dental implant therapy-related bone augmentation procedures, including extraction socket grafting and alveolar ridge augmentation, are promising. Surface modification of dental implants to release BMP-2, enhanced delivery, or immobilization methods, are still under preclinical development (Haimov *et al*. 2017). Numerous randomized controlled clinical trials have proven that rhBMP-2 applications for ridge preservation or augmentation for implant therapy are effective and promising (Jung *et al*. 2003; Fiorellini *et al*. 2005).

Cell therapy

Cells are central to new tissue growth and differentiation. Cell-based therapy is a specific branch of tissue engineering in which a defined population of cells is transplanted into a defect site to promote accelerated and enhanced wound healing in that area (Moreno-Sancho *et al*. 2019). Cell delivery approaches are used to accelerate edentulous ridge regeneration through two primary mechanisms: (1) use of cells as carriers to deliver growth factors that promote tissue regeneration to host cells; and (2) provision of cells that are able to differentiate into multiple cell types directly involved in the regenerative response. For successful regenerative outcomes, this population of cells must integrate into the host tissues. Such therapies

can involve a wide variety of cell types, including somatic cells and stem cells. Due to the inherent challenges in reconstruction of large bone defects, identification and characterization of the cell populations being used is essential to clinical grafting success.

Stem cell research has soared in the past few years and the effects of these cells on healing and regenerative potential have been extensively studied. Cell therapy approaches involving mesenchymal stem cells (MSCs) are emerging as a potentially viable therapeutic modality undergoing preclinical and clinical investigation. MSCs are self-renewing cell populations originally identified in the bone marrow (Friedenstein *et al*. 1978; Caplan *et al*. 1991). First described as non-hematopoietic precursor cells with fibroblast morphology, they were initially characterized by their clonogenicity but later demonstrated to exhibit *in vivo* bone-forming potential and multipotency, having the capacity for their differentiation to be driven toward osteogenic, chondrogenic, and adipogenic phenotypes (Krebsbach *et al*. 1997; Kuznetsov *et al*. 1997; Pittenger *et al*. 1999). In addition to bone marrow, it has more recently been recognized that MSCs can be isolated from a variety of other tissues including adipose, muscle, alveolar bone, and tooth-related tissues (i.e. dental pulp, gingiva, periodontal ligament) (Gronthos *et al*. 2000; Zuk *et al*. 2001; Miura *et al*. 2003; Seo *et al*. 2004; Zhang *et al*. 2012; Mason *et al*. 2014). MSCs have tremendous potential in periodontal and alveolar bone regenerative procedures owing to their multipotency and capability to form a variety of tissues. In addition to tissue differentiation, their trophic and immunomodulatory properties are being investigated as factors influencing their capacity for bone regeneration indirectly through promoting tissue neovascularization and modulating inflammation during surgical wound healing. In periodontal and alveolar bone tissue engineering, both extraoral and intraoral derived stem cells can be harvested and then subjected to enrichment and expansion techniques to exponentially increase their numbers for transplantation. Within this context, multiple sources of stem cells have been evaluated for the treatment and regeneration of the edentulous ridge (Huang *et al*. 2009). There is strong potential for the use of MSC sources from outside the oral cavity for transplantation to the oral and craniofacial complex (Ward *et al*. 2010; Polymeri *et al*. 2016).

Bone marrow stromal cells have also been shown to promote bone healing and dental implant osseointegration (Bueno & Glowacki 2009). In a series of studies, Yamada *et al*. (2004) used a combination of platelet-rich plasma as an autologous scaffold with *in vitro*-expanded bone marrow stromal cells to increase osteogenesis in dental implant surgery. This "autogenous injectable bone treatment" (Fig. 41-12) resulted in higher marginal bone levels, better bone–implant contact, and increased bone density compared with controls. Recently, cells harvested from the bone marrow were driven down MSC pathways via an automated single-pass perfusion process to promote bone regeneration in a number of different clinical situations including tooth extraction socket defects, sinus floor augmentation, and large horizontal and vertical defects secondary to trauma and congenital cleft deformities (Kaigler *et al*. 2010, 2013, 2015; Rajan *et al*. 2014; Bajestan *et al*. 2017).

Scaffolding matrices to deliver genes, proteins, and cells

Scaffolding matrices are used in tissue engineering to provide an environment where space is created and maintained over a period of time for cellular growth and tissue in-growth. These matrices serve as 3D template structures to physically support and facilitate periodontal tissue regeneration when combined with cell- or gene-based tissue engineering. Over the

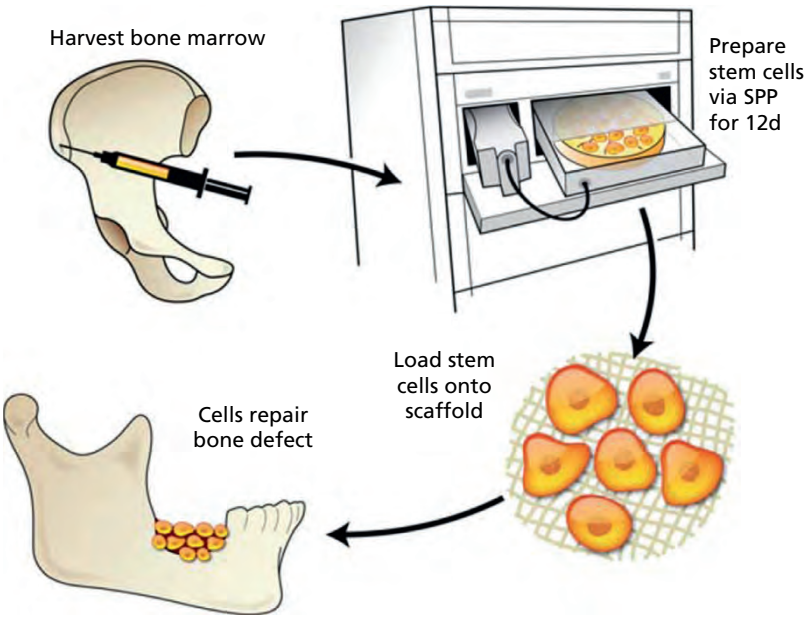

Fig. 41-12 Bone repair cell production. After harvest of bone marrow aspirates, cells are cultured using an automated, closed-system, single-pass perfusion (SPP) process. After 12 days of cell expansion in this bioreactor system, cells are packaged and delivered to the bone regenerative site on a biodegradable sponge. (Source: Kaigler *et al*. 2020.)

past two decades, scaffolds have been extensively developed, studied, and utilized. Regardless of the type and structure of the scaffold, there are a few key fundamental requirements of scaffold design that have served as the basis for scaffold development (Murphy & Mooney 1999). When applied to tissue engineering, scaffolds should: (1) provide a 3D architecture that supports a desired volume, shape, and mechanical strength; (2) have a high porosity and surface-to-volume ratio with a well-interconnected open pore structure to promote high seeding density and embrace bioactive molecules; (3) be biocompatible; and (4) degrade at a controlled rate and pattern that allows sufficient support until tissue defects are fully resolved.

Transplantation of cells for dental and craniofacial tissue engineering can be carried out via tissue-engineered scaffolds (Kaigler & Mooney 2001; Pagni *et al*. 2012) that provide adhesion and anchorage for interacting stem cells in order to control the presentation of adhesion sites, thereby improving cell survival and participation (Alsberg *et al*. 2003; Davis *et al*. 2005). Through similar cell therapy approaches, extensive reconstructions are becoming more predictable, as demonstrated by the regeneration of a mandible formed in a patient by using a metal and polymer scaffold seeded with stem cells and BMP (Warnke *et al*. 2004).

Bioactive molecules, such as growth factors, may also be encapsulated into nano-/micro-particles that are embedded in matrices to aid their sustained release, thereby enhancing stimuli for tissue formation. Other approaches using scaffolds include mimicking stem cell niches to regulate daughter cell proliferation, differentiation, and dispersion into surrounding tissue or attracting useful cells to a desired anatomic site (Discher *et al*. 2009).

Scaffold fabrication technologies as applied to periodontal tissue engineering include conventional prefabricated scaffolds, such as a particulated, solid form; injectable scaffolds that are adapted or administered into a periodontal defect; and novel image-based designs that result in a 3D-printed scaffold that is customized to fit into a defect.

Prefabricated scaffolding matrices

Personalized scaffolding technology utilizing 3D-imaging and 3D-printing has been very useful in the development of new prototype biomaterials for craniofacial reconstruction. Conventionally, dental and skeletal relationships are analyzed through wax-ups, 2D radiographs, photographs, and articulators, which is time consuming and cumbersome. In many complex cases, such as facial asymmetry, the analysis of skeletal movements using traditional 2D approaches is difficult (Janakiraman *et al*. 2015). In these cases, 3D-imaging builds a platform in which dental and skeletal features are documented accurately allowing a precise diagnostic system that increases the efficiency of treatment planning (Edwards 2010). Conventional scaffolds used to regenerate tissue *in vivo* are prefabricated, and many techniques have been described that produce both natural and synthetic polymeric scaffolds. Naturally derived scaffolds include autografts, allografts, and xenografts. Alloplasts and other polymers are synthetically engineered materials consisting of bioactive molecules that serve a similar purpose to natural scaffolds.

Naturally derived scaffolds

There are many naturally derived scaffolds used for tissue engineering applications. Freeze-dried bone allograft (FDBA) is a mineralized bone graft that has been suggested to promote osteoinductive and osteoconductive bone regeneration, although reports of its regenerative effectiveness have been mixed (Altiere *et al*. 1979; Dragoo & Kaldahl 1983; Goldberg & Stevenson 1987). Variability in preparations of the allograft, and its regenerative potential and osteoinductive ability, is seen between different bone banks (Shigeyama *et al*. 1995; Schwartz *et al*. 1996). Nonetheless, FDBA appears to be a practical material for regeneration of periodontal attachment apparatus. Xenogenic grafts show physical and chemical similarities to human bone matrix, and they have been successful in various periodontal and implant-related bone repair cell delivery applications (Nevins *et al*. 2006). Deproteinized bovine bone mineral has osteoconductive properties (Hämmerle *et al*. 1998).

Synthetic biomimetic polymer scaffolds

Synthetic polymers have been studied extensively as gene therapy delivery systems since it is easier to modify their properties, such as by controlling their macrostructure and degradation time, compared with naturally derived scaffolds (Jang *et al*. 2004). Furthermore, the release mechanism and exposure duration of bioactive molecules, such as growth factors, can be controlled (Ramseier *et al*. 2006). By acting as a localized gene depot, synthetic polymer scaffolds have the ability to maintain the therapeutic level of encoded proteins, which limits unwanted immune responses and potential side effects (Ghali *et al*. 2008).

Polymers such as the poly(lactic-co-glycolic acid) (PLGA) have drawn much attention for their excellent properties for encapsulation of genes (Mundargi *et al*. 2008). PLGA microspheres have been used to deliver antibiotics, as an occlusive membrane for GTR, as a growth factor carrier for periodontal regeneration, and for cementum and complex tooth structure engineering (Williams *et al*. 2001; Kurtis *et al*. 2002; Young *et al*. 2002; Jin *et al*. 2003; Cetiner *et al*. 2004; Moioli *et al*. 2006). However, while microsphere systems have demonstrated promising results, new microtechnology approaches today are focusing on nano-sized particles (Agarwal & Mallapragada 2008). Nanotechnology has been

attracting much attention for therapeutic agent and gene delivery and a number of studies and reviews have delineated its contribution and capability to meet challenges of current regeneration therapy (Agarwal & Mallapragada 2008; Mundargi *et al*. 2008; Sanvicens & Marco 2008).

The nanoscaled fibrillar structure of collagen shows promising effects on cellular biologic activities and suggests potential for a synthetic polymer scaffold that mimics the nanofibrous structure of collagen (Woo *et al*. 2007). Furthermore, a recent study has developed macroporous polymer scaffolds with varying pore wall architecture in order to enhance the environment for induction of cellular activity and provide guidance for 3D regeneration (Wei & Ma 2009). Therefore, a delivery scaffold can provide a suitable environment for targeted cells and tissues, as well as controlling the dynamic release of entrapped biologics. Periodontal therapy based on these systems, however, remains in its infancy.

The use of hyaluronic acid (HA) in the dental field has been demonstrated to restore periodontal defects and to carry and deliver growth factors such as BMP and FGF-2 (Wikesjo *et al*. 2003). An *in vitro* study has shown an HA and collagen (Col) combination scaffold to be a suitable environment for the growth of human periodontal ligament cells and therefore its potential in periodontal tissue engineering (Wang *et al*. 2009).

Inorganic calcium phosphate-based materials have also been used as delivery systems. Materials such as β-TCP are synthetic scaffolds that can be used to repair osseous defects around teeth or dental implants by acting as a bone substitute or as a carrier for growth factor delivery (Gille *et al*. 2002).

Hydrogels, formed by the cross-linking or self-assembly of a variety of natural or synthetic hydrophilic polymers to produce structures that contain >90% water, are obtained from natural materials such as collagen chitosan, dextran, alginate, or fibrin. They are favorable for tissue engineering due to their innate ability to interact with cells while undergoing controlled degradation (De Laporte & Shea 2007; Moioli *et al*. 2007; Agarwal & Mallapragada 2008). Vector release from hydrogels is dependent upon the physical structure and degradation of the hydrogel, and its interactions with the vector (De Laporte & Shea 2007).

Computer-based applications in scaffold design and fabrication

Computer-based and image-based scaffolding technology has been increasingly used in the alveolar ridge reconstruction for implant site development (Yu *et al*. 2019). 3D-printed diagnostic models and preoperative templates are widely applied for ridge augmentation in severe vertical and horizontal bony defects (Draenert *et al*. 2017; Al-Ardah *et al*. 2018). Despite the advanced applications of cone-beam computed tomography (CBCT) combined with computer aided design/manufacturing (CAD/CAM) fabrications, current 3D-printing for alveolar ridge augmentation is limited using printing templates, which might not directly induce bone regeneration as inert biomaterials. Considering its clinical potential in other specialties, future directions suggest applying 3D technology using osseoinductive and osseoconductive biomaterials will better enhance bone and tissue regeneration for vertical and horizontal ridge augmentation supporting implant placement.

In the rehabilitation of partially or fully edentulous patients with a lack of maxillary posterior bone support, sinus floor augmentation is required prior to dental implant placement. An anatomically sinus-specific block graft that can be fabricated via 3D technology for bone augmentation has recently been introduced in a clinical trial for lateral sinus augmentation (Mangano *et al*. 2013). Briefly, the scaffold manufacturing process applies a virtual plan and designs a custom-made scaffold. The 3D fabrication of the scaffold is performed using the CAM technique. The customized block graft is created from an original hydroxyapatite (HA) block using a cutting guide also made from 3D-image-based analysis and planning. The use of 3D-imaging and 3D-printing for fabrication of customized scaffolding technology to regenerate alveolar ridges is a rapidly growing research field. With continued advancement of novel 3D-imaging technologies, broader and more accurate clinical applications are anticipated combining printing with imaging to customized reconstructive scaffolds to repair large bone defects in the jaws (Yu *et al*. 2019). As bioprinting technology evolves to meet the scrupulous criteria that human tissues demand for their repair and regeneration, it can be expected that tissue engineering will become increasingly feasible and predictable. Continued development of precise and reproducible techniques will eventually facilitate translation into clinical practice.

Future perspectives

Tissue engineering is making an important impact on alveolar bone regeneration therapy. The use of cell and gene therapy to enhance and direct periodontal wound repair into a more predictable regenerative path is being exploited in bioengineering efforts aimed at developing a therapeutic system to promote bone repair (Yu *et al*. 2019). Various novel delivery scaffolding systems are being extensively studied and fabricated, and are demonstrating capabilities to meet the challenges of current regeneration therapy. However, numerous challenges remain. A major obstacle is how to maximize the utility of cells/genes delivered to a passive or permissive environment where there is context for the type of cell needed, but in which very few biologic signals are given to encourage normal cell function (Polymeri *et al*. 2016).

Other obstacles, such as identifying cell sources and clinically relevant cell numbers, the integration of new cells into existing tissue matrices, and the achievement of functional properties of tissue equivalents using an expanded repertoire of biomaterials, also need to be confronted in the field of tissue engineering. Practical and regulatory requirements will also need to be met before the technologies of cell and gene transfer can be applied in the clinical arena.

Collectively, the cell-based, scaffold, and gene therapy methods interface and complement each other to enhance the potential to restore tissue function and structure in a predictable manner (Figs. 41-13, 41-14, 41-15). It is expected that in the future that there will be greater usage of bioactive molecules such as growth factors or bone anabolic agents to accelerate and enhance the healing potential of the defects, bringing about faster, easier, and predictable treatment outcomes. The success and the future of alveolar bone regenerative medicine will need to be supported by the understanding of and the ability to recognize clinical scenarios that will benefit from one or an integration of these new emerging technologies for both horizontal and vertical ridge reconstruction.

Conclusion

In general, ridge augmentation procedures have become increasingly predictable. The correct selection and application of the available techniques and biomaterials are key determinants of implant survival/success rates. Currently, research in the field of advanced bone grafting is directed at overcoming the technical and biologic limitations that continue to challenge implant dentistry. The use of novel scaffolding biomaterials, bioactive molecules, and advanced surgical techniques offers potential in the creation of increased bone volume and predictability in the treatment of challenging bone defects. Only through further research and development in the area of scaffold fabrication, along with cell-based and gene therapy, can tissue engineering continue to advance.

Acknowledgments

The authors thank Dr. Hector Rios for valuable contributions to this chapter. The authors appreciate the assistance of Mr. Chris Jung with the figures.

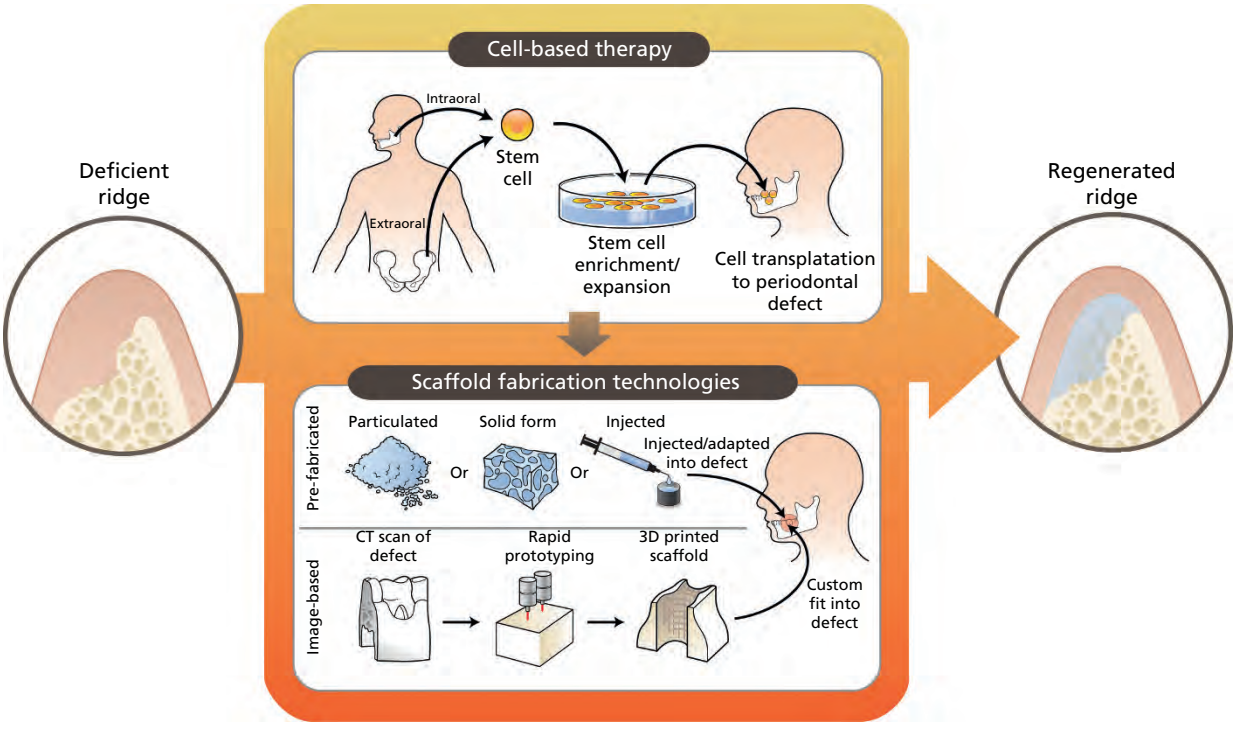

Fig. 41-13 New emerging technology for the treatment of edentulous ridge deficiencies. Research advances enable the integration of cell therapy and novel scaffold fabrication technologies. This promising modality could enhance predictable rapid tissue regeneration and ultimately the outcome of implant therapy. Extraoral and intraoral stem cells represent a viable and accessible source from which to harvest and expand multipotent colonies. Adequate cell density could be reached *in vitro* in a controlled environment and made readily available. Prefabricated and image-based scaffolds are becoming an essential component in regenerative medicine. A defined supporting structure allows the localization and guidance of the appropriate cells and proteins, and the establishment of a mechanically competent environment.

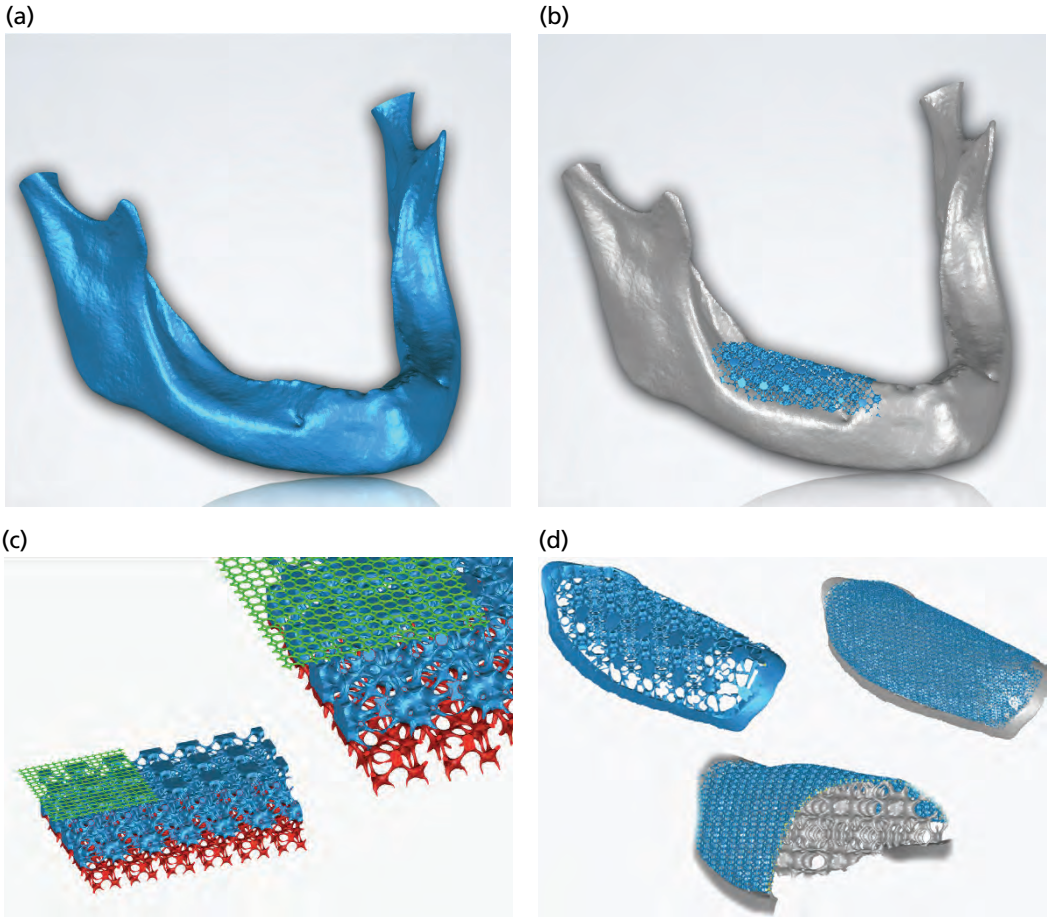

Fig. 41-14 (a) Volume rendering of cone-beam computed tomography (CBCT) scan of an edentulous ridge deficiency. CT provides a reliable digitized image dataset that is adequate for the assessment of mineralized tissue defects. (b) Custom-fit scaffold design. (c) Multilayer design. Based on 3D-image data, a scaffold structure is designed using a computer-aided design (CAD) system. Scaffold topography could be used to enhance or modulate cell/tissue incorporation. (d) Enhanced scaffold topography. (Source: Courtesy of I. Rudek.)

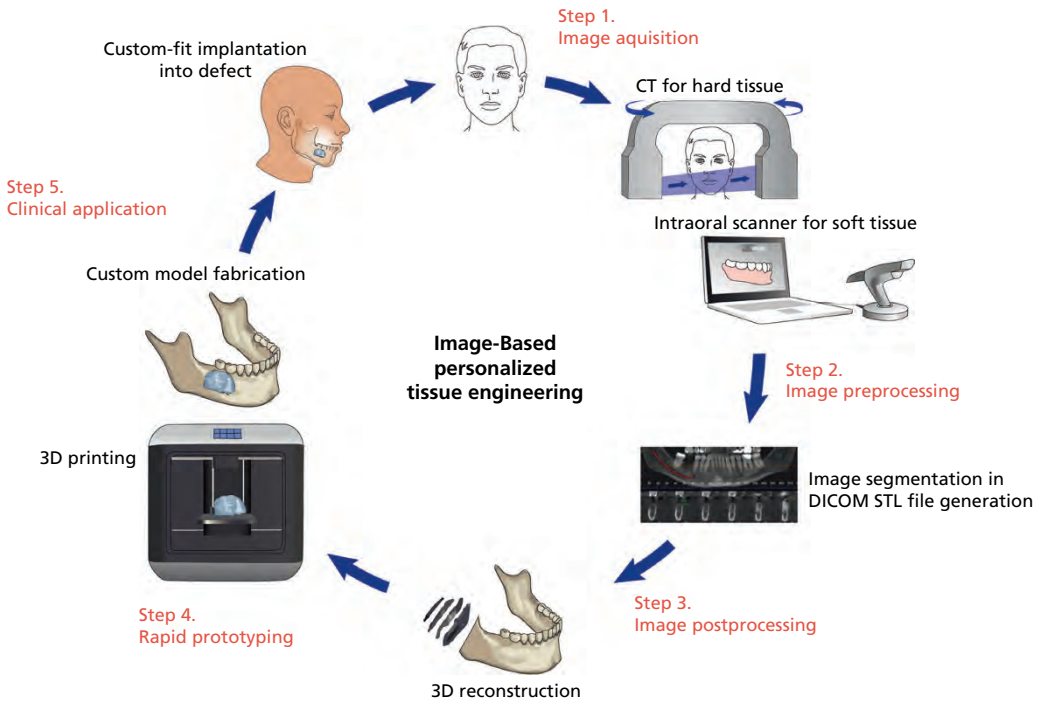

Fig. 41-15 Image-based scaffold design for alveolar bone reconstruction. Step 1: Image acquisition with a cone-beam CT scan for hard tissue and intraoral scan for soft tissue. Step 2: Image preprocessing; the images from step 1 are integrated as a DICOM file, then converted to an STL file for preparing a 3-D printable condition. Step 3: Image postprocessing; 3-D volume visualization for optimization of scaffold shape. Step 4: Rapid prototyping; based on image processing, scaffolds are manufactured by the 3-D printer. Step 5: Clinical application; custom-fit scaffold is applied at the time of reconstructive surgery. (Source: Adapted with permission from Yu *et al*. 2019. Reproduced with permission from John Wiley & Sons, Inc.)

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Chapter 42

Maxillary Sinus Floor Augmentation

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The maxillary sinus

The maxilla is an osseous structure of enormous relevance in the craniofacial complex. The maxilla is formed by two bilateral maxillary bones, which are fused at the midline by the intermaxillary suture (Fig. 42-1).

Each maxillary bone has one body and four processes. These are the alveolar, frontal, zygomatic, and palatine processes. The alveolar process is a crested basal extension that houses the maxillary teeth and gives its curved shape to the upper dental arch. The frontal process is an anterior projection of the maxillary body that articulates with the frontal bone and contains the lacrimal groove. The zygomatic process extends laterally from the body of the maxilla to articulate with the zygomatic bone. The palatine process is a horizontal bony plate that extends medially; it provides support to the soft tissues that line the hard palate and articulates with the more posteriorly located palatine bone. The maxillary sinus is a hollow cavity contained within the body of the maxillary bone (Fig. 42-2).

The maxillary sinus is one of the four paranasal sinuses, which also include the frontal, ethmoid, and sphenoid sinuses. The paranasal sinuses are air cavities lined with a pseudo-stratified ciliated columnar respiratory epithelium that covers a connective tissue layer (Fig. 42-3).

The stratum immediately beneath the epithelium is comprised of highly vascular, loose connective tissue. Underneath, a fibrous and irregular connective tissue layer, which is in intimate contact with the surrounding bony walls, may be observed (Insua *et al*. 2017). These three structures (epithelium, loose connective tissue, and dense connective tissue) are collectively referred to as the Schneiderian or sinus membrane (Fig. 42-4).

The physiologic functions of the paranasal sinuses have been the subject of debate, but may include lightening the total weight of the head for functional advantage, provide a buffer against trauma, humidify and heat the inhaled air (which contributes to olfaction), provide resonance to the voice (sinus cavities are usually more voluminous in males), assist in the regulation of intranasal pressure (e.g. in response to sudden height changes, such as those that occur when flying), secrete mucus, and immunological defense (Cappello & Dublin 2019; Watelet & Van Cauwenberge 1999).

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

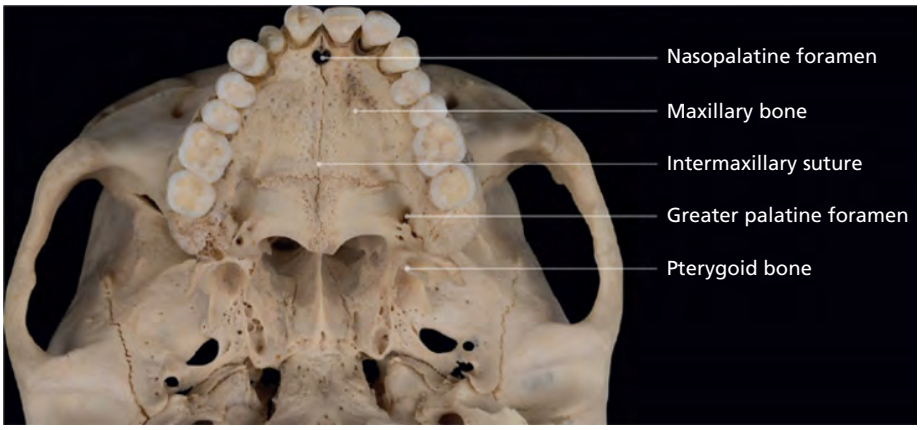

Fig. 42-1 Basal view of a dry skull.

Fig. 42-2 Different spatial views of a left maxillary bone. (a) Medial (note the maxillary sinus cavity upon partial removal of the nasal wall). (b) Frontal. (c) Inferior. (d) Lateral. (e) Dorsal. (f) Superior.

The maxillary sinus, also known as antrum of Highmore, is the largest of all the paranasal sinuses (Fig. 42-5). According to a cadaveric study, the average volume of this cavity is 12.5 cc (Gosau *et al*. 2009), but its dimensions and architecture may vary widely from individual to individual (Fig. 42-6) depending on factors such as age, dentate status, and history of pathosis in the area (Lovasova *et al*. 2018; Rani *et al*. 2017; Velasco-Torres *et al*. 2017). Maxillary sinuses widely vary in shape and size, but typically have a morphological configuration that resembles a pyramid (Fig. 42-7).

The base of the pyramid is at the medial wall, facing the lateral nasal wall, and its apex points laterally towards the zygomatic arch. The boundaries of the maxillary sinus are six bony walls: anterior, posterior, superior, inferior, medial, and lateral. The anterior wall typically consists of thin, compact bone extending from the orbital rim to approximately the position of the apex of the maxillary canine. The posterior wall separates the sinus cavity from the temporal fossa, which is located in the pterygomaxillary region. The superior wall of the sinus corresponds to the orbital floor. The configuration of the inferior wall, or sinus floor, varies widely from sinus to sinus and is determined by the position of the apices of the posterior maxillary teeth and patterns of bone remodeling after tooth loss, if one or multiple teeth are missing. The medial wall rises in an apical direction from the palatal aspect of the alveolar process and forms part of the lateral bony wall of the nasal cavity. The lateral wall of the maxillary sinus is part of the lateral aspect of the posterior maxilla and the zygomatic process.

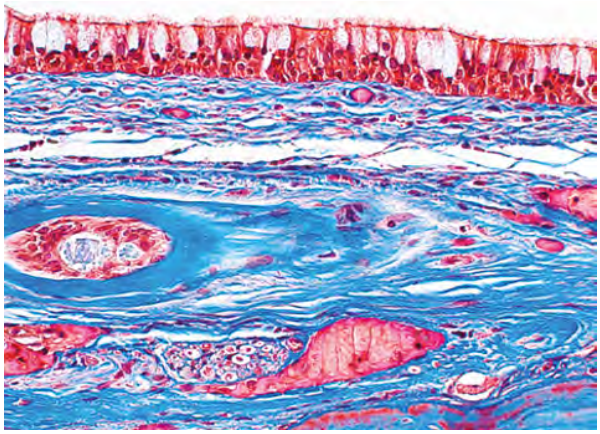

Fig. 42-3 High magnification histomicrophotograph illustrating the structural features of human pseudostratified ciliated columnar respiratory epithelium, predominantly stained in light red, and its relationship with the underlying connective tissue, which appears stained in blue (Masson's trichrome staining). (Source: Courtesy of Drs. Alberto Monje, Universitat Internacional de Catalunya, Barcelona, Spain and Ángel Insua, Private Practice, La Coruña, Spain.)

Each maxillary sinus has at least one non-physiologic drainage port, known as the maxillary ostium or maxillary hiatus, that is located on the medial wall and opens into the nasal cavity between the middle and lower nasal conchae (Fig. 42-8). Cadaveric studies have reported the occurrence of accessory ostia in approximately 20% of the specimens analyzed (Prasanna & Mamatha 2010; Yenigun *et al*. 2016).

The maxillary sinus produces mucus containing lysozymes and immunoglobulins, which have been linked to the defense against bacterial infections of the upper respiratory tract. Non-hemolytic and alpha-hemolytic *Streptococci* and *Neisseria* spp. are part of the normal commensal microbiota of the maxillary sinus. Diphtheroids, *Staphylococci*, *Hemophilus* spp., *Pneumococci*, *Mycoplasma* spp., and *Bacteroides* spp. may also be found in low amounts in health (Timmenga *et al*. 2003). The abundant vascularity of the Schneiderian membrane helps maintain a healthy status by allowing cellular and molecular diffusion to both the membrane and the sinus cavity. A healthy maxillary sinus is self-maintaining by postural drainage and the action of the ciliated epithelial lining, which propel fluids and microorganisms toward the ostium. The fact that the maxillary sinus opening to the nasal cavity is not in the lower part of the sinus, where a bone graft may be placed, is of high importance and provides an anatomic rationale for sinus floor augmentation, as the grafting procedure does not usually interfere with normal maxillary sinus functions.

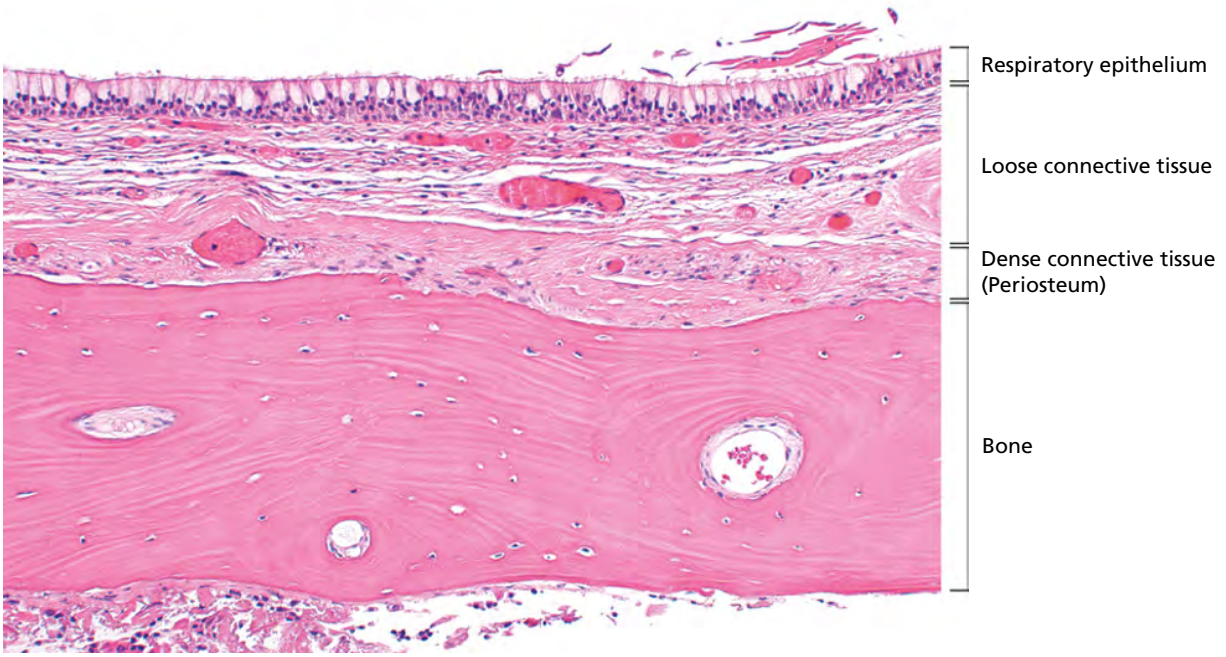

Fig. 42-4 Low magnification histomicrophotograph showing the three layers of the Schneiderian membrane and the underlying bone from a human specimen. Hematoxylin and eosin staining. (Source: Courtesy of Drs. Alberto Monje, Universitat Internacional de Catalunya, Barcelona, Spain and Ángel Insua, Private Practice, La Coruña, Spain.)

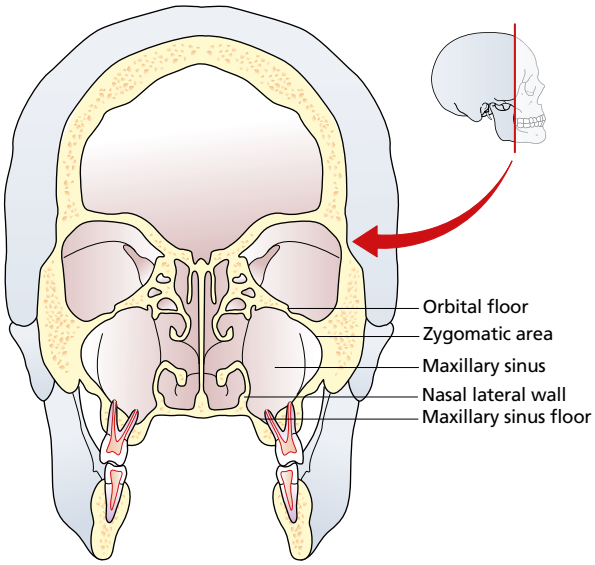

Fig. 42-5 Frontal section of the craniofacial complex. Note the anatomical boundaries of the maxillary sinus.

The blood supply to the maxillary sinus is primarily derived from branches of the internal maxillary artery (i.e. the posterior superior alveolar or alveolar antral artery, the infraorbital artery, and the posterior lateral nasal artery) and, to a lesser degree, from the greater palatine, anterior ethmoidal, and superior labial arteries. These vessels penetrate the bony plates and ramify within the medial, lateral, and inferior walls of the sinus (Fig. 42-9).

The posterior superior alveolar artery has tributary branches that primarily perfuse the posterior and lateral walls. The posterior superior alveolar and infraorbital arteries frequently anastomose at the bony lateral wall, forming a so-called *arterial arcade* (Solar *et al*. 1999). Venous drainage goes into the sphenopalatine vein and pterygomaxillary plexus. Innervation of the maxillary sinus is primarily provided by the anterior, middle, and posterior superior alveolar branches of the maxillary nerve, which is the second division of the fifth cranial pair (trigeminal nerve), as well as by branches

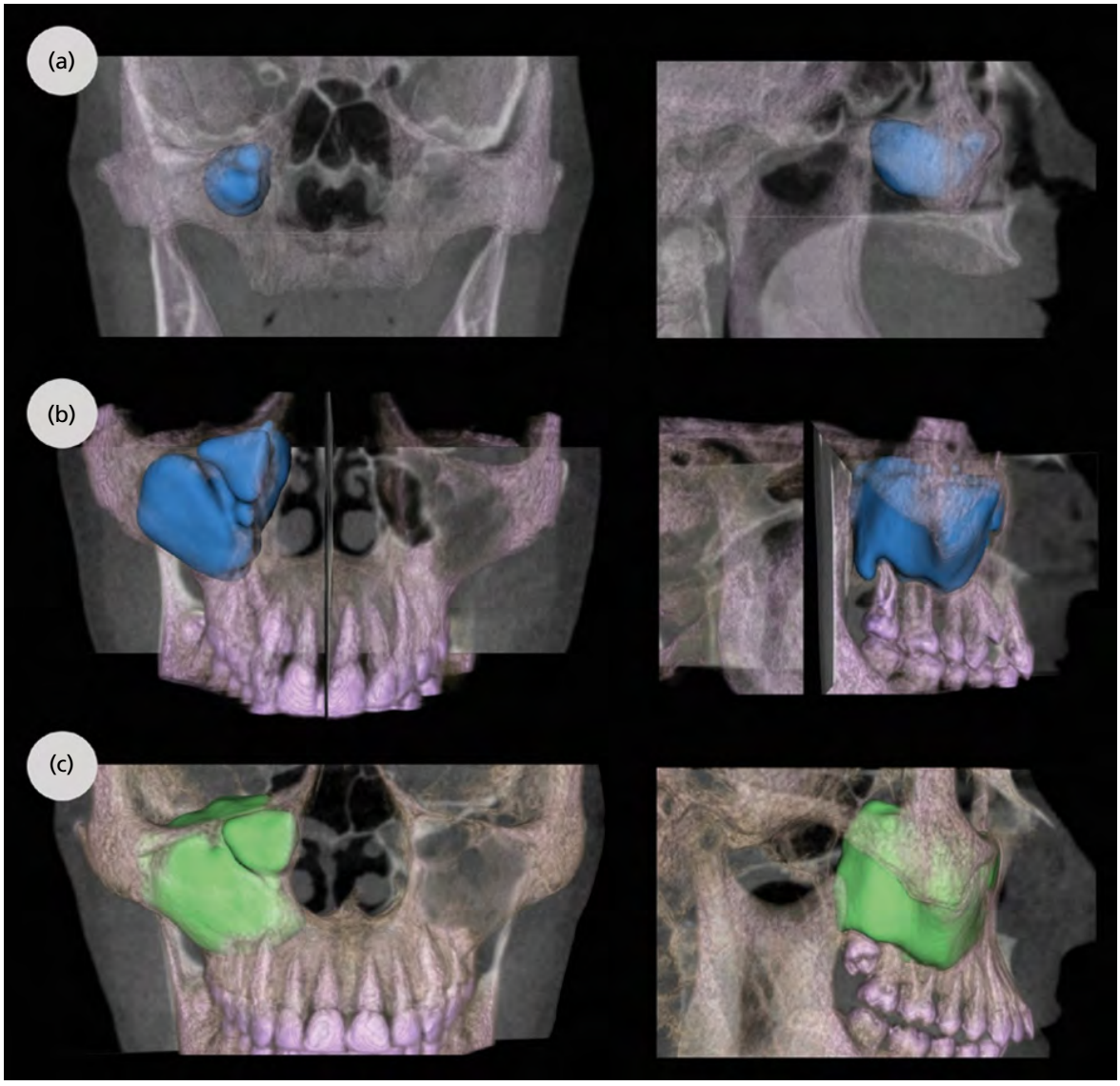

Fig. 42-6 Tridimensional reconstructions depicting the volume of the right maxillary sinus of three different patients. (a) Small size (~3 cm^3). (b) Medium size (~15 cm^3). (c) Large size (~25 cm^3). (Source: Courtesy of Dr. Miguel Velasco-Torres, Private Practice, Granada, Spain.)

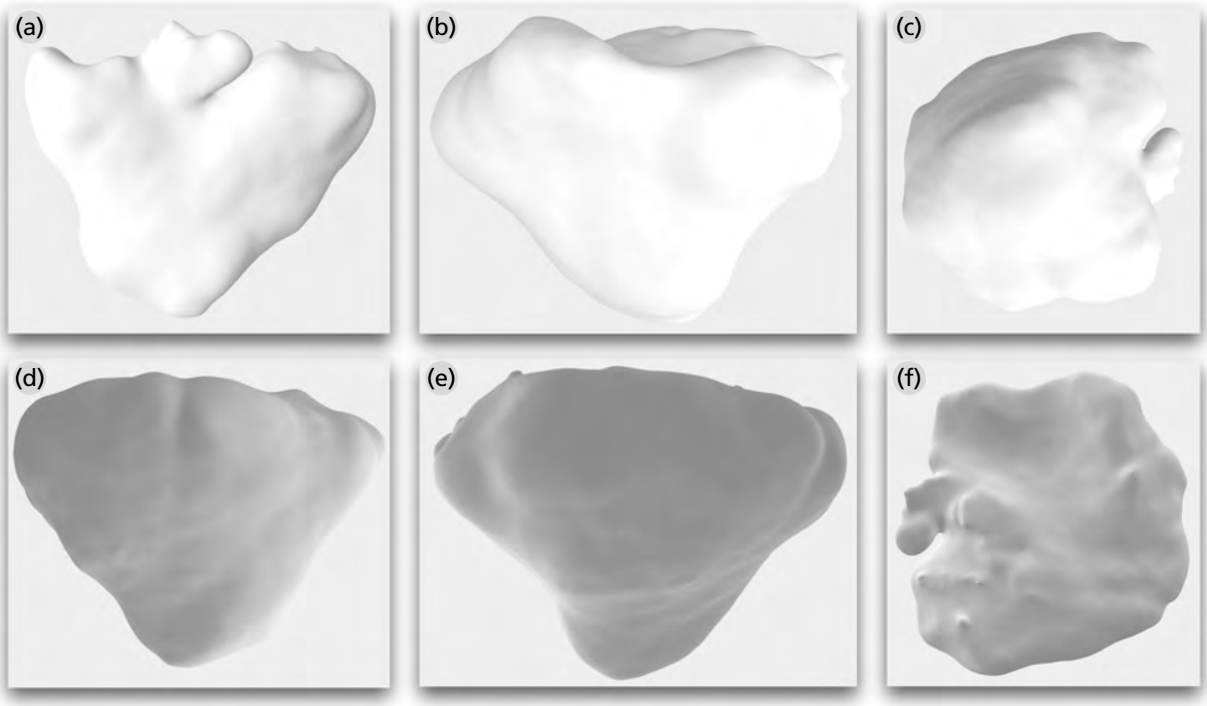

Fig. 42-7 Different spatial views of a 3D reconstruction of a right maxillary sinus using digital technology. (a) Medial. (b) Frontal. (c) Inferior. (d) Lateral. (e) Dorsal. (f) Superior. (Source: STL file courtesy of Dr. Miguel Velasco-Torres, Private Practice, Granada, Spain.)

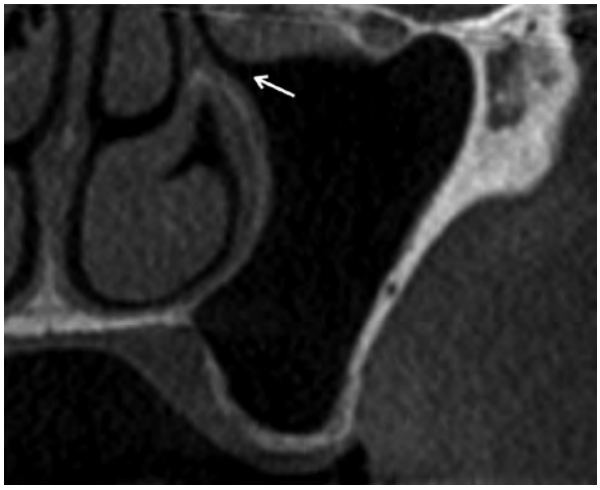

Fig. 42-8 Radiographic sagittal section illustrating the location of the ostium (arrow) in a left maxillary sinus.

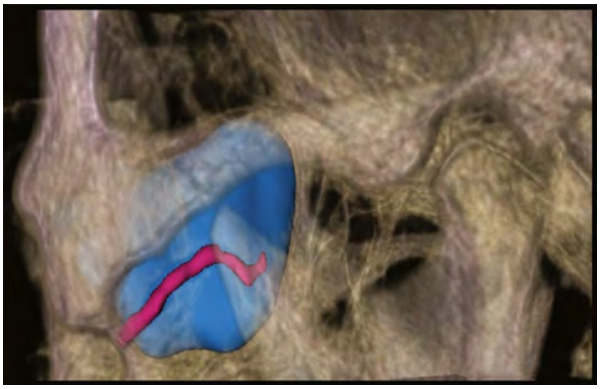

Fig. 42-9 Tridimensional reconstruction showing the volume of a left maxillary sinus (blue) and the lateral course of the posterior superior alveolar artery (pink). (Source: Courtesy of Dr. Miguel Velasco-Torres, Private Practice, Granada, Spain.)

of the infraorbital nerve and the greater palatine nerve (Iwanaga *et al*. 2019).

Septa, or Underwood's septa, are intrasinusal bony walls of variable location, dimension, and morphology that may form during the development of the sinus cavity (i.e. primary septa) or as the result of functional adaptation or pathological processes (i.e. secondary septa). Some authors have pointed at a possible relationship between the presence of septa and maxillary exostoses, particularly in completely edentulous subjects (Naitoh *et al*. 2009). As reported in several studies, the prevalence of antral septa may range between 24% and 44.8% (Ulm *et al*. 1995; Velasquez-Plata *et al*. 2002; Sakhdari *et al*. 2016) and it appears to be significantly higher in edentulous patients (Kim *et al*. 2006). Septa are usually found in the inferior wall, or floor, of the sinus cavity (Fig. 42-10), although they can also be observed on the lateral, medial, or even superior wall (Fig. 42-11). In exceptional situations, a septum may completely divide the sinus cavity into several recesses (Fig. 42-12).

Conflicting information regarding the most common location of septa in the antero-posterior dimension has been reported. Although most studies have found them to be more commonly located in the middle or posterior regions of the sinus, in proximity to the typical location of maxillary molars, Krennmair and coworkers observed as many as 70% of septa in the anterior, more mesial, segment of the antral cavity (Krennmair *et al*. 1999).

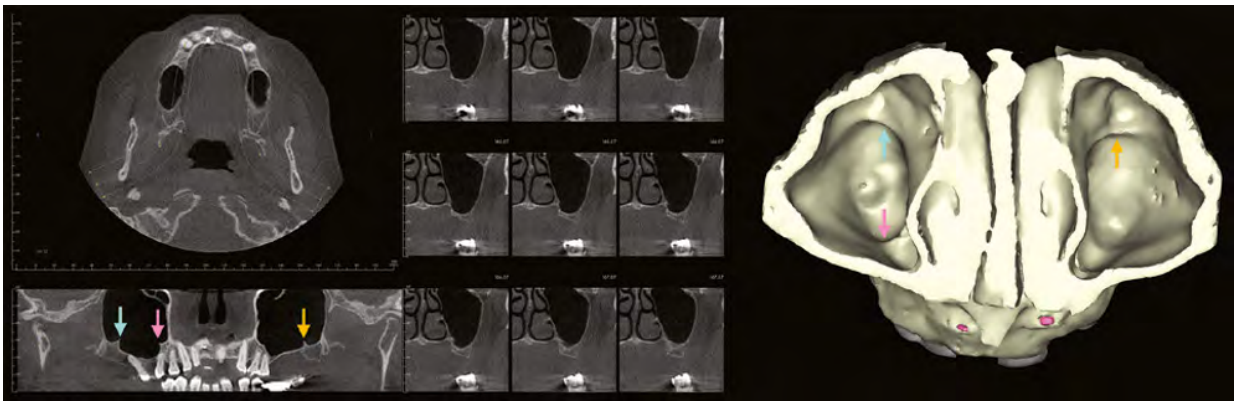

Fig. 42-10 Radiographic study using DICOM data of a patient presenting three septa (highlighted by the blue, pink, and orange arrows) on the maxillary sinus floor.

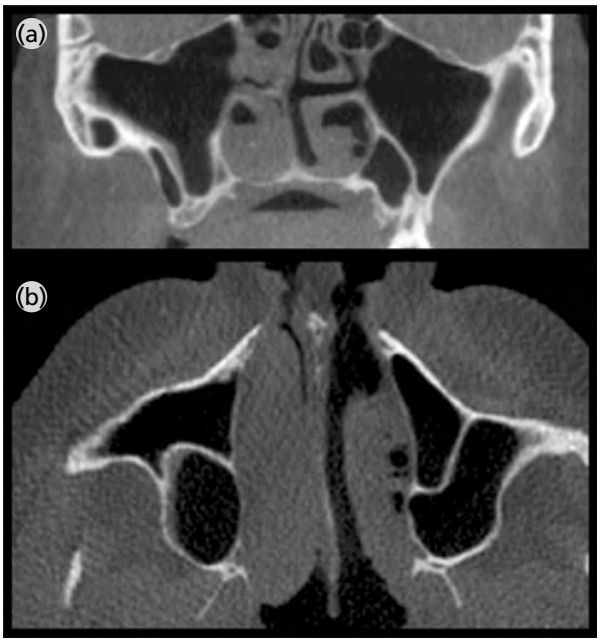

Fig. 42-11 Radiographic sagittal (a) and transversal (b) CBCT sections illustrating the presence of abnormal bilateral septa of the maxillary sinus. (Source: Courtesy of Dr. Miguel Velasco-Torres, Private Practice, Granada, Spain.)

Options for the rehabilitation of the posterior edentulous maxilla

Studies on patterns of tooth loss caused by periodontitis have reported that posterior teeth, particularly maxillary molars, are lost more frequently (Hirschfeld & Wasserman 1978; McFall 1982; Baelum & Fejerskov 1986). This trend can be attributed to different factors involved in the process of disease onset and progression, including difficult access to maintain adequate plaque control compared with anterior sites and the presence of inherent local anatomical features (e.g. multirooted configuration, cervical enamel projections, enamel pearls, and close root proximity between the first and the second molar).

Although it is well established that the total volume of the maxillary sinus cavity decreases with age (Rani *et al*. 2017; Velasco-Torres *et al*. 2017), the morphology of the sinus floor does not undergo major changes over time as long as the posterior teeth remain in function. Nonetheless, preclinical and clinical studies have demonstrated that the removal of a tooth from its alveolus triggers a cascade of biological events that results in an alteration of the structural configuration of the alveolar ridge and its surrounding structures (Araujo & Lindhe 2005; Chappuis *et al*. 2013). In fact, it has been shown that, following extraction of posterior teeth that are in close proximity to the maxillary sinus, the antral cavity expands both inferiorly and laterally in a phenomenon known as maxillary sinus pneumatization (Cavalcanti *et al*. 2018). This is accompanied by a process of alveolar bone atrophy which has been primarily attributed to the absence of stimulation from occlusal function as a result of posterior tooth loss (Schropp *et al*. 2003). A radiographic study using cone-beam computed tomography (CBCT) scans from 23 subjects who underwent extraction of maxillary molars revealed that bone remodeling between 2 and 60 months after tooth extraction is largely because of alveolar ridge resorption, whereas changes in maxillary sinus floor position contribute to a lesser extent (Hameed *et al*. 2019).

Clinicians may consider several options for the management of atrophic posterior edentulous maxillary segments (Fig. 42-13). However, in clinical scenarios in which posterior maxillary teeth planned for extraction are still present, the possibility of performing an alveolar ridge preservation procedure should be considered. Current evidence supports the effectiveness of alveolar ridge preservation via socket grafting and sealing performed immediately after tooth extraction as a means to minimize alveolar ridge remodeling and facilitate subsequent tooth replacement therapy (Avila-Ortiz *et al*. 2019; Tonetti *et al*. 2019). In fact, clinical studies focused on the posterior maxilla have demonstrated that alveolar ridge preservation via socket grafting directly contribute to attenuating alveolar ridge remodeling and sinus pneumatization, which may subsequently reduce the need for ancillary augmentation procedures (Rasperini *et al*. 2010; Levi *et al*. 2017; Park *et al*. 2019), as shown in Fig. 42-14.

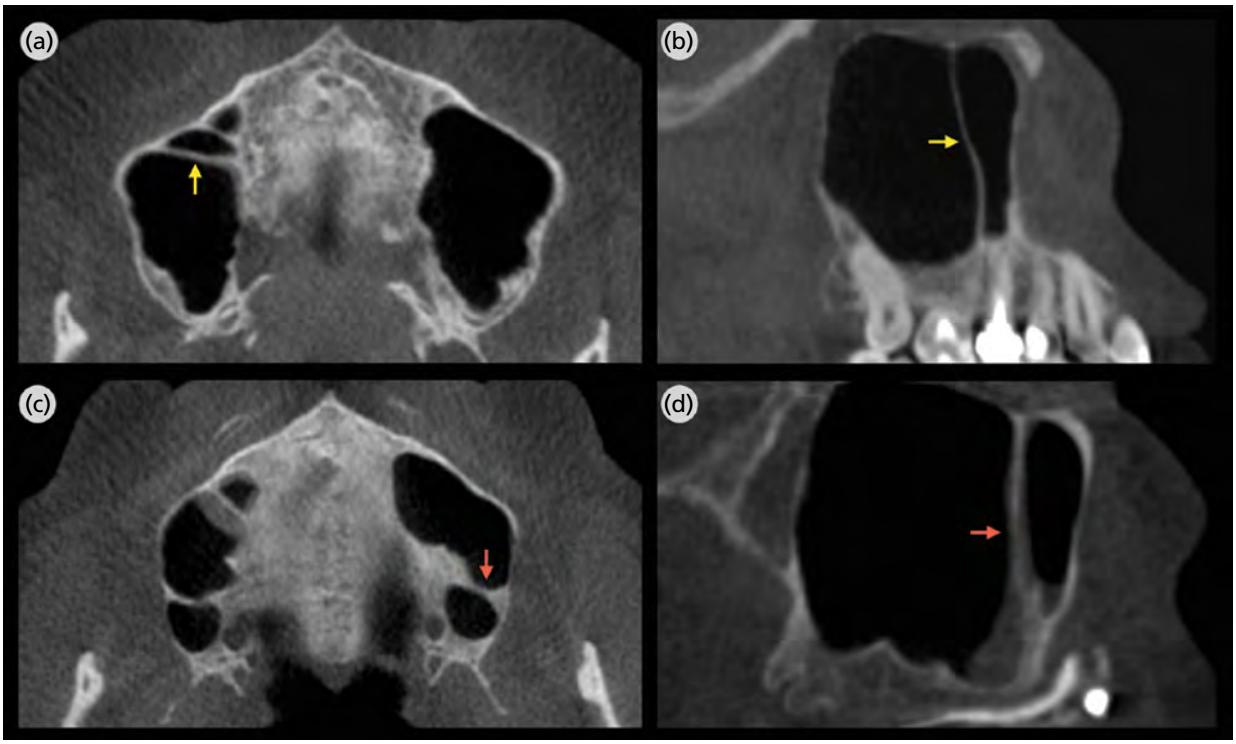

Fig. 42-12 Two examples of septa dividing the maxillary sinus into two separate cavities. An anterior septum is highlighted by a yellow arrow (a and b) and a more posterior septum is identified by a red arrow (c and d). (Source: Courtesy of Dr. Miguel Velasco-Torres, Private Practice, Granada, Spain.)

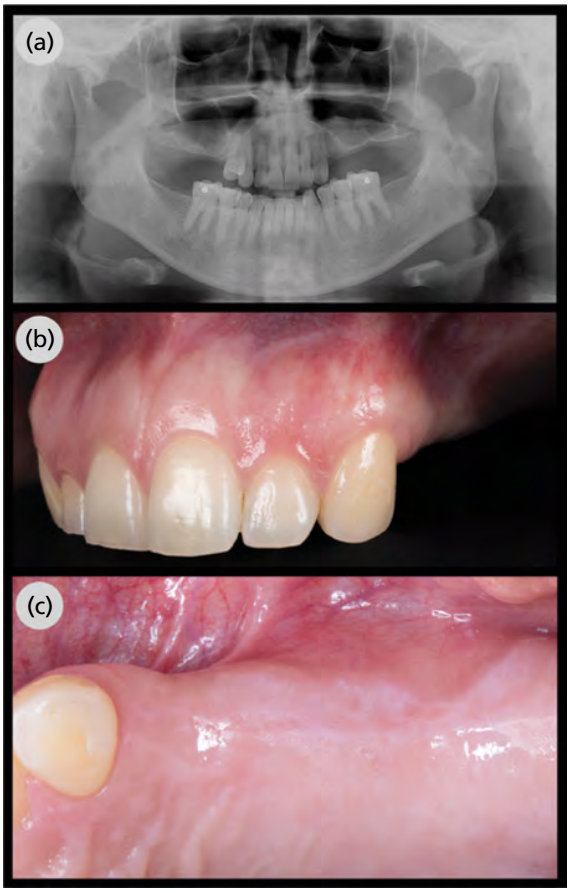

Fig. 42-13 (a) Orthopantomograph of a patient presenting bilateral bone atrophy associated with posterior maxillary edentulism. (b) Oblique intraoral photograph showing the left side. (c) Occlusal photograph of the upper left sextant.

However, there are situations in which alveolar ridge preservation does not render the expected outcomes or in which teeth are already missing, making it necessary to consider different therapeutic options.

Although a shortened dental arch compatible with adequate function (Fig. 42-15) may be a viable alternative to tooth replacement therapy (Kayser 1981; Wolfart *et al*. 2012), rehabilitation of the posterior edentulous maxilla is frequently requested by patients whose quality of life is affected by the absence of teeth (Gerritsen *et al*. 2010; Haag *et al*. 2017). Whether it is for the replacement of a single unit or multiple teeth, tooth replacement options may include removable and fixed dental prostheses. Removable dental prostheses can be supported by implants, remaining teeth (if any), and/or oral mucosa, whereas fixed dental prostheses can be implant- and/or tooth-supported. Given the scope of this chapter, the focus will be placed on the discussion of implant-based therapeutic alternatives for the management of posterior edentulous maxillary sectors exhibiting alveolar bone atrophy in the vertical dimension.

In clinical scenarios presenting limited bone height availability in the posterior maxilla, placement of standard-length implants often requires maxillary sinus floor augmentation (MSFA). MSFA can be defined as a surgical intervention aimed at gaining bone volume in the edentulous, atrophic posterior maxillary segments by displacing the existing sinus floor in an apical direction with the purpose of facilitating implant placement in a restoratively driven position. Analogous terms

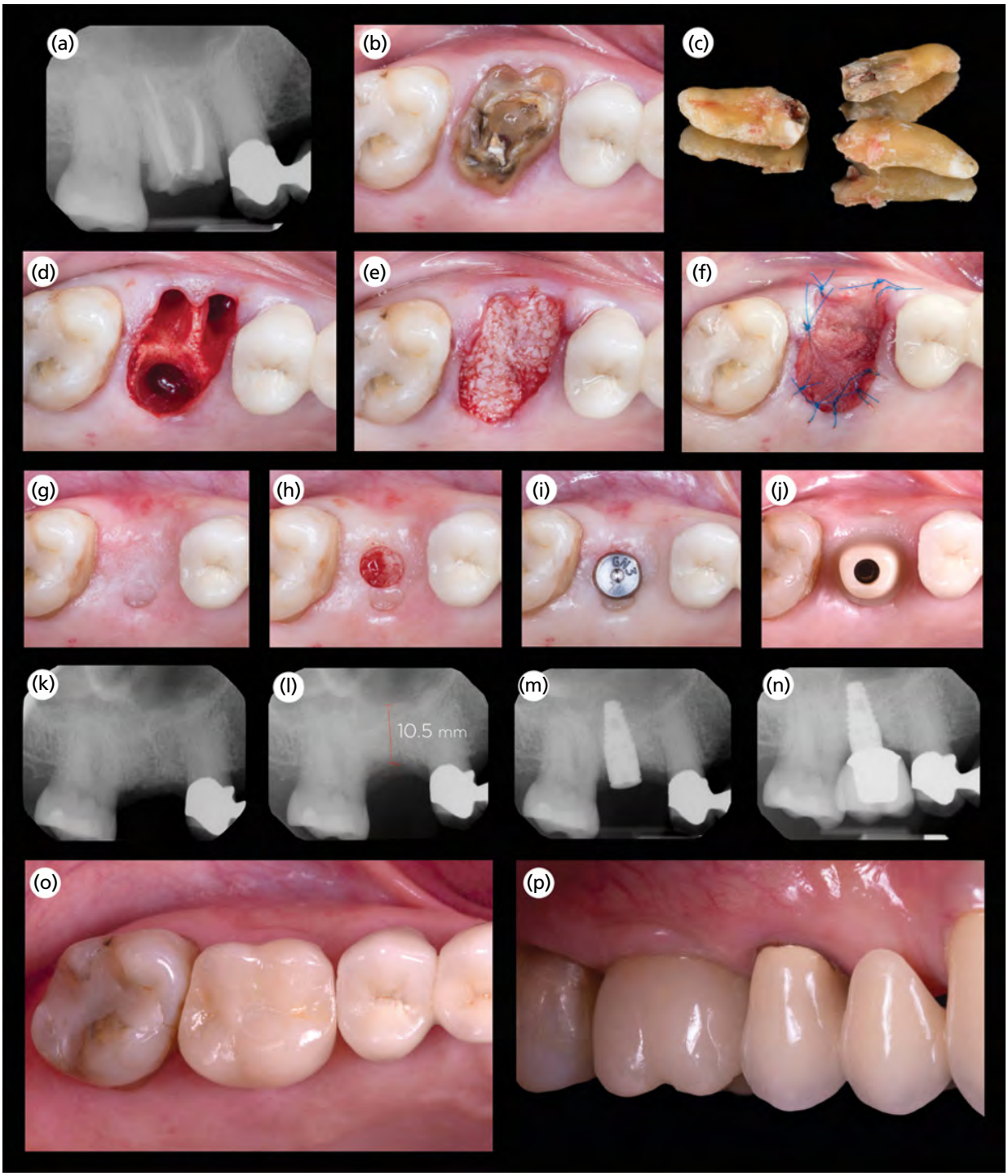

Fig. 42-14 Sequence of a case of tooth replacement therapy of a maxillary right first molar with an implant-supported prosthesis involving alveolar ridge preservation via socket grafting and sealing. (a) Baseline periapical radiograph. (b) Intraoral occlusal view of non-restorable tooth remnants. (c) Extracted roots after selective odontosection. (d) Fresh extraction socket. (e) Socket grafted with bovine bone particles up to the crestal bone level. (f) Socket sealed with a porcine collagen matrix. (g) Aspect of the site after 4 months of healing. (h) Preparation of the site for flapless implant placement. (i) Implant and healing abutment inserted. (j) Try-in of the final custom-made abutment after 3 months of healing. (k) Periapical radiograph obtained immediate after tooth extraction and ridge preservation. (l) Radiograph obtained after 3 months of healing. Additional site augmentation was deemed unnecessary. (m) Control radiograph obtained at the time of implant placement. (n) Radiograph obtained at 1 year after delivery of final prosthesis. (o, p) Occlusal and lateral view of the final restoration. (Case restored by Dr. Chris Barwacz, University of Iowa.)

to MSFA include maxillary sinus floor lift, maxillary sinus floor elevation, and maxillary sinus grafting, among others. MSFA involves entering the antral cavity with the purpose of elevating the Schneiderian membrane to displace the sinus floor. This can be accomplished with either a transalveolar, a lateral window, a crestal window, or a palatal window approach, with or without the use of a bone grafting material or space filler, and with or without simultaneous implant placement. These and other

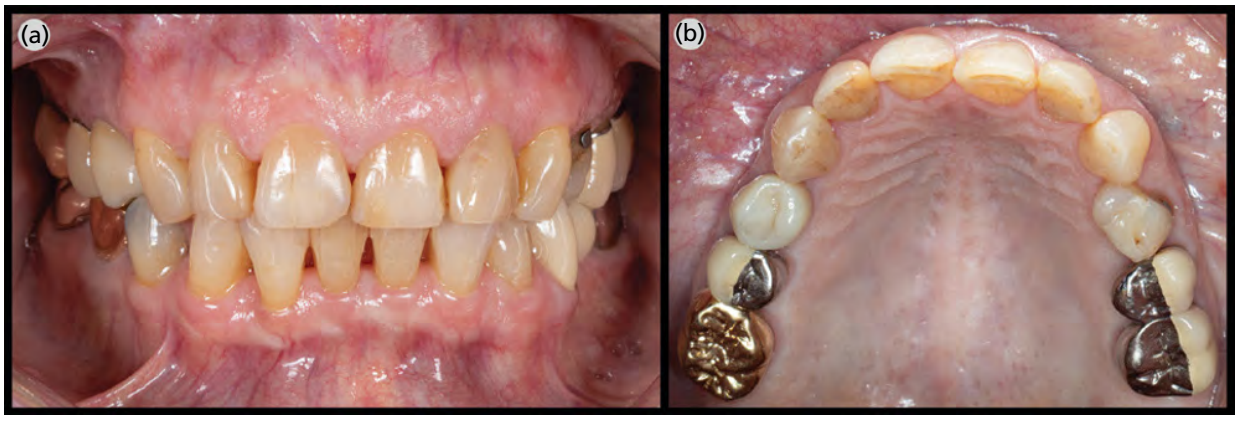

Fig. 42-15 Intraoral photographs showing a shortened dental arch up to first molar occlusion. (a) Occlusal view. (b) Frontal view in maximum intercuspation.

specific aspects of MSFA will be discussed in depth in subsequent sections of this chapter.

Short or tilted/angled implants may be an alternative to MSFA in some scenarios. These approaches offer the advantage of minimizing or completely avoiding the need for ancillary bone augmentation procedures, which may potentially reduce morbidity, treatment time, and expense.

The threshold of length that defines a short implant is a subject of discussion in the scientific literature. Whereas some authors consider this value to be <10 mm, others draw the line at <8 mm, or even at ≤6 mm to define extra-short implants (Ravida *et al*. 2019). Earlier reports on the short-term (up to 5 years) survival rate of short implants were not particularly encouraging and linked implant failure with the so-called "poor bone quality" (i.e. lower mineral density) that is typically encountered in posterior maxillary segments (Friberg *et al*. 1991; Jemt & Lekholm 1995). A multicenter study conducted a few years later evaluated the outcomes of non-submerged, rough-surface dental implants. The investigators found that only one out of 208 short implants (6 mm) placed in the mandible was lost compared with six out of 45 short implants placed in the maxilla. The survival rates were 99.5% and 86.7%, respectively, after a follow-up of up to 7 years (ten Bruggenkate *et al*. 1998). Based on these and other studies, the clinical "dogma" that, generally, only long implants, regardless of the surface characteristics, should be inserted in type IV bone in the posterior maxilla gained popularity in the dental community (Jaffin & Berman 1991). Interestingly, two multicenter studies on rough-surface implants conducted in the 1990s evaluated the survival and success rates of implants of different lengths (Buser *et al*. 1997; Brocard *et al*. 2000). In these studies, no significant differences were found between 8-, 10-, and 12-mm implants after up to 8 years of follow-up. Further clinical studies on short implants with either machined or rough surfaces, reported survival rates of about 95% between 2 and 7 years after functional loading (Fugazzotto *et al*. 2004; Renouard & Nisand 2005), which is in congruence with the 5-year survival rate reported in different systematic reviews for standard implants (Berglundh *et al*. 2002; Jung *et al*. 2012). In contrast, a recent systematic review prepared for the Sixth ITI Consensus on the basis of 10 randomized controlled trials (RCTs) comparing long (>6 mm) and short (≤6 mm) implants, observed that short implants are associated with higher variability and lower predictability, in terms of survival rate, compared with longer implants after periods of 1–5 years in function (Papaspyridakos *et al*. 2018). Nevertheless, the reported mean survival rate was still high, at 96% (range: 86.7–100%) for short implants and 98% (range: 95–100%) for longer implants. It can be concluded that current evidence generally supports the efficacy of short implants as a viable treatment alternative in the rehabilitation of edentulous ridges, including the posterior maxilla (Fig. 42-16), as long as meticulous case selection, proper execution of surgical and restorative procedures, and an adequate maintenance program drive the delivery of care (Annibali *et al*. 2012; Monje *et al*. 2014b; Lorenz *et al*. 2019).

Another way to avoid maxillary sinus augmentation is to place tilted implants in a position mesial or distal to the sinus cavity, provided these areas have adequate bone (Fig. 42-17). Furthermore, extra-long zygomatic or pterygoid implants can be placed in the lateral aspect of the zygomatic bone or anchored in the pterygoid bone, respectively (Fig. 42-18).

Recent evidence supports the clinical performance of tilted, zygomatic, and pterygoid implants, as compared with standard, axially loaded implants, for the management of posterior edentulous maxillae, in terms of implant survival rate (Chrcanovic *et al*. 2015, 2016; Lin & Eckert 2018; Araujo *et al*. 2019). However, increased invasiveness, and surgical and prosthetic complexity associated with these procedures must be taken into consideration when presenting this option to potential candidates. Hence, the use of tilted or zygomatic implants should be primarily considered in sites thought unfavorable for placement of standard-length or short implants, such as those associated with extreme alveolar ridge

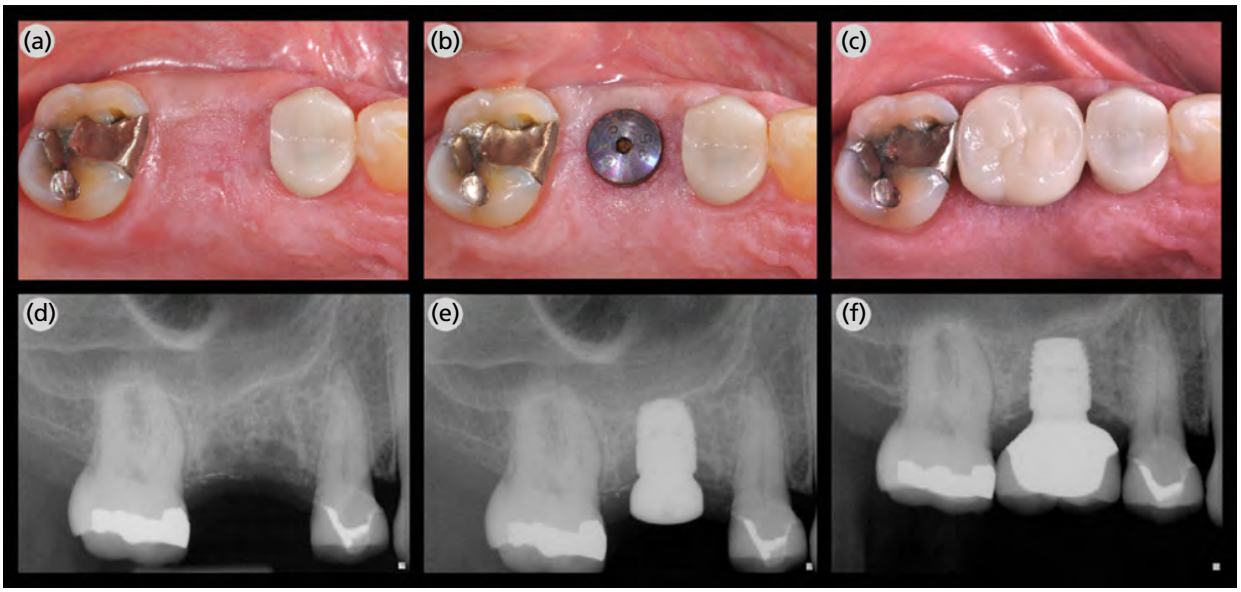

Fig. 42-16 Sequence of a case of tooth replacement therapy of a maxillary right first molar with an implant-supported prosthesis involving the use of a short implant to avoid MSFA. The upper row shows the occlusal view of the site at baseline (a), 2 months after implant placement (b), and 1 year after the delivery of the final prosthesis (c). The lower row displays a periapical radiographic sequence of the area at baseline (d), 2 months after implant placement (e) and 1 year after the delivery of the final prosthesis (f). (Source: Courtesy of Dr. Chris Barwacz, University of Iowa.)

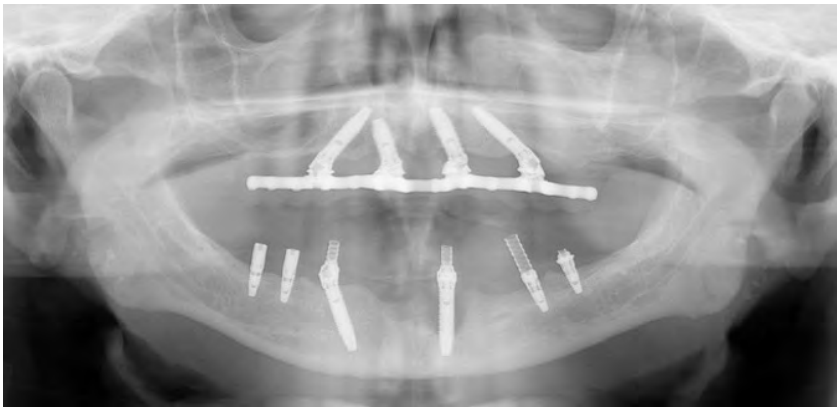

Fig. 42-17 Orthopantomograph showing the bilateral use of angled implants mesial to the maxillary sinus cavity to avoid the indication of maxillary sinus floor augmentation. The most anterior implant in the lower left quadrant was affected by peri-implantitis. (Source: Courtesy of Dr. Clark Stanford, University of Illinois at Chicago.)

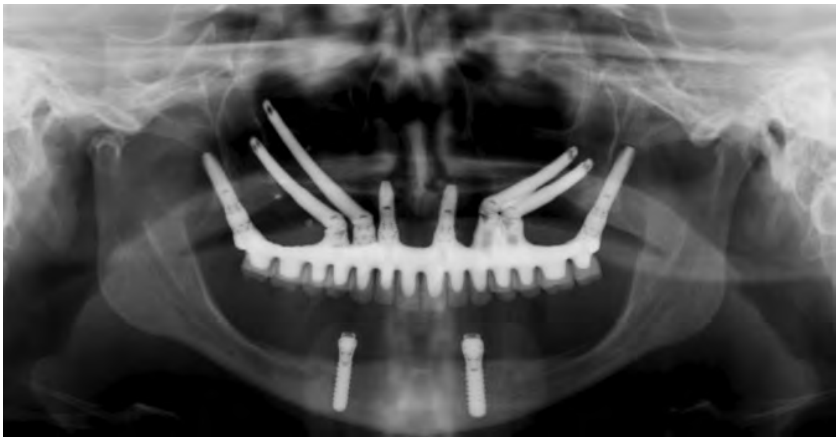

Fig. 42-18 Orthopantomograph showing the combined use of zygomatic and pterygoid implants to support a fixed full-arch implant-supported prosthesis.

deficiencies (e.g. sites with a history of severe trauma or cancer resection) and/or in patients presenting absolute medical contraindications that preclude the performance of MSFA procedures.

Maxillary sinus floor augmentation techniques

Surgical modalities

The goal of MSFA in the context of contemporary dental practice is to gain bone volume in posterior maxillary segments presenting edentulism and vertical bone atrophy in order to facilitate tooth replacement therapy with implant-supported prostheses. The origin of this technique is controversial. Whereas some claim that MSFA was first described by Philip J. Boyne in lectures to postgraduate students in the 1960s as a preprosthetic surgical intervention to allow the delivery of removable appliances in areas of limited interocclusal space, others attribute the original idea to Hilt Tatum Jr. At any rate, a formal description of the technique was not published by Boyne and James until 1980 (Boyne & James 1980). In that original report the authors described a two-stage surgical procedure aimed at the elevation of the maxillary sinus floor in patients with large, pneumatized sinus cavities in preparation for the placement of intraosseous blade implants. According to the proposed technique, which was based on a procedure originally described in the field of otorhinolaryngology known as radical antrostomy or the Caldwell–Luc operation (Macbeth 1971), the maxillary sinus floor was grafted using autogenous particulate iliac bone, after gaining access through a lateral window and elevating the Schneiderian membrane. In the second surgical stage, approximately 3 months later, the site was surgically re-entered and implants were placed to later support fixed or removable dental prostheses. Other terms analogous to MSFA through a lateral window approach are direct MSFA, external MSFA, or lateral window osteotomy (LWO) sinus elevation.

Since the original description of the lateral window approach, other MSFA protocols and subsequent modifications have been proposed, namely transalveolar, crestal window, and palatal window approaches (Fig. 42-19).

The *transalveolar approach*, also referred to as transcrestal, internal, or indirect MSFA, was described by Hilt Tatum Jr. in 1986 as an alternative to the lateral window approach with the purpose of simplifying the bone augmentation technique and minimizing the occurrence of complications (Tatum 1986). According to the original description of this technique, a surgical instrument that was referred to as a "socket former" was used to prepare the implant site. A "green-stick fracture" of the sinus floor was manually accomplished by tapping the socket former with a mallet in a vertical direction. After preparation of the implant site, a cylindrical implant was placed in a submerged approach. In 1994, Robert B. Summers proposed a variation of this technique consisting of the use of a set of straight osteotomes of varying diameters (Fig. 42-20) to prepare the implant site without using drills with the purpose of achieving bone preservation and horizontal ridge expansion (Summers 1994).

This technique is also aimed at increasing the density of the maxillary bone surrounding the osteotomy to provide a higher chance to achieve implant primary stability. The Summers or BAOSFE (bone-added osteotome sinus floor elevation) technique is initiated by a small osteotomy that is made through the crest of the edentulous ridge, avoiding the perforation of the sinus floor. The pilot osteotomy creates a pathway for the insertion of osteotomes of increasing diameter to both compact the surrounding alveolar bone and elevate the sinus membrane, thus creating a "tent" and space for bone graft placement at the floor of the sinus, using the final osteotome to push it in a vertical direction. It should be noted that, in this technique, bone grafts are placed blindly into the space below the sinus membrane. Hence, one of the disadvantages of transalveolar MSFA is the possibility of inadvertent perforation of the sinus membrane. However, an endoscopic study has shown that, if the technique is carefully executed in the presence of favorable local anatomy, the sinus floor may be elevated by up to 5 mm without perforating the membrane (Engelke & Deckwer 1997). Although the essentials of the technique originally described by Summers still prevail, subsequent modifications of

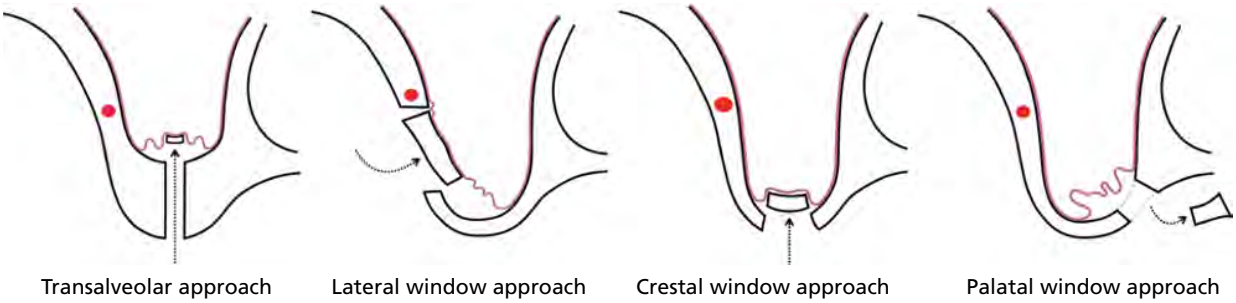

Fig. 42-19 Maxillary sinus floor augmentation modalities. Note the larger diameter of the posterior superior alveolar artery in the illustration representing the crestal window approach

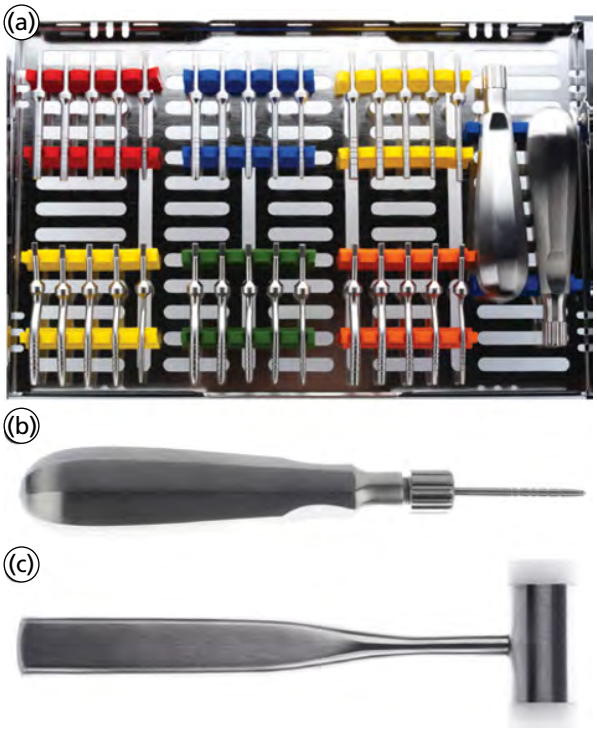

Fig. 42-20 (a) Contemporary osteotome kit. Note the variety of straight and angled tips of different diameters. (b) Osteotome handle assembled with a thin tapered blunt-ended tip. (c) Mallet composed of a surgical steel body and solid polytetrafluoroethylene working ends.

the transalveolar approach have been proposed over the past two decades involving the use of different devices, such as elastic balloons (Kfir *et al*. 2006), piezoelectric tips (Sohn *et al*. 2009), bone reamers (Ahn *et al*. 2012), and specially designed drills (Cosci & Luccioli 2000; Huwais *et al*. 2018).

The *crestal window approach* is a variation of the lateral window access. This approach was originally described by Alan A. Winter and collaborators in 2003 (Winter *et al*. 2003), and subsequently modified by Carlo Soardi and Hom-Lay Wang in 2012 (Soardi & Wang 2012). This technique may be useful to prevent a large perforation in clinical situations in which the oral mucosa and the Schneiderian membrane are fused at the level of the alveolar crest, which may result from inadequate healing after a complicated and/or traumatic extraction or because of a previous history of sinus pathosis (Block 2018). Although technically more demanding than accessing the antral cavity through a conventional lateral window, this approach may also serve as a viable alternative in cases in which avoiding the management a large posterior superior alveolar artery is desired. Given the nature of this approach, delayed implant placement is primarily indicated because of the difficulty of achieving primary stability.

The *palatal window approach* was originally described in 1992 in conjunction with a nasal approach, which can be a viable alternative in cases of extreme bone atrophy (Jensen *et al*. 1992). In these situations, the transverse dimension of the posterior maxilla can be reduced to an extent in which the alveolar process is in alignment with the lateral wall of the nasal cavity, making a lateral window approach inviable. Another possible indication for MSFA using a palatal window approach would be a scenario in which the lateral bony wall of the maxillary sinus is so thick, such as in cases of incomplete previous grafting, that accessing the maxillary sinus from the palate would be more time efficient and technically feasible (Ueno *et al*. 2015; Florio *et al*. 2017), as shown in Fig. 42-21.

Nevertheless, considering that these clinical situations are relatively infrequent, as well as other important technical implications (e.g. difficult access and proximity of major vascular structures), the palatal window approach should be reserved to very specific scenarios in which no other MSFA alternative is feasible.

In contemporary dental practice, two main MSFA approaches are commonly indicated: (1) the lateral window approach, which may involve simultaneous or delayed implant placement, or (2) the transalveolar approach, which usually involves simultaneous implant placement.

Residual bone height (RBH), also known as residual sub-antral bone, is considered a critical anatomic factor in the planning and execution of MSFA procedures. Although baseline RBH *per se* does not seem to play a critical role on implant integration (Fenner *et al*. 2009) or new bone formation after MSFA (Avila-Ortiz *et al*. 2012a), it has a direct influence on the likelihood of achieving implant primary stability. Hence, RBH is commonly utilized in clinical practice not only as the primary factor to determine the implant placement protocol (either simultaneous or delayed),

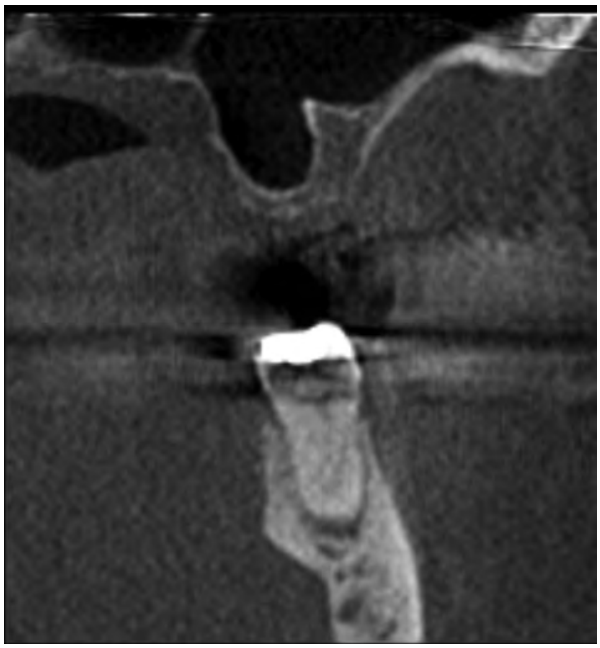

Fig. 42-21 Sagittal radiographic image showing a maxillary sinus presenting an unusually thick lateral wall. This scenario may be an indication for MSFA via a palatal window approach.

but also the MSFA approach (either transalveolar or lateral window). Since the publication of clinical guidelines originally proposed by Carl E. Misch in 1987 (Misch 1987), other RBH classifications have been developed to guide clinicians in the decision-making process that would lead to the indication of a specific MSFA modality, with or without simultaneous implant placement, or an alternative option (Wang &Katranji 2008; Wagner *et al*. 2017).

The following are general recommendations proposed by the authors of this chapter on the basis of contemporary evidence (Fig. 42-22):

- RBH >9 mm: standard implant (length ≥8 mm) placement.
- RBH of >5 to ≤9 mm: MSFA with a transalveolar approach and simultaneous standard implant placement or short implant (length <8 mm) placement with no bone augmentation.
- RBH of >3 to ≤5 mm: MSFA with a lateral window approach and simultaneous implant placement.
- RBH ≤3 mm: MSFA with a lateral window approach and delayed implant placement.

It is important to remark that these and other numeric thresholds proposed elsewhere must always be interpreted with caution prior to making treatment planning decisions, factoring in the skill and preferences of the surgeon, the characteristics of the implant system employed, the planned contour of the final prosthetic restoration relative to the vertical location of the implant restorative platform, the presence of concomitant pathosis (Manji *et al*. 2013; Friedland & Metson 2014) and additional anatomic variables that may play a role in the execution of the technique, such as configuration and cortication of the sinus floor (Niu *et al*. 2018; Choucroun *et al*. 2017), presence and morphology of septa (Wen *et al*. 2013), mediolateral sinus width (Teng *et al*. 2016), thickness of the lateral sinus wall (Monje *et al*. 2014a; Danesh-Sani *et al*. 2017b), size and location of the posterior superior alveolar artery (Anamali *et al*. 2015), and thickness of the Schneiderian membrane (Monje *et al*. 2016; Rapani *et al*. 2016). As a general surgical principle, the most predictable and conservative approach should always be indicated after consideration of relevant individual local and systemic factors.

Presurgical examination and care

Prior to executing any advanced intraoral surgical procedure, such as MSFA, a thorough preoperative examination should be conducted for adequate case selection and treatment planning (see Chapter 22). This includes a detailed review of the patient's medical, dental, and periodontal history. The dental and periodontal status should be evaluated according to clinical and radiographic examination methods aligned with current diagnostic standards. Prior to performing a MSFA procedure, all partially edentulous patients should have completed infection control therapy (see Part 11). Additionally, the vitality of teeth neighboring the edentulous space should be tested. It is also important to examine the keratinized mucosa width, vestibulum depth, and interocclusal space.

A complete anatomical analysis based on meticulous clinical and radiographic assessments of the maxillary sinus and parasinusal structures should be conducted prior to indicating MSFA procedures

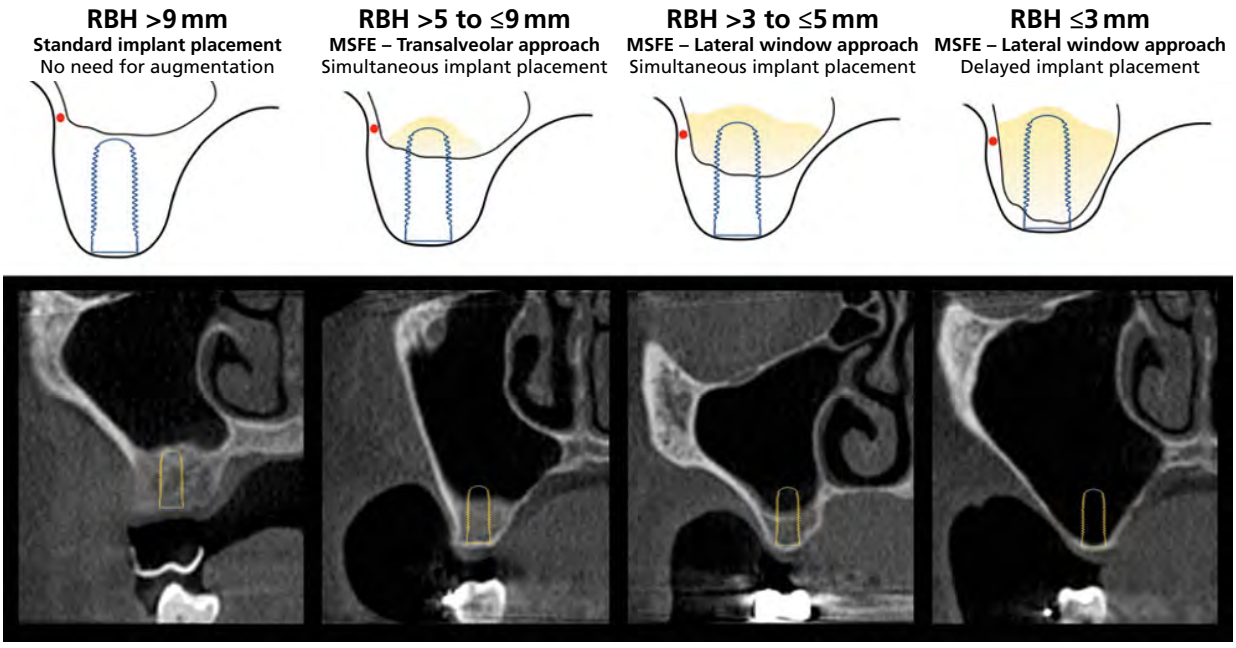

Fig. 42-22 Recommendations for the indication of different maxillary sinus floor augmentation (MSFA) and implant placement protocols in function of the residual bone height (RBH) with corresponding examples of sagittal CBCT sections. Note the increasing alveolar ridge atrophy and maxillary sinus pneumatization from the left to the right.

with the purpose of identifying and evaluating local factors that may influence the execution of the technique and the outcomes of therapy, such as unfavorable anatomic variations and/or presence of pathosis. The infraorbital, lateral nasal, and superior labial areas of the face should be examined extraorally for tenderness to palpation, abnormal swelling, or asymmetry. Likewise, the functional range of mouth opening should be assessed to confirm that surgical access will be favorable. Preoperative radiographic screening may include the analysis of periapical radiographs, orthopantomography, computed tomography (CT) or CBCT scans (see Chapter 23). Although some important information (e.g. remaining subantral bone height) may be obtained through the analysis of conventional 2D radiographs, critical diagnostic elements may go unnoticed if clinicians rely exclusively on these diagnostic tools. Therefore, the use of advanced imaging techniques, such as CBCT, is strongly recommended for the planning of MSFA (Benavides *et al*. 2012). CBCT imaging enables clinicians to perform a tridimensional assessment of the maxillary sinus and adjacent structures, detecting deviations from normal anatomy and the presence of pathosis. If pathosis that may interfere with the success of the surgical procedure is identified, appropriate medical consultations (e.g. otorhinolaryngological) and subsequent therapy (e.g. management of acute sinusitis, removal of polyps, or tumors) must be completed prior to MSFA in order to minimize the risk of intra- and postoperative complications (Chan & Wang 2011).

The prescription of prophylactic antibiotics to minimize the occurrence of an infection after MSFA is a controversial topic. A group of clinical experts that provided guidelines for the prevention and treatment of postoperative infections after MSFA advocated for the indication of presurgical antibiotic prophylaxis (Testori *et al*. 2012). However, it must be mentioned that, as recognized by the members of this expert panel, these recommendations are solely based on clinical experience and empirical observations. No clinical trial aimed at testing the need for antibiotic prophylaxis prior to the performance of MSFA procedures in order to reduce the incidence of postoperative complications has been conducted to date.

Healing dynamics

Progressive apposition of new bone in the subantral space intentionally created during the surgical intervention is expected in the course of a normal reparative response following MSFA procedures. This process consists of different healing phases (i.e. inflammatory, bone apposition, maturation, and remodeling), which partially overlap in time, in congruence with an intramembranous pattern of bone formation (Fuerst *et al*. 2004). In normal conditions of healing, if a bone grafting material and/or a dental implant are utilized to fill and/or maintain the space, new bone will be formed around the biomaterial and on the surface of the dental implant, followed by consolidation and maturation of the hybrid substrate, functional osseous remodeling, and a variable degree of resorption of the remaining bone grafting material (Watzek *et al*. 2006). Interestingly, preclinical and clinical studies on MSFA via a lateral window approach have demonstrated that the front, or gradient, of new bone formation primarily originates from the bony boundaries, on the periphery of the sinus cavity (Busenlechner *et al*. 2009; Scala *et al*. 2010; Kolerman *et al*. 2019), as shown in Fig. 42-23.

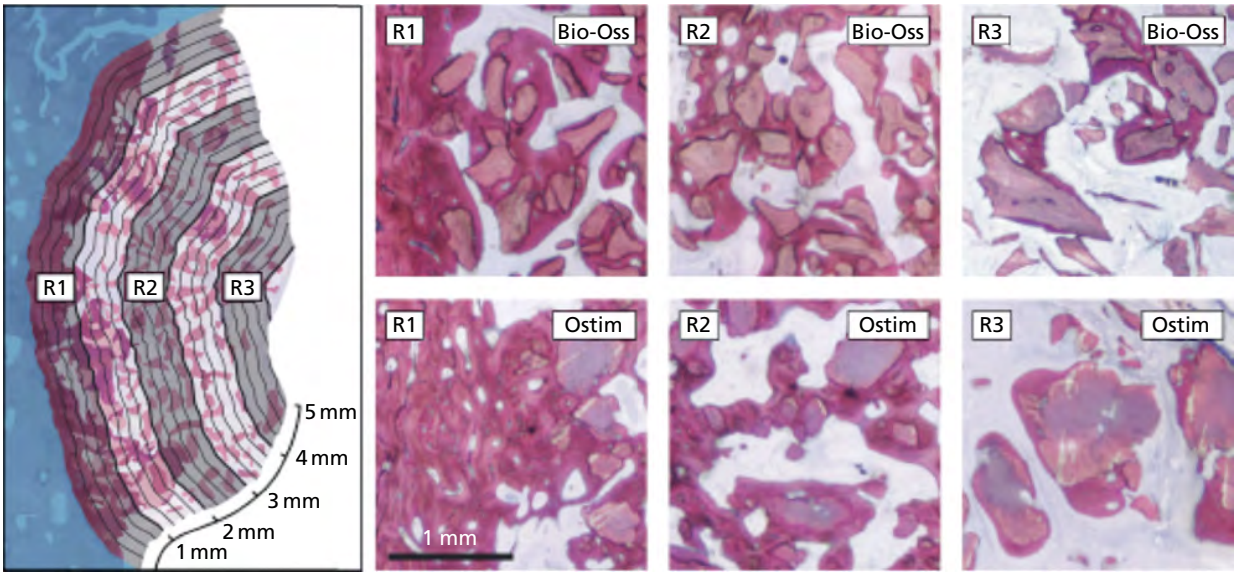

Fig. 42-23 Histologic sections illustrating the gradient of bone graft consolidation of two different biomaterials in different regions respective to the maxillary sinus bony boundaries in a minipig model. Source: This is Fig. 2 in the following publication: Busenlechner D, Huber CD, Vasak C, Dobsak A, Gruber R, Watzek G. 2009. Sinus augmentation analysis revised: the gradient of graft consolidation. Clin Oral Implants Res. 20(10):1078-1083. Reprinted with permission from Wiley and Sons.

Some authors have also commented on the osteogenic potential of the Schneiderian membrane, because it contains pluripotential mesenchymal cells that may differentiate into osteoblasts (Srouji *et al*. 2010; Graziano *et al*. 2012). However, the clinical significance of this concept is questionable. According to different preclinical studies the bone-forming capacity of the Schneiderian membrane seems to be modest, at best, and not critical in the success of MSFA procedures (Scala *et al*. 2012; Jungner *et al*. 2015; Caneva *et al*. 2017). This notion is supported by the findings of a recently published systematic review (Dragonas *et al*. 2020).

A normal process of bone formation and maturation requires a stable osteoconductive scaffold (e.g. blood clot and/or bone grafting material) in the early stages of healing, as well as adequate angiogenesis, migration, and attachment of cells involved in bone apposition and remodeling (i.e. osteoblasts and osteoclasts). Successful bone formation and graft consolidation depend on the inherent properties of the bone grafting material(s) employed and the osteogenic potential of the recipient bed. Delayed or insufficient bone maturation after MSFA may occur in patients with systemic conditions known to affect normal healing (e.g. uncontrolled diabetes), heavy smokers (Galindo-Moreno *et al*. 2012a), and in the presence of concomitant pathosis (Chan & Wang 2011) or unfavorable anatomical features, such as large sinus cavity dimensions (Avila *et al*. 2010; Stacchi *et al*. 2018). As with any other surgical intervention, careful assessment of local and systemic factors that may play a role in the healing process after MSFA is crucial for proper case selection and optimization of therapeutic outcomes.

Maxillary sinus floor augmentation: lateral window approach

Indications and contraindications

MSFA utilizing a lateral window approach is indicated for the prosthetic rehabilitation of edentulous spaces in the posterior maxilla presenting reduced RBH (≤5 mm), which may be incompatible with standard implant placement or transalveolar MSFA with simultaneous implant placement. In cases of reduced bone height caused by alveolar bone resorption and maxillary pneumatization combined with horizontal and/or vertical ridge deficiency, simultaneous MSFA and alveolar ridge augmentation (e.g. horizontal and/or vertical) may be indicated.

Contraindications for sinus floor augmentation may be relative (reversible) or absolute (irreversible) and can by divided into three groups: medical, behavioral, and local.

Medical contraindications

Medical contraindications include cancer treatment involving chemotherapy and/or radiotherapy of the head and neck area at the time of MSFA or in the preceding 6 months, immunocompromised patients, systemic diseases that affect the mucociliary function (e.g. cystic fibrosis), medical conditions known to affect bone metabolism, severe blood dyscrasias, uncontrolled diabetes, and psychological and/or psychiatric conditions that affect patient understanding or compliance. Additionally, drug regimens that may interfere with normal wound healing (e.g. bisphosphonates) should be carefully considered on an individual basis.

Behavioral contraindications

Whether or not smoking is an absolute contraindication for MSFA remains controversial. A case series involving 52 patients who underwent MSFA via a lateral window approach linked smoking with an impaired healing response (Galindo-Moreno *et al*. 2012a). In this study, a histomorphometric assessment of core biopsies obtained at 6 months after bone augmentation revealed that smoking habits were associated with lower counts of osteoblasts and smaller proportions of new bone formation. In another case series study, the survival of implants placed in combination with bone augmentation (horizontal/vertical) and MSFA was evaluated (Mayfield *et al*. 2001). The survival rate of these implants was 100% for non-smokers compared with only 43% for smokers after a maximum of 6.5 years of functional loading. The detrimental impact of smoking on implant survival rate has also been corroborated in other studies (Bain & Moy 1993; Gruica *et al*. 2004). However, a large study evaluating 2132 implants after sinus floor augmentation with simultaneous implant placement reported conflicting results (Peleg *et al*. 2006a). Two hundred and twenty-six sinus floor augmentations involving the placement of 627 implants were performed on smokers, whereas 515 sinus floor augmentations for a total of 1515 implants were done on non-smokers. After a follow-up time of up to 9 years, the survival rate of the implants was 97.9%, and there were no statistically significant differences in terms of implant survival rate between smokers and non-smokers. A systematic review published in 2008 investigated the survival rate of implants inserted in combination with sinus floor augmentation utilizing the lateral window approach (Pjetursson *et al*. 2008). Five of the included studies reported on the influence of smoking status of the patients on implant survival after sinus floor augmentation. A group of non-smokers who received 2159 implants and a group of smokers who received 863 implants were analyzed. Although the smoking habits were not homogenously reported across studies, smoking was associated with a higher annual implant failure rate (3.54%) compared with non-smokers (1.86%). A recent systematic review aimed at evaluating the effect of smoking on the survival rate of dental implants placed in sites that underwent MSFA rendered similar results (Chambrone *et al*. 2014). The data from seven different studies that met the eligibility criteria were extracted and pooled in a

quantitative analysis that revealed a statistically significantly increased, but modest risk of implant failure in smokers (relative risk [RR] = 1.87; [95% CI: 1.35, 2.58], $P = 0.0001$). However, this effect was not statistically significant when only data from prospective studies ($n = 3$) was analyzed (RR = 1.55; [95% CI: 0.91, 2.65], $P = 0.11$). Excessive alcohol consumption and recreational drug abuse should also be considered as potential contraindications for MSFA.

Local contraindications

Alterations of the naso-maxillary complex that interfere with normal ventilation or mucociliary clearance of the maxillary sinus may be a contraindication for MSFA with a lateral window approach. It is important to keep in mind that patients with such abnormal conditions may be asymptomatic or only present mild clinical symptoms. These conditions include anatomical alterations (e.g. stenosis of maxillary ostium, concha bullosa of the middle turbinate, paradoxical curve of middle turbinate, enlarged agger nasi or infraorbital Haller cell, hypertrophic uncinate process, and aberrant septa), large mucous retention cysts, local aggressive benign (e.g. polyps) and malignant tumors, hypofunctional ciliary mucosae, viral, bacterial or mycotic rhinosinusitis, allergic rhinitis, allergic sinusitis, sinusitis caused by foreign bodies, odontogenic sinusitis, and acute, subacute, chronic, or recurrent bacterial sinusitis. Performing MSFA in the presence of any of the above conditions may disturb the fine mucociliary balance, resulting in mucus stasis, suprainfection, and subacute sinusitis.

Surgical technique

Since the original description of the lateral window approach by Boyne and James (Boyne & James 1980), numerous modifications of this modality of MSFA have been proposed in the literature to facilitate the performance of this surgical intervention, increase its predictability, and decrease the incidence of complications (Wallace *et al*. 2012). The generic protocol outlined below, proposed by the authors, is based on previous descriptions of this technique:

1. A presurgical rinse with an aqueous solution containing chlorhexidine (0.12% or 0.2%) is performed for a period of 1 minute.
2. Perioral cutaneous surfaces may be disinfected (e.g. wiping with iodine solution, unless contraindicated because of allergy).
3. Local infiltrative anesthesia is delivered buccal and palatal to the surgical area. In most cases, blocking the infraorbital, greater palatine, and posterior superior alveolar nerves is sufficient to obtain the necessary anesthesia to perform MSFA. Additional infiltrations along the mucogingival junction and the palatal mucosa using an anesthetic containing epinephrine may be administered to reduce intraoperative bleeding. Sedation should be considered in patients with a history of dental anxiety.
4. With the purpose of minimizing postoperative pain and discomfort for the patient, and to favor an uneventful postoperative period, MSFA procedures should be as minimally traumatic as possible. An initial mid-crestal or slightly palatal incision, if the amount of keratinized mucosa is limited, is made (Fig. 42-24c). This initial incision usually extends between the remaining teeth, in cases of partial edentulism, or from the canine or premolar area to the tuberosity, in cases of edentulous distal extension. In cases of partial edentulism, mesial and distal intrasulcular incisions may be done to increase the flap area. Then, vertical releasing incisions are made anteriorly and posteriorly, passing the mucogingival junction and extending into the buccal vestibulum for adequate surgical access after the reflection of a mucoperiosteal flap. It is important to place the incisions at a safe distance (a minimum of approximately 5 mm) from the boundaries of the planned lateral window in order to minimize the potential impact of a possible premature wound opening on the healing outcomes.
5. The trapezoid mucoperiosteal flap is raised slightly superior (2–3 mm) to the anticipated height of the lateral window. Precautions must be taken to avoid perforation of the flap. Unless simultaneous implant placement is planned, elevation of the palatal mucosa is not necessary in this surgical procedure (Fig. 42-24d). After the lateral sinus wall has been exposed, the window is outlined, which can be done using instruments such as a round diamond bur attached to a high-speed rotary handpiece, piezoelectric equipment, a bone scraper (Fig. 42-24e), which allows for the harvesting of autogenous bone, or a combination of them (Vercellotti *et al*. 2001; Peleg *et al*. 2004; Galindo-Moreno *et al*. 2007). In accordance with minimally invasive surgery principles and to maximize the amount of new mineralized tissue formation (Avila-Ortiz *et al*. 2012b), it is important to outline a lateral window that is as small as possible, but large enough to gain the necessary access to achieve the surgical goal (Fig. 42-24g). To aid in the elevation of the Schneiderian membrane, the most inferior boundary of the window should be delineated in proximity to the floor of the sinus. The position of the mesial and distal window boundaries within the edentulous segment is dictated by the location of the anterior and posterior maxillary sinus walls and by the presence of adjacent teeth. When adjacent teeth are present the window should be delineated at least 2 mm away from the root contours to avoid tooth damage. In cases of complete absence of posterior teeth, the mesial boundary should be outlined at approximately 2 mm distal from the anterior sinus wall and at a

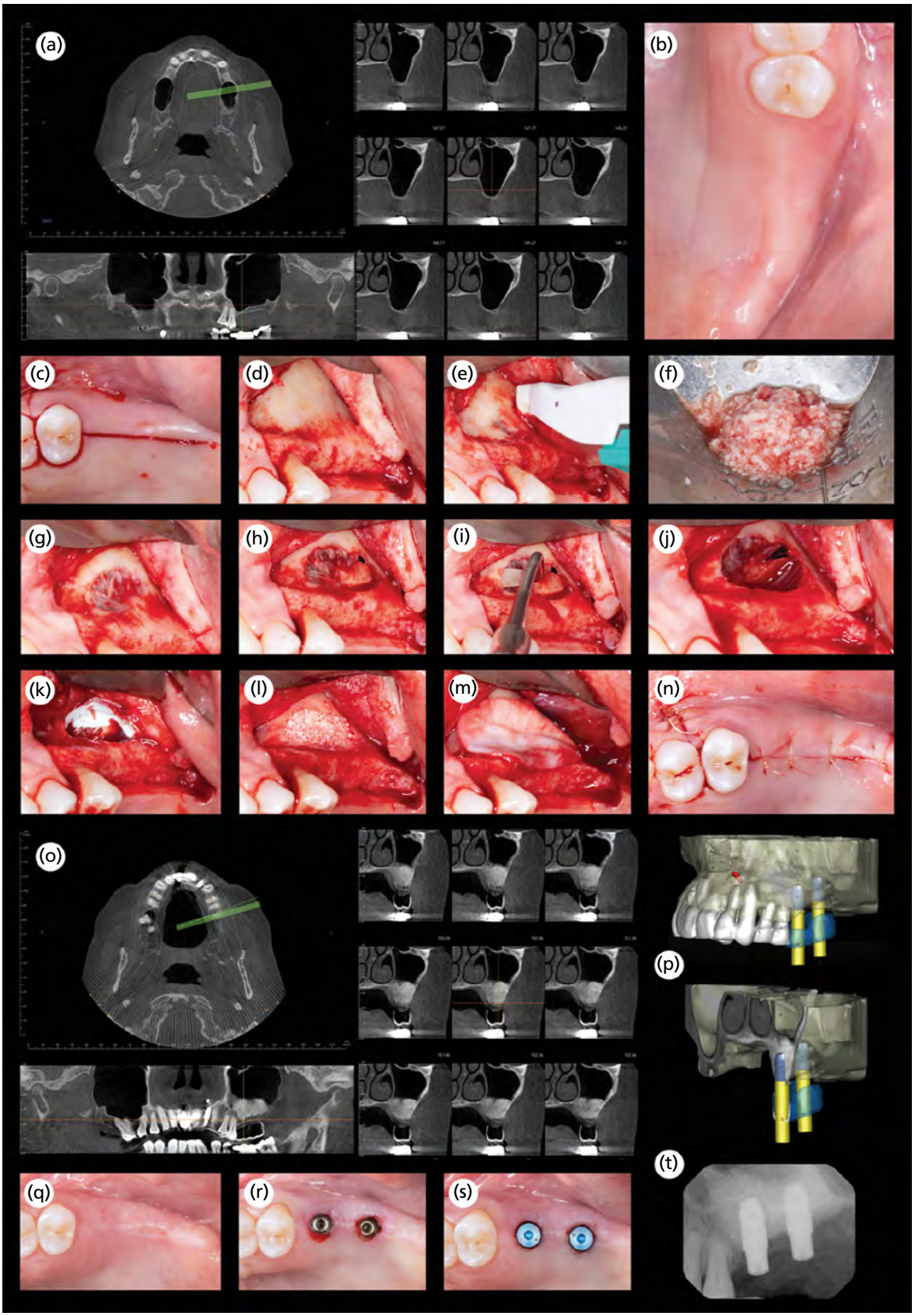

Fig. 42-24 Sequence of a case of MSFA via a lateral window approach and delayed implant placement. (a) Radiographic study of the baseline scenario. (b) Intraoral occlusal view of the edentulous segment. (c) Supracrestal and vertical releasing incisions. (d) Mucoperiosteal flap elevation. (e) Bone scraper is used to harvest autogenous bone from the lateral sinus wall. (f) Mix of autogenous bone (~20%) and bovine xenograft particles (~80%). (g) Aspect of Schneiderian membrane as the lateral window access is created. (h) A perforation was noticed on the upper and posterior corner of the window. (i) A sinus membrane elevator was applied on the opposite side of the perforation. (j) The perforation got slightly larger upon complete elevation of the membrane. (k) An absorbable porcine collagen membrane was used to seal the perforation. (l) The bone graft mix was used to fill the subantral space. (m) Another porcine collagen membrane was applied to cover the window. (n) Primary closure was achieved. (o) Radiographic study of the augmented area after 6 months of healing. (p) Virtual planning for static computer-aided implant placement. (q) Occlusal view of the site. (r) Implants were placed following a flapless approach through the surgical guide. (s) Primary stability was achieved. Healing abutments were delivered. (t) Control periapical radiograph obtained immediately after implant placement.

variable distance from the posterior wall, because it is usually not necessary to augment all the way to the most posterior aspect of the antral cavity. The most apical boundary of the window should be placed at a distance that permits the placement of standard length implants (>8 mm), accounting for an approximate 10–25% of remodeling respective to the original grafted volume (Kirmeier *et al*. 2008; Mazzocco *et al*. 2014; Younes *et al*. 2019). The outline of the lateral window may require additional modifications to avoid septa (Fig. 42-25). Creating two or more separate windows is recommended to overcome tall septa (i.e. >2.5 mm) located on the sinus floor in order to minimize the risk of Schneiderian membrane perforation (Beretta *et al*. 2012).

Four methods for handling the lateral cortical bone plate have been proposed. A common approach is thinning of the buccal bone using a round bur or a piezoelectric tip and removing the overlying bone prior to maxillary sinus membrane elevation (Fig. 42-26).

Another method is to fracture the cortical bony plate like a trapdoor and use it as the superior border to the surgically created compartment, leaving it attached to the Schneiderian membrane. The third method is to remove the cortical bony plate during sinus floor elevation and replace it on the lateral aspect of the graft at the end of the grafting procedure. The rationale for this method is based on the notion that the lateral window would not completely heal without replacement of its cortical plate. However, healing of the lateral window by bone apposition without replacing the cortical bony plate has been demonstrated (Boyne 1993). The fourth method involves utilizing the lateral bone plate to harvest particulate autogenous bone that can be utilized in combination with a larger amount of a bone substitute (Fig. 42-24f). This can be accomplished by retrieving and processing the cortical bony plate using a bone mill or, as aforementioned, by using a bone scraper.

6. Once exposed, careful elevation of the Schneiderian membrane, which typically presents a bluish hue (Fig. 42-24g), may be performed using blunt piezoelectric tips and/or sinus membrane elevators (Fig. 42-27). Care should be taken not to perforate the membrane, reflecting it as much as necessary to create the compartment required for bone grafting and implant placement, but not overextending, to minimize the risk of complications (Fig. 42-24i). In order to avoid occlusion of the nasal meatus and a subsequent complication, the Schneiderian membrane should never be lifted

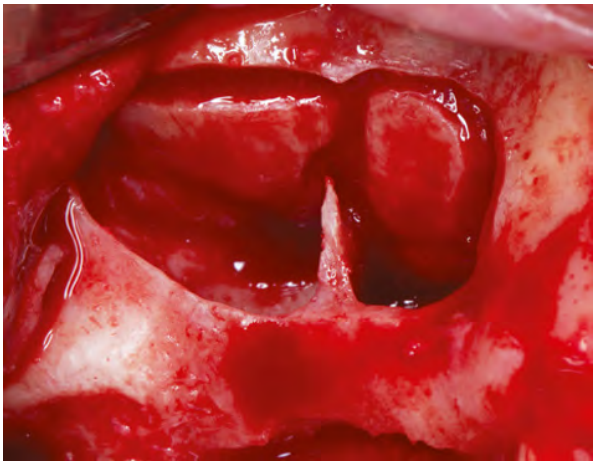

Fig. 42-25 Modified lateral access creating two separate windows to overcome the presence of a tall septum.

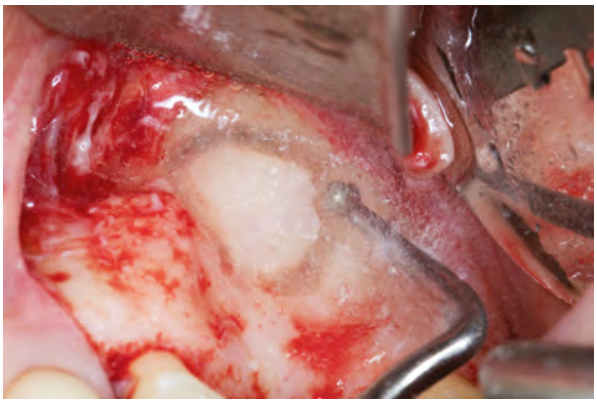

Fig. 42-26 Irrigated round diamond-coated piezosurgery tip in use as the lateral window is outlined.

Fig. 42-27 Maxillary sinus membrane elevators with different tip designs.

beyond the ostium (Maksoud 2001). Care should be taken to reach the medial wall in order to allow for homogeneous graft distribution and avoid a medial void or recess (Fig. 42-28).

It is generally recommended to start releasing the areas of less tension and favorable access. Another useful tip is to apply careful and gentle pressure when the membrane elevators are used, feeling the underlying bony structures, to prevent the occurrence of a membrane perforation and/or damage to the posterior superior alveolar artery, which is crucial to avoid a significant hemorrhage if the artery is particularly large and has an intraosseous course (Fig. 42-29).

If a perforation occurs, a sealing material, such as an absorbable barrier membrane, can be placed over the perforation to prevent extravasation of the grafting material into the antral cavity, which may lead to severe complications (Fig. 42-24k). It is generally recommended to abort the bone grafting procedure if the perforation cannot be sealed intraoperatively (Vlassis & Fugazzotto 1999). Complete repair of the Schneiderian membrane after trauma may take up to 4 months (Huang *et al*. 2006), therefore surgical reentry to attempt a secondary procedure is not recommended before then.

Depending on anatomical variables, such as RBH, and the surgeon's preference, MSFA through a lateral window approach may be performed with delayed or simultaneous implant placement.

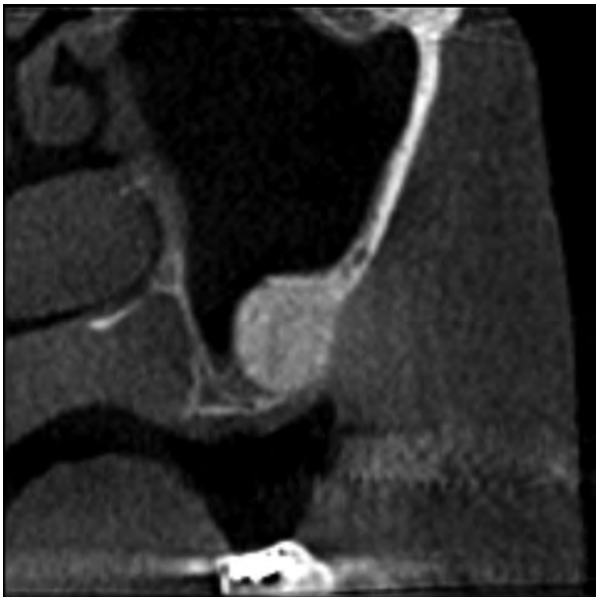

Fig. 42-28 Sagittal section of a posterior edentulous maxillary segment approximately 6 months after MSFA via a lateral window approach using bovine xenograft particles. Note the void medial to the grafted substrate resulting from an incomplete elevation of the Schneiderian membrane.

MSFA with a lateral window approach and delayed implant placement

1. Unless a graftless approach is followed, a bone grafting material is placed in the compartment created after the elevation of the sinus membrane (Fig. 42-24l). The total amount of grafting material required differs between cases depending on the dimensions and configuration of the maxillary sinus cavity. The grafting material should not be aggressively packed, because this may reduce the space needed for angiogenesis, cell migration, and in-growth of new bone. In addition, stretching a thin sinus membrane by exerting excessive pressure when packing the grafting material may result in a perforation.
2. The lateral window may be covered with an absorbable or a non-absorbable barrier membrane (Fig. 42-24m). Barrier membranes may aid in preventing soft tissue ingrowth into the grafted compartment. However, available evidence is equivocal regarding the effect of a barrier membrane to cover the lateral window. Although some studies have found a beneficial effect associated with use of a barrier in terms of new bone formation and increased implant survival (Froum *et al*. 1998; Tarnow *et al*. 2000; Tawil & Mawla 2001), others have reported no significant differences between sites that received a membrane and those which did not (Choi *et al*. 2009; Yu *et al*. 2017). A systematic review found that the cumulative

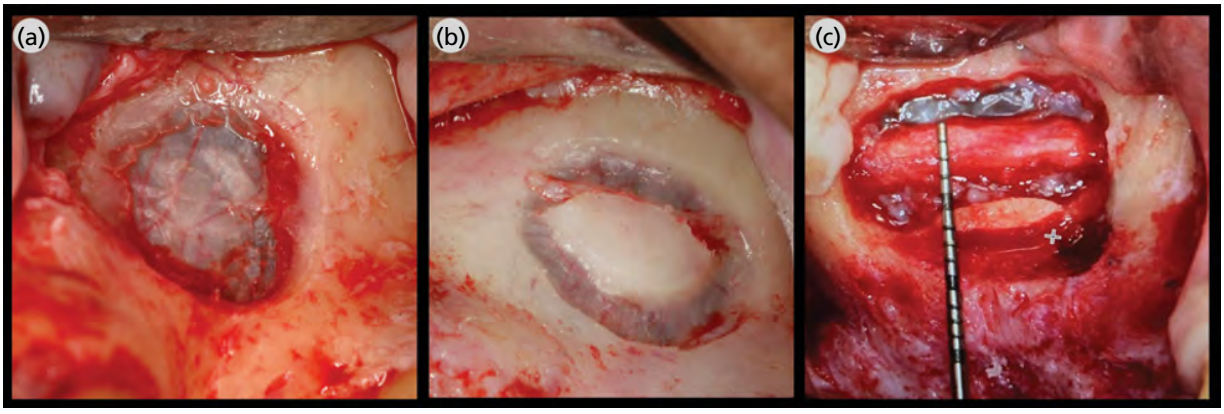

Fig. 42-29 Clinical images showing the presence of three right posterior superior alveolar arteries of different sizes when performing MSFA via a lateral window approach. (a) Small. (b) Medium. (c) Large. (Source: (c) is courtesy of Dr. Nikolaos Tatarakis, Queen Mary University and Private Practice, London, UK.)

3-year annual failure rate of dental implants placed in sites that underwent MSFA with a membrane covering the lateral access window was lower (0.79%) compared with those placed in sites that did not receive a membrane (4.04%) (Pjetursson *et al*. 2008). If a barrier membrane is used, it is generally recommended to use an absorbable membrane in order to avoid the need for elevating a larger flap for non-absorbable membrane retrieval at the time of delayed implant placement. Subsequently, the flap is repositioned and sutured to achieve primary closure (Fig. 42-24n). Periosteal releasing incisions are generally not necessary to achieve tension-free closure, unless simultaneous horizontal or vertical ridge augmentation is performed in combination with MSFA.

MSFA with a lateral window approach and simultaneous implant placement (Fig. 42-30)

1. After the sinus membrane has been elevated, the implant site(s) are prepared. The use of a surgical stent based on the prosthetic plan is recommended. If rotary instruments (e.g. drills) are used, the sinus membrane should be protected using a solid instrument, such as a large periosteal elevator. Alternatively, osteotomes of different diameters may be used to prepare the implant site. In these situations, the membrane can be protected by inserting sterile, lint-free gauze into the sinus compartment.
2. Unless a graftless approach is followed, the bone grafting material is inserted and gently packed towards the medial part of the sinus compartment, followed by implant placement and, finally, by grafting of the lateral aspect. This sequence allows for improved visibility and reduces the chance of leaving a void medial to the implant(s). The subsequent steps coincide with those described for the delayed implant placement approach, with the exception that, if adequate primary stability is achieved, a healing abutment may be delivered according to a non-submerged implant placement protocol.

Grafting material selection

There are differences of opinion regarding the need to employ bone grafting materials in MSFA procedures.

No grafting material: blood clot

An early preclinical study by Philip J. Boyne demonstrated that bone formation around osseointegrated implants protruding into the maxillary sinus after elevation of the Schneiderian membrane without the application of a bone grafting material is feasible (Boyne 1993). In the same study, it was also observed that implant design influenced the amount of spontaneous bone formation. New bone formation was insufficient around implants with open apices or deep-threaded configurations. On the other hand, implants with rounded apices that penetrated 2–3 mm into the maxillary sinus were associated with bone formation around their entire circumference. However, when the same implants penetrated 5 mm into the maxillary sinus, only a partial growth of new bone, up to approximately half of the total implant length, was achieved. A similar outcome was observed in a preclinical investigation in dogs (Kim *et al*. 2010).

This concept has also been demonstrated in human research models. Lundgren and co-workers conducted several studies in which, after removing the lateral bony wall, the sinus membrane was elevated and sutured against the lateral wall in an elevated position, in order to create and maintain a compartment for blood clot formation. Implants were placed simultaneously, which is a *sine qua non* for the graftless approach protocol. Comparisons of pre- and postoperative CT images obtained at 6 months after the surgical procedure clearly demonstrated the presence of new bone within the compartment created between the implants and the Schneiderian membrane (Lundgren *et al*. 2004; Hatano *et al*. 2007).

In another clinical study, 131 implants were placed simultaneously with MSFA via a lateral window approach. Implants were inserted with intentional protrusion into the sinus cavity, after Schneiderian membrane elevation. The sinus membrane was allowed to settle onto the apex of the implants, thus creating a space to be filled with a coagulum. After a mean follow-up of 5 years, the survival rate of these implants was 90% (Ellegaard *et al*. 2006).

A longitudinal study that monitored 84 patients who underwent a total of 96 sinus floor elevations procedures with simultaneous placement of 239 implants without using any bone grafting material, demonstrated an average vertical bone gain of 5.3 mm on intraoral radiographs after 6 months of healing. Implant survival was 98.7% at 3 years (Cricchio *et al*. 2011). Along the same lines, a systematic review aimed at analyzing the implant survival rates up to 5 years of follow up following MSFA using bone grafting materials or not. The survival rate of implants placed in grafted sites was 99.6%, whereas implants placed in sites that received no bone grafting exhibited a survival rate of 96.0% (Silva *et al*. 2016).

Hence, it may be concluded that graftless MSFA is a predictable and valid procedure associated with a low incidence of implant failure (Duan *et al*. 2017). It is also important to remark that simultaneous placement of implants protruding into the sinus cavity is required in this technique to tent the Schneiderian membrane and maintain an adequate space for blood clot stabilization. However, simultaneous implant placement is not always feasible when performing MSFA procedures, particularly in sites with limited RBH. In order to successfully manage a wide range of anatomical situations in the context of MSFA, it is

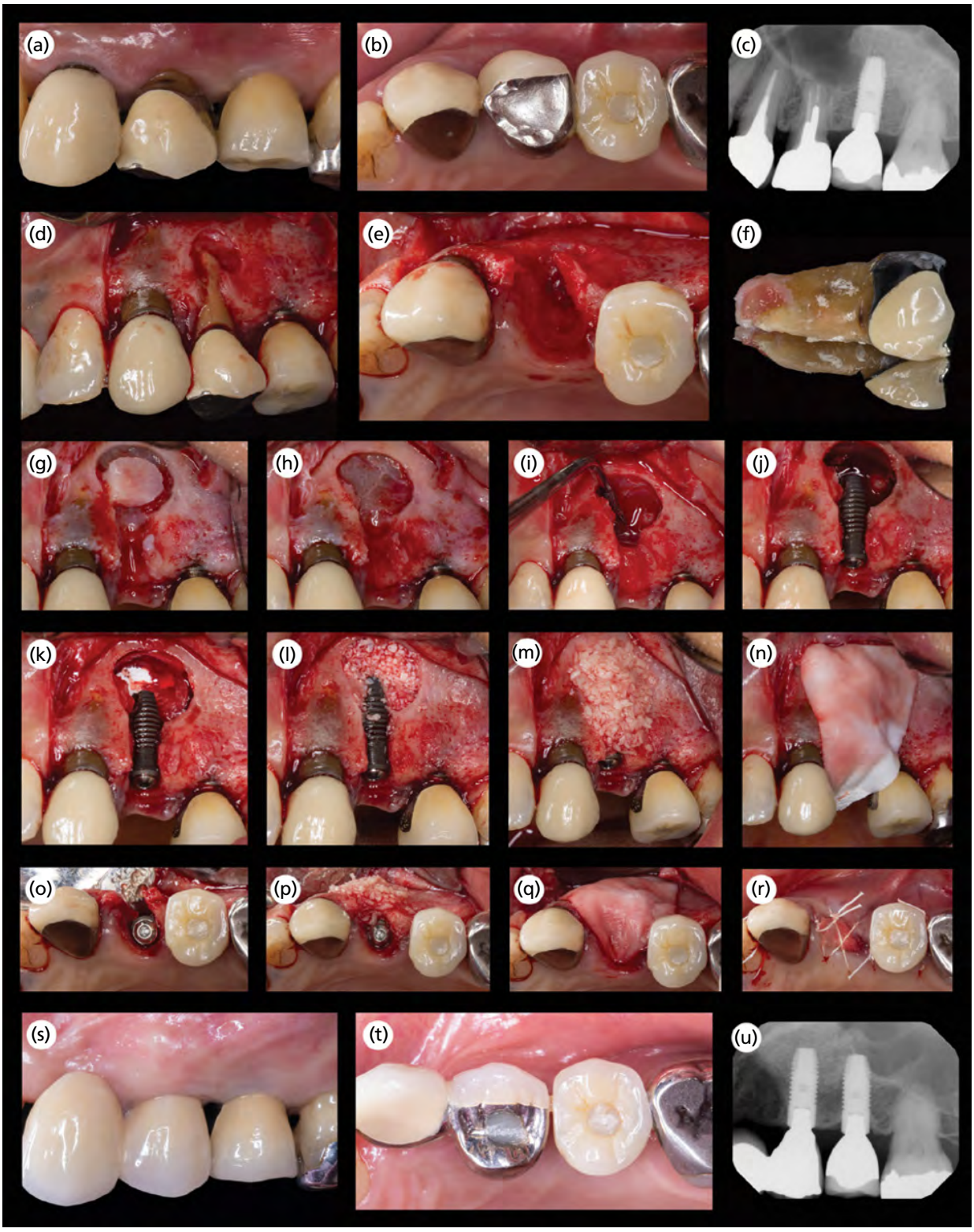

Fig. 42-30 Sequence of a case of MSFA via a lateral window approach with simultaneous implant placement to replace a hopeless maxillary left first premolar which exhibited a mid-buccal vertical root fracture. (a, b) Lateral and occlusal view of the site. (c) Periapical radiograph showing an apical radiolucency. Note that the second premolar was previously replaced with an implant-supported prosthesis and MSFA. (d) Complete absence of the buccal wall was verified upon elevation of a full-thickness flap. (e) Occlusal view immediately after tooth extraction and debridement. (f) Detail of the extracted tooth. (g) The lateral window was outlined using a piezosurgery unit. (h) The bony wall was carefully detached from the Schneiderian membrane. (i) A sinus membrane elevator was used. (j) An implant was placed after the osteotomy was completed. (k) Even though no perforation occurred, an absorbable porcine collagen membrane was used to facilitate the bone grafting procedure. (l) A bone graft mix consisting of bovine xenograft particles and milled autogenous bone from the lateral window was used to fill the subantral space. (m) The facial aspect of the ridge was grafted using cortical allograft particles. (n, p, q, r) Occlusal view of the site upon implant placement (o), grafting with the allograft material (p), covering with the porcine collagen membrane (q) and suturing (r). (s, t) Lateral and occlusal view of the site at the 5-year follow-up visit. The canine was eventually lost, also caused by a vertical root fracture. The prosthodontist (Dr. Galen Schneider, University of Iowa) opted for a mesial cantilever to replace the missing crown. (u) Periapical radiograph obtained at 5 years after implant placement.

therefore necessary to consider the indication of other surgical protocols involving the use of bone grafting materials.

Autogenous bone

Autogenous bone grafts have been considered historically as the gold standard for bone augmentation procedures because of their osteoconductive, osteoinductive, and osteogenic capacity. Autogenous grafts may be harvested intra- or extraorally. Common intraoral donor sites are the maxillary tuberosity, the zygomaticomaxillary buttress and the mandibular symphysis, body or ramus. Examples of extraoral donor sites are the anterior and posterior iliac crest, tibial plateau, fibula, rib, and calvaria. Bone may be harvested as a block or in particulate form. Aside from osteogenic cells, autologous bone grafts contain signaling molecules that play a crucial role in bone formation, such as growth factors and bone morphogenic proteins (BMPs).

Processing of autografts with grinding or morselizing devices does not seem to disturb the viability of the osteogenic cells (Springer *et al*. 2004). This was corroborated by a study aimed at evaluating the effect that different harvesting methods has on cell viability and release of growth factors of autogenous bone samples. Interestingly, this study found that bone mill and bone scraper samples revealed significantly higher expression of growth factors compared with bone obtained by drilling (bone slurry) or using a piezosurgery device (Miron *et al*. 2013).

Autogenous bone graft was the first documented material applied in MSFA (Boyne & James 1980). In early reports, autogenous bone was applied as a sole grafting material and was associated with successful outcomes. However, the use of autogenous bone in MSFA has two major disadvantages: (1) the need to harvest a large amount of bone that may range from 1 to 5 cm^3 (Arias-Irimia *et al*. 2012) from, at least, a second surgical site, which increases the surgical time and the risk of morbidity, and (2) the high resorption rate associated with particulate autogenous bone (Shanbhag *et al*. 2014), which may exceed the rate of new bone formation during the consolidation phase and render a suboptimal augmentation outcome.

Bone graft substitutes

With the purpose of overcoming the limitations of autogenous bone grafts, the use of readily available bone graft substitutes (i.e. alloplastic materials, allografts, and xenografts), alone or in combination with bone autografts (Fig. 42-24f), has become the most commonly indicated option for the performance of MSFA procedures in contemporary practice.

Over the past three decades, multiple preclinical and clinical studies in MSFA have demonstrated successful clinical and histomorphometric outcomes in association with the use of a wide range of bone graft substitutes. Histologic analyses of human biopsy specimens obtained at different time points from sinuses augmented with bone graft substitutes have demonstrated that the vast majority of these materials are biocompatible, osteoconductive, and present a low resorption rate. For example, several studies have documented the presence of bovine xenograft particles in biopsies obtained after 7, 9, or even 11 years from the time of grafting (Traini *et al*. 2007; Mordenfeld *et al*. 2010; Galindo-Moreno *et al*. 2013), demonstrating its long-term stability, biocompatibility, and clinical viability in MSFA procedures (Fig. 42-31).

Furthermore, a histologic study by Pablo Galindo-Moreno and colleagues found the presence of small capillaries, cells, and new bone formation within the existing Haversian canal of bovine xenograft particles in samples obtained at 6 months after MSFA using a combination of autogenous bone and bovine xenograft particles (Galindo-Moreno *et al*. 2010), as shown in Fig. 42-32.

Although some authors have suggested the use of particulate autogenous bone in combination with a larger proportion of a bone substitute, such as bovine xenograft or allograft particles (Froum *et al*. 1998; Mordenfeld *et al*. 2014), to maximize the therapeutic outcomes, several systematic reviews on this topic are coincidental in that no specific bone grafting material or combination thereof has been shown to be patently superior (Wallace &Froum 2003; Aghaloo & Moy 2007; Pjetursson *et al*. 2008; Corbella *et al*. 2016; Danesh-Sani *et al*. 2017a). Specifically, a recently published systematic review aimed at analyzing long-term (≥5 years) implant-therapy outcomes after MSFA with particulate autogenous bone graft compared to MSFA with a mix of particulate autogenous bone graft and bone graft substitutes or bone graft substitutes alone (Starch-Jensen *et al*. 2018). Of the nine included studies, eight exclusively reported data after MSFA with a lateral window approach. The 5-year implant survival after MSFA using solely autogenous bone or bovine xenograft particles was 97% and 95%, respectively.

Nevertheless, there is a need for targeted long-term studies evaluating the performance of different bone grafting materials in MSFA to collect information that may aid clinicians in discerning what protocol may render more favorable and predictable results in a wide range of clinical scenarios.

Tissue engineering approaches

The application of tissue engineering strategies to enhance the predictability and outcomes of bone augmentation procedures, such as MSFA, is a therapeutic option (Avila-Ortiz *et al*. 2016). Tissue engineering therapies may include the use of biologics, such as such as recombinant human bone morphogenic protein 2 (rhBMP-2) (Triplett *et al*. 2009; Lin *et al*. 2016) or recombinant human platelet-derived growth factor BB (rhPDGF-BB) (Nevins *et al*. 2009), autogenous blood-derived products (Dragonas *et al*. 2019a, b) and cell therapy (Kaigler *et al*. 2015). These strategies have

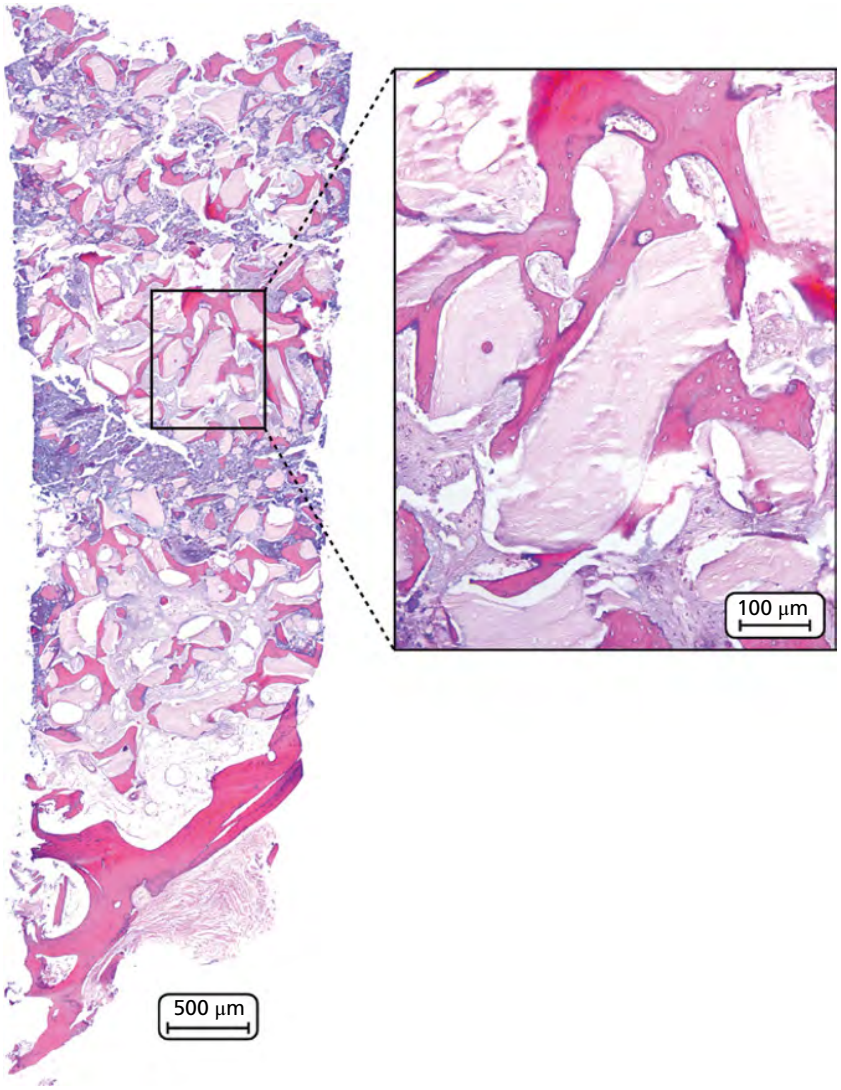

Fig. 42-31 Core biopsy obtained at the time of implant placement, approximately 6 months after MSFA using bovine xenograft particles. Hematoxylin and eosin staining. On the lower magnification image (left), note the presence of native bone at the bottom, corresponding with the residual bone height. On the higher magnification image (right), note the newly formed mineralized tissue in direct contact with remaining xenograft particles.

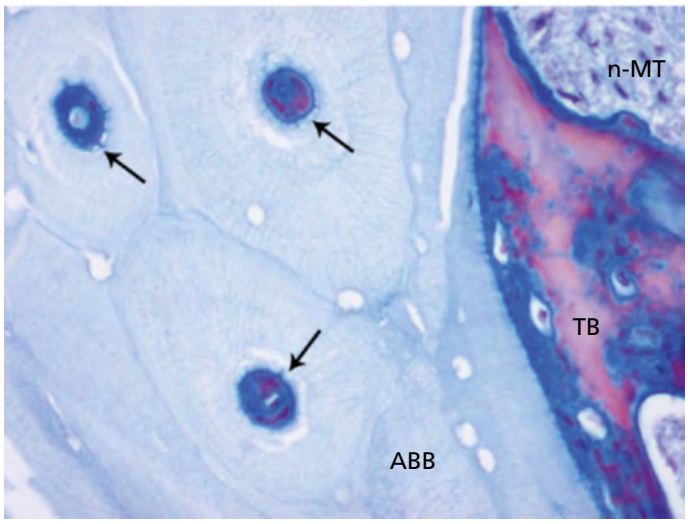

Fig. 42-32 Histomicrophotograph showing microvessels and newly formed mineralized tissue (n-MT) in intimate contact (TB) with and occupying the Haversian canals (arrows) of a bovine xenograft particle (ABB), illustrating the osteoconductivity of this material. Source: This was obtained from Fig. 1 in the following publication: Galindo-Moreno P, Padial-Molina M, Fernandez-Barbero JE, Mesa F, Rodriguez-Martinez D, O'Valle F. 2010. Optimal microvessel density from composite graft of autogenous maxillary cortical bone and anorganic bovine bone in sinus augmentation: Influence of clinical variables. Clin Oral Implants Res. 21(2):221-227. Reprinted with permission from Wiley and Sons.

shown promise and may be adopted to complement the osteoconductive properties of conventional bone graft substitutes or as monotherapy. However, their indication in MSFA is controversial because of the high degree of success and predictability associated with the use of conventional bone grafting materials, as well as the increased cost, preparation time, lack of structural integrity, and safety concerns associated with some of these strategies. Further studies to gather data on the most suitable indications and optimization of cost-effectiveness are required for tissue engineering therapies to be widely embraced in daily clinical practice.

Postoperative care

The level of postoperative pain experienced by patients undergoing MSFA procedures is generally mild and mostly limited to the first few days after surgery. Facial swelling and bruising are not uncommon and may extend from the inferior border of the orbit to the lower border of the mandible, or even to the neck. In order to reduce swelling, the local temperature of the treated area may be kept low by intermittent application of cooling pads on the face over the first 6–8 hours after surgery. A group of experts agreed that preoperative or postoperative corticosteroid therapy may be recommended to reduce the level of postsurgical swelling and discomfort. However, a consensus was not reached on the dosage because of the heterogeneity of the pharmacological regimens utilized by the members of the panel (Testori *et al*. 2012). Additionally, patients may be provided with prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs), to control postoperative swelling and discomfort, and oral antibiotics, to reduce the risk of a postoperative infection, which is a controversial issue. Although there is no solid evidence supporting the therapeutic benefit of postoperative antibiotic regimens after MSFA, the same group of experts determined that there is a current trend in favor of the indication of such pharmacologic protocols and, therefore, recommended the indication of antibiotics prior to and/or after MSFA based on empirical experience (Testori *et al*. 2012). Patients should be instructed to avoid mechanical disturbance of the surgical area, such as direct, vigorous brushing. The use of antiseptic rinses (e.g. chlorhexidine 0.12 or 0.2%) twice daily may be indicated until suture removal for plaque control purposes. Occasionally, minor nasal bleeding (epistaxis) may occur within the first week. It is important to inform patients of this possibility in advance. If the patient needs to sneeze, the nostrils should not be blocked so that air pressure can be relieved, preventing early wound stability alterations.

Complications

According to a recent systematic review, intra- and postoperative complications after MSFA are typically minor and unrelated to the bone grafting material applied (Raghoebar *et al*. 2019). In this review, it was found that the most common intraoperative complication is perforation of the Schneiderian membrane, accounting for an approximate occurrence of 20% during MSFA procedures, which is coincidental with the findings of a previous systematic review on this topic (Pjetursson *et al*. 2008). Whether or not this complication influences implant survival rate has been debated. Although some studies have reported an association between membrane perforation and implant failure (Al-Moraissi *et al*. 2018), others found no correlation (Al-Dajani 2016; de Almeida Ferreira *et al*. 2017). However, Schneiderian membrane perforation, if not properly managed, appears to be associated with an increased risk of postoperative sinusitis and graft failure (Nolan *et al*. 2014). In the event of membrane perforation, it is recommended to elevate the membrane in the opposite direction to prevent further enlargement of the perforation. Smaller perforations (<5 mm) may be closed by using fibrin glue, suturing, or by covering them with an absorbable barrier, such as a collagen membrane, as shown in Fig. 42-33. In instances of larger perforations, where a stable seal cannot be achieved, aborting the grafting procedure should be considered.

According to the aforementioned systematic review, the second most common complication is abnormal postoperative bleeding (14.5%), whereas the occurrence of overall postoperative infections and subacute sinusitis was found to be very low, at 1.0% and 0.2%, respectively (Raghoebar *et al*. 2019). Sinusitis typically manifests at 3–7 days postsurgically and may lead to complete graft failure. A possible complication of sinusitis is a secondary infection that may spread to the orbita or even to the brain (Pereira *et al*. 2017). Therefore, infected sinus grafts must be treated immediately and effectively. Surgical re-entry and removal of the entire graft

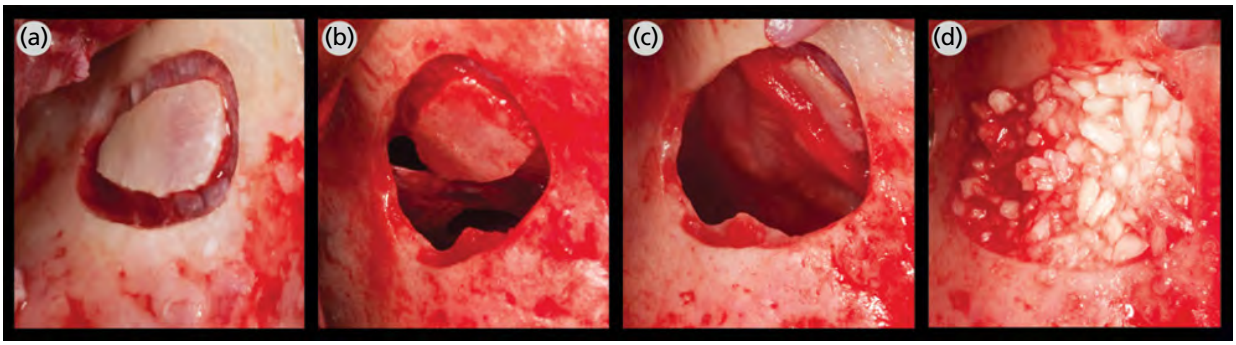

Fig. 42-33 (a) Lateral window outlined after using a piezosurgery instrument. (b) Two separate perforations occurred upon Schneiderian membrane elevation. The membrane was very thin in some areas. (c) An absorbable porcine collagen membrane was trimmed and carefully applied to seal the perforations. (d) Once the perforations were sealed, a particulate cortical allograft material was safely used to augment the maxillary sinus floor.

from the sinus cavity, plus administration of high doses of wide-spectrum antibiotics, are essential pillars of the clinical protocol.

Other reported causes of late MSFA failure include chronic infection (longer than 12 weeks), graft exposure and/or infection caused by premature wound dehiscence (Fig. 42-34a), idiopathic resorption of the entire bone graft, replacement of the bone graft with granulomatous tissue, ingrowth of soft tissue through the lateral window, oroantral fistula, and secondary sinus cysts. Rare iatrogenic complications after MSFA include adjacent tooth sensitivity or devitalization (Beck *et al*. 2018), implant migration into the sinus cavity (Galindo-Moreno *et al*. 2012b), severe antral hematoma (hemosinus) (Fig. 42-34b), injury to the infraorbital neurovascular bundle from deep flap dissection, or blunt trauma caused by the compression of the flap during retraction.

Outcomes

A wide variety of outcomes may be considered when assessing the short- and long-term success of MSFA. These may be categorized into clinical (e.g. wound healing patterns, incidence and type of surgical and prosthetic complications, implant survival and success), radiographic (e.g. linear or volumetric graft dimensional changes, marginal bone loss around implants), histologic/histomorphometric (e.g. structural features and proportion of different tissue compartments, cellularity and vascularity), molecular (e.g. expression of proteins of interest), and patient-reported outcome measures (e.g. perceived postoperative discomfort and quality of life). Nevertheless, MSFA is essentially an implant site development procedure. Hence, it can be argued that implant survival and success are the most relevant outcomes. Although the literature offers abundant information regarding implant survival after MSFA with a lateral window approach, there is limited data on implant success rates. Hence, this section will be focused on reviewing relevant information pertaining to implant survival in the context of MSFA via a lateral window approach from a historical perspective.

The findings from the 1996 Sinus Consensus Conference of the Academy of Osseointegration, which were based on retrospective data collection from 38 clinicians that collectively performed 1007 MSFA and placed 2997 implants over a 10-year period, revealed an overall survival rate of 90.0%. The majority of implants had been followed for at least 3 years. Of the 900 patient records that were screened, only 100 had radiographs of adequate quality for analysis of the effect of RBH on implant survival outcomes. In total, only 145 sinus grafts in 100 patients with 349 implants were analyzed. After a mean follow-up period of 3.2 years, 20 out of 349 implants were lost. Of the implants lost, 13 were placed in residual bone with a height of 4 mm and seven in residual bone with a height of 5–8 mm. None of the implants placed in sites presenting an RBH of >8 mm were lost. There was a statistically significant difference in implant loss when RBH was ≤4 mm as compared to ≥5 mm. However, data were so variable that no conclusions regarding the effect of bone grafting material, characteristics of the implants, and timing of implant placement could be drawn (Jensen *et al*. 1998).

As aforementioned, timing of implant placement (i.e. delayed or simultaneous with MSFA) is primarily dictated by the baseline RBH. Peleg and collaborators conducted a study to evaluate the survival rate after performing a one-stage sinus floor augmentation in sites presenting between 3 and 5 mm of RBH. Using the modified Caldwell–Luc technique, the maxillary sinus was elevated with composite grafts of symphyseal autograft and DFDBA in a 1:1 ratio. One hundred and sixty implants were placed in 63 elevated sinuses. A 100% survival rate of the implants was reported after 4 years (Peleg *et al*. 1999). In a follow-up study involving the placement of 2132 implants simultaneously with lateral MSFA in 731 patients presenting 1–5 mm of RBH, the same group reported an implant survival rate of 97.9% after 9 years of function (Peleg *et al*. 2006b).

In 2003, Stephen S. Wallace and Stuart J. Froum published a seminal systematic review on the survival rate of implants placed in areas that received MSFA (Wallace & Froum 2003). Clinical studies

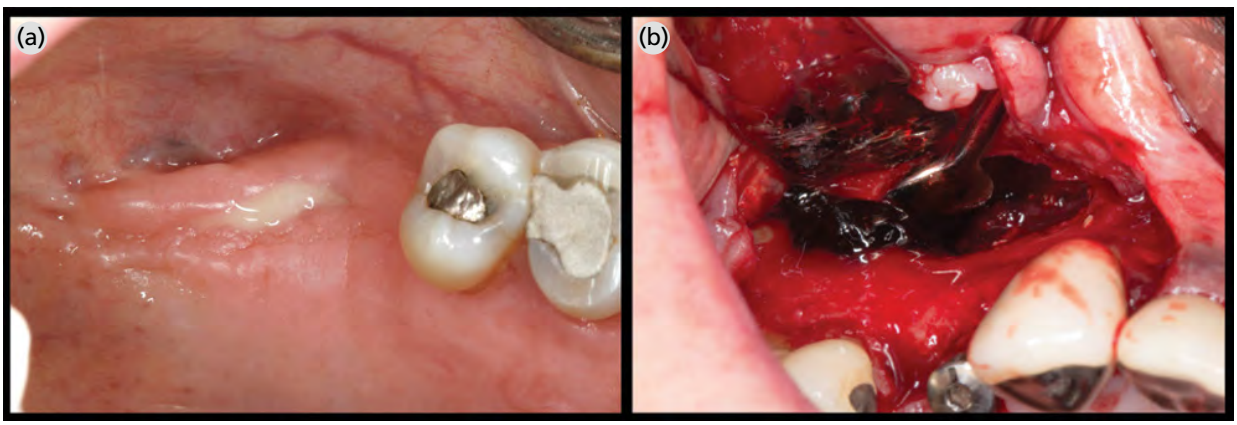

Fig. 42-34 (a) Premature wound dehiscence and acute infection. (b) Antral hematoma.

reporting a minimum of 20 MSFA interventions with a follow-up time of at least 1 year after functional loading were included. A total of 43 studies were selected, including three randomized controlled trials, five non-randomized controlled trials, 12 case series and 23 retrospective analyses. Thirty-four of the studies involved the performance of MSFA via a lateral window approach. The main findings were:

- Survival rate of implants placed in conjunction with MSFA via lateral window varied widely (61.7–100%), with an average of 91.8%.
- Survival rates of implants placed in sites that underwent MSFA compared favorably to those reported for implants placed in maxillary pristine bone that did not receive any bone grafting.
- Rough surface (textured) implants yielded higher survival rates than machined surface implants placed in conjunction with MSFA (91.6% vs. 84.0%, respectively).
- Implants placed into sinuses augmented with particulate autografts showed higher survival rates than those placed in sinuses that had been augmented with autogenous block grafts (92.3% vs. 83.3%, respectively).
- Implant survival rates were higher when barrier membranes were placed over the lateral window (93.6% vs. 88.7%, respectively).
- The utilization of grafts consisting of 100% autogenous bone or the inclusion of autogenous bone as a component of composite grafts did not affect implant survival.

Another systematic review published 5 years later included 48 prospective and retrospective studies reporting on 12 020 implants inserted in combination with MSFA using the lateral window approach (Pjetursson *et al*. 2008). Meta-analysis of data reported in the included studies indicated an estimated annual implant failure rate of 3.48%, translating into a 3-year implant survival rate of 90.1% (95% CI 86.4–92.8%). However, when data were analyzed at the subject level, the estimated annual implant failure rate was 6.04%, which translates to 16.6% of the subjects experiencing at least one implant loss over a period of 3 years. One of the main conclusions of the meta-analysis was that the implant surface significantly affected the outcome of the treatment. The annual failure rate of machined surface implants was 6.86%, which contrasts with the annual failure rate of 1.20% for rough surface implants. The overall 3-year survival rate for rough surface implants was 96.4% (95% CI 94.6–97.7%). The effect that delayed or simultaneous implant placement had on the survival rate was also assessed. Data from a total of 24 studies reporting the placement of 5672 simultaneous implants and 24 studies that involved the placement of 3560 delayed implants after MSFA was analyzed. The annual failure rates for the two methods were similar: 4.07% for the simultaneous approach and 3.19% for the delayed approach.

A recent systematic review including 11 prospective studies that reported the placement of 1517 implants with a minimum follow-up of 5 years after functional loading in 383 patients who underwent a total of 615 MSFA with a lateral window approach, reported an estimated annual implant loss of 0.43% (95% CI: 0.37–0.49) representing a 5-year implant survival rate of 97.8% (Raghoebar *et al*. 2019). Quantitative analyses showed no significant differences in terms of implant survival between edentulous or dentate patients and implants placed simultaneously or in a delayed approach. Likewise, the type of bone grafting material, whether it was autogenous, a substitute, or a combination, did not influence the survival rates. On the basis of contemporary evidence, it can be concluded that MSFA via a lateral window approach is a reliable procedure to facilitate the management of the partially and fully edentulous maxilla with implant-supported prostheses, and it is associated with high implant survival rates (Jepsen *et al*. 2019).

Maxillary sinus floor augmentation: transalveolar approach

Many of the principles and concepts already presented and discussed in regard to MSFA with a lateral window approach pertain to transalveolar MSFA. Hence, subsequent sections of this chapter will expand on distinctive aspects that specifically replace transalveolar MSFA.

Indications and contraindications

Transalveolar MSFA is indicated for the prosthetic rehabilitation of edentulous spaces in the posterior maxilla presenting >5 mm of RBH, a flat sinus floor, and adequate crestal bone width for simultaneous implant installation. Placement of short implants may be an alternative to transalveolar MSFA in some cases. Transalveolar MSFA is compatible with either single or multiple implant placement, although single implant placement is most commonly indicated. General contraindications for this technique are similar to those previously described for the lateral window approach. In addition, patients with a history of inner ear alterations and positional vertigo are not good candidates for a transalveolar MSFA involving the use of a mallet. In these patients, other alternatives should be explored. Regarding local contraindications, the presence of robust septa, a steep sinus floor (>45° inclination), and sites of close proximity between the lateral and the medial sinus walls may not be suitable for transalveolar MSFA, particularly when using osteotomes. In these situations, there is a high risk of perforating the sinus membrane.

Surgical technique

As previously acknowledged, several modifications of the original technique described by Summers have

been proposed since 1994. The following describes a contemporary surgical protocol to perform transalveolar MSFA, based on a previous publication (Pjetursson & Lang 2014):

1. A presurgical rinse with an aqueous solution containing chlorhexidine (0.12% or 0.2%) is performed for a period of 1 minute.
2. Perioral cutaneous surfaces may be disinfected (e.g. wiping with iodine solution, unless contraindicated because of allergy).
3. Local infiltrative anesthesia is delivered on the buccal and palatal mucosa adjacent to the surgical site. Different from the recommendations for MSFA with a lateral window approach, blocking the infraorbital, greater palatine, and posterior superior alveolar nerve is usually not required.
4. Either an open flap or a flapless approach can be followed. For an open flap approach, a minimally invasive mid-crestal incision, or slightly palatal incision if the amount of keratinized mucosa is limited, is made and a mucoperiosteal flap is raised (Fig. 42-34a). For a flapless approach, which should be only indicated in sites presenting sufficient keratinized mucosa, a circular scalpel (punch) of a diameter slightly larger than that of the planned implant is utilized to outline the overlying mucosa, which is subsequently excised using a small periosteal elevator.
5. Once the bone has been exposed, the implant positions are marked on the alveolar crest with a small round bur or a similar instrument (Fig. 42-35a). The use of a surgical stent based on the prosthetic plan is recommended.
6. After precisely marking the implant position(s), the implant osteotomy is prepared with drills of increasing size up to a diameter about 1–1.5 mm smaller than that of the planned implant and staying approximately 2 mm coronal to the maxillary sinus floor (i.e. estimated RBH minus 2 mm), to avoid perforating the Schneiderian membrane.
7. After radiographically confirming the distance to the sinus floor, an osteotome with the same or slightly wider diameter of the last drill utilized is inserted in the osteotomy towards the bony wall that separates the osteotomy space and the sinus floor (Fig. 42-35b). After manual resistance is encountered, the osteotome is progressively advanced in a vertical direction with light malleting in order to create a "greenstick" fracture on the bone and slightly push the Schneiderian membrane apically (Fig. 42-35c). An osteotome with a tapered tip may be used to minimize the force needed to fracture the compact bone (Fig. 42-36).

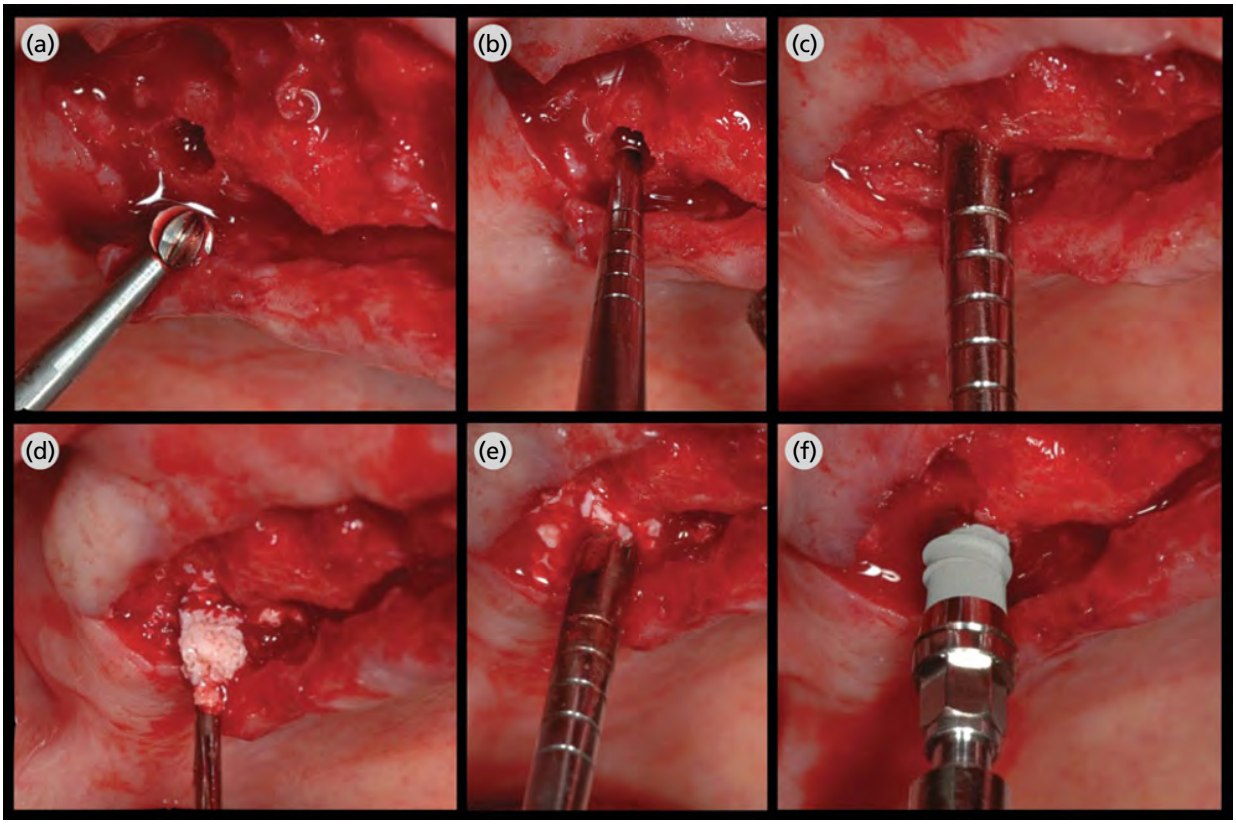

Fig. 42-35 Sequence showing the essential steps of a transalveolar MSFA procedure with simultaneous implant placement. (a) Upon elevation of a full-thickness flap, a round bur is used to mark the osteotomy site and facilitate the insertion of the first osteotome. (b) First osteotome is progressively inserted with gentle malleting to create a greenstick fracture of the sinus floor. (c) An osteotome of wider diameter is inserted to expand the osteotomy. (d) Bovine xenograft particles are placed into the site after the osteotomy is created. (e) The final osteotome is used to carefully push the bone grafting material in the subantral space. (f) The implant is inserted once the grafting procedure is completed.

Fig. 42-36 Osteotome tips of different design. From left to right: tapered rounded, tapered concave, and parallel flat.

Instead of using osteotomes to fracture the sinus floor, piezoelectric tips can be employed. The main advantage of the piezosurgery tips is that the risk of membrane perforation is reduced (Sohn *et al*. 2009). This could also reduce the risk of benign paroxysmal positional vertigo as a direct consequence from the malleting. A potential disadvantage, however, is that it is more time consuming than malleting, especially when the cortical bone at the sinus floor is thick and dense. Another emerging, although not fully validated, alternative to elevate the Schneiderian membrane through a transalveolar canal is the use of a balloon device (Asmael 2018).

From this point onwards, the subsequent steps are determined by whether the transalveolar MSFA procedure is completed by using a bone grafting material or not.

Implant placement without bone grafting material

1. An osteotome with a diameter about 0.5–1 mm narrower than that of the planned implant is progressively advanced into the sinus cavity by gentle malleting until it penetrates the sinus floor up to the desired length respective to the crestal bone. Extreme care should be taken to avoid increasing the diameter of the osteotomy excessively, which may compromise primary stability, or advancing the osteotome too deep, which may result in the perforation of the sinus membrane. Hence, the tip of the last osteotome to be used must have a shape and diameter that are suitable for the implant to be placed. For example, for a cylindrical implant with a diameter of 4.1 mm, the last osteotome should be a straight osteotome with a diameter that does not exceed 3.5 mm. It is also important that the last osteotome only enters the preparation site once. If several attempts have to be made in sites presenting soft bone, there is a high risk of increasing the diameter of the bone preparation, which, again, may jeopardize achieving primary stability. On the contrary, if the diameter of the last osteotome is too small compared with the implant diameter, too much force would be required to insert the implant, creating more trauma, which may be detrimental for successful osseointegration (Abrahamsson *et al*. 2004; Wang *et al*. 2017).
2. The final step before placing the implant is to check that the preparation is patent to the planned insertion depth. A narrower osteotome with a rounded tip or a depth gauge may be pushed to a depth that is congruent with the implant dimensions.

Implant placement with bone grafting materials

1. When performing transalveolar MSFA using bone grafting materials (Fig. 42-35d), the osteotomes are not supposed to enter the sinus cavity *per se*. As the bone graft is gently pushed vertically using an osteotome, the trapped fluid creates a hydraulic pressure effect that displaces both the fractured sinus floor and the Schneiderian membrane upwards (Fig. 42-35e). Prior to inserting the bone grafting material, it is very important to evaluate whether a perforation of the Schneiderian membrane occurred. This may be done by direct visualization using high magnification equipment and/or with the Valsalva maneuver (Farina *et al*. 2018). This maneuver is done by blocking the nostrils and asking the patient to blow air through the nose while looking at the implant osteotomy. If air leaks out, the sinus membrane is likely perforated, and no particulate grafting material should be placed or an attempt should be made to seal the perforation with a barrier material (e.g. collagen sponge or membrane), which may be technically challenging. However, it is important to keep in mind that the Valsalva maneuver may render a high number of false negatives, depending on the location and extent of the perforation. Hence, the validity of this assessment should be taken with caution when making clinical decisions.
2. As aforementioned in the graftless approach, the preparation should be checked for patency before implant placement (Fig. 42-35f).

If the procedure involved flap elevation, tension-free primary closure is necessary. Whether an open flap or a flapless approach was followed, if implant

primary stability is adequate, healing abutments may be delivered according to a non-submerged implant placement protocol.

Grafting material selection

As previously discussed in the section addressing the lateral window approach, the need to use bone grafting materials for adequate bone formation and implant survival is a controversial topic that has also been extensively debated in the context of transalveolar MSFA.

In the original publication describing the transalveolar approach, placement of harvested autogenous bone into the subantral space created after displacing the Schneiderian membrane was recommended to maintain the volume of the elevated area (Tatum 1986). Several years later, Summers introduced the BAOSFE technique, which was not restrictive regarding the type of bone grafting material to be employed (Summers 1994). Subsequently, a multicenter retrospective study involving nine clinicians, including Robert B. Summers, was carried out to determine the outcomes of the BAOSFE technique in function of the use of different bone grafting materials. A total of 174 implants placed in 101 patients was evaluated. Autogenous bone, allografts, and xenografts were employed as sole grafting materials or in different combinations. The authors concluded that the type of grafting material did not influence implant survival up to 66 months (Rosen *et al*. 1999).

In another retrospective study, sinus floor remodeling after implant insertion using a modified transalveolar technique without the use of a bone grafting material was assessed radiographically (Schmidlin *et al*. 2008). A total of 24 patients was included. Implant survival rate was 100% after a mean follow-up period of approximately 18 months. Bone fill around the apex of the implants in radiographs obtained at different time points was compared with baseline assessments. The reported mean bone height gain was 2.2 mm on the mesial and 2.5 mm on the distal. A later prospective clinical study reported the outcomes of 25 dental implants with a length of 10 mm placed using transalveolar MSFA without bone grafting material. The implants were protruded into the sinus cavity an average of 4.9 mm. After a 5-year follow-up, the implant protrusion was reduced to 1.5 mm. Hence, the authors reported that an average of 3.4 mm of the penetrating part of the implants was surrounded by new bone, which represented approximately 70% of bone gain from the time of implant placement (Nedir *et al*. 2010). Although these studies provide radiographic evidence of new bone formation in absence of a bone grafting material after transalveolar MSFA, the results must be taken with caution because of the relatively low sample size, short follow-up time and lack of standardization of the radiographic measurements.

The patterns of radiographic bone remodeling after placement of 25 implants in 19 patients using a transalveolar MSFA approach with a composite graft (i.e. mix of bovine xenograft particles and autogenous bone) were evaluated in another study. Periapical radiographs were obtained pre- and postsurgically at 3 and 12 months. The mean height of the bone contour apical and mesial to the implant body was 1.52 mm at the time of surgery, but this was significantly reduced to 1.24 mm at 3 months and 0.29 mm after 12 months. It was concluded that the grafted area apical to the implants underwent shrinkage and remodeling, and the original outline of the sinus was eventually consolidated and replaced by a new cortical plate (Bragger *et al*. 2004).

In a prospective comparative study, 252 implants were inserted using a transalveolar MSFA technique with or without grafting material (Pjetursson *et al*. 2009a). Bovine xenograft particles were used as the sole bone grafting material in the placement of 88 implants, whereas the remaining 164 implants were inserted in absence of a grafting material. Mean radiographic bone gain at 1 year measured in periapical radiographs was 4.1 ± 2.4 mm in the sites that received a bone grafting material, whereas the observed gain was 1.7 ± 2.0 mm in sites that did not receive bone grafting.

A recent systematic review aimed at analyzing the survival rate of implants placed using transalveolar MSFA with and without bone grafting (Shi *et al*. 2016). Thirty-four studies met the inclusion criteria. These studies reported the outcomes of a total of 3119 implants placed in 1977 patients. Most of the reported implant failures (84 of 102) occurred within 12 months of functional loading. Cumulative survival rates were higher in the sites that did not receive a bone grafting material (97.30% vs. 95.89%; $P = 0.05$). Although this comparison reached statistical significance, its clinical significance is questionable, particularly considering the relatively short follow-up period.

Postoperative care

Standards of postsurgical care after transalveolar MSFA with simultaneous implant insertion are similar to those after standard implant placement. Additionally, as aforementioned, patients should be instructed to avoid mechanical disturbance of the surgical area, especially if implants are placed in a non-submerged fashion. The use of antiseptic rinses (e.g. chlorhexidine 0.12 or 0.2%) twice daily may be indicated until suture removal for plaque control purposes. As with MSFA via a lateral window approach, minor nasal bleeding may occur within the first week. It is important to inform patients in advance. If the patient needs to sneeze, the nostrils should not be blocked so that air pressure can be adequately relieved, preventing early wound stability disturbance. Although there have been no studies comparing the outcomes associated with and without the intake of antibiotics after transalveolar MSFA, antibiotic prophylaxis for 10 days has been recommended by some authors (Wang *et al*. 2019).

Complications

As with the lateral window approach, the most common intraoperative complication in transalveolar MSFA is perforation of the Schneiderian membrane. The inevitable "blind" use of osteotomes and insertion of the bone grafting material increases the possibility of inadvertent sinus membrane perforation when performing these techniques. A systematic review aimed at assessing the outcomes of implants placed in sites that underwent transalveolar MSFA reported that the rate of perforation of the Schneiderian membrane varied between 0% and 21.4%, with a mean occurrence of 3.8%, out of a subsample of 1621 implants from eight of the 19 studies that met the eligibility criteria of this review (Tan *et al*. 2008). Small perforations (<1 mm) may be sealed through the transalveolar preparation using tissue fibrin glue or a collagen sponge. If a large perforation is identified before a particulate bone grafting material is inserted, aside from aborting the surgical procedure, clinicians may opt for: (1) using a bone grafting material with different properties (e.g. collagenated xenograft), (2) proceeding with no bone grafting material (graftless approach), and/or (3) the placement of a shorter implant.

Postoperative infections after transalveolar MSFA are rare, ranging from 0% to 2.5%, with a mean rate of 0.8% (Tan *et al*. 2008). Other possible complications may include abnormal postoperative hemorrhage, nasal bleeding, nasal obstruction, hematoma, and benign paroxysmal positional vertigo. Vertigo episodes are usually associated with aggressive malleting and may cause substantial stress to patients if not correctly identified and properly managed (Vernamonte *et al*. 2011).

Outcomes

As already stated regarding MSFA via a lateral window approach, a plethora of outcomes (i.e. clinical, radiographic, histologic/histomorphometric, molecular, and patient-reported) may also be assessed in the context of transalveolar MSFA. However, being a procedure primarily indicated for implant site development, the most relevant, and also most commonly reported, clinical outcome following transalveolar MSFA is implant survival (Fig. 42-37).

In the aforementioned multicenter retrospective study conducted by Paul S. Rosen and collaborators to evaluate the BAOSFE technique, implant survival rate up to 66 months was 96% if baseline RBH was at least 5 mm, but it dropped to 85.7% if RBH was ≤4 mm (Rosen *et al*. 1999). Similar results were reported in a prospective study in which 20% of the implants were placed in sites with a RBH of <5 mm, which tested the limits of the transalveolar MSFA technique (Pjetursson *et al*. 2009b). The survival rates were 91.3% for implants placed in sites with a baseline RBH ≤4 mm and 90% for implants placed in sites that exhibited a baseline RBH between 4 and 5 mm, which strongly contrasts with the 100% survival rate

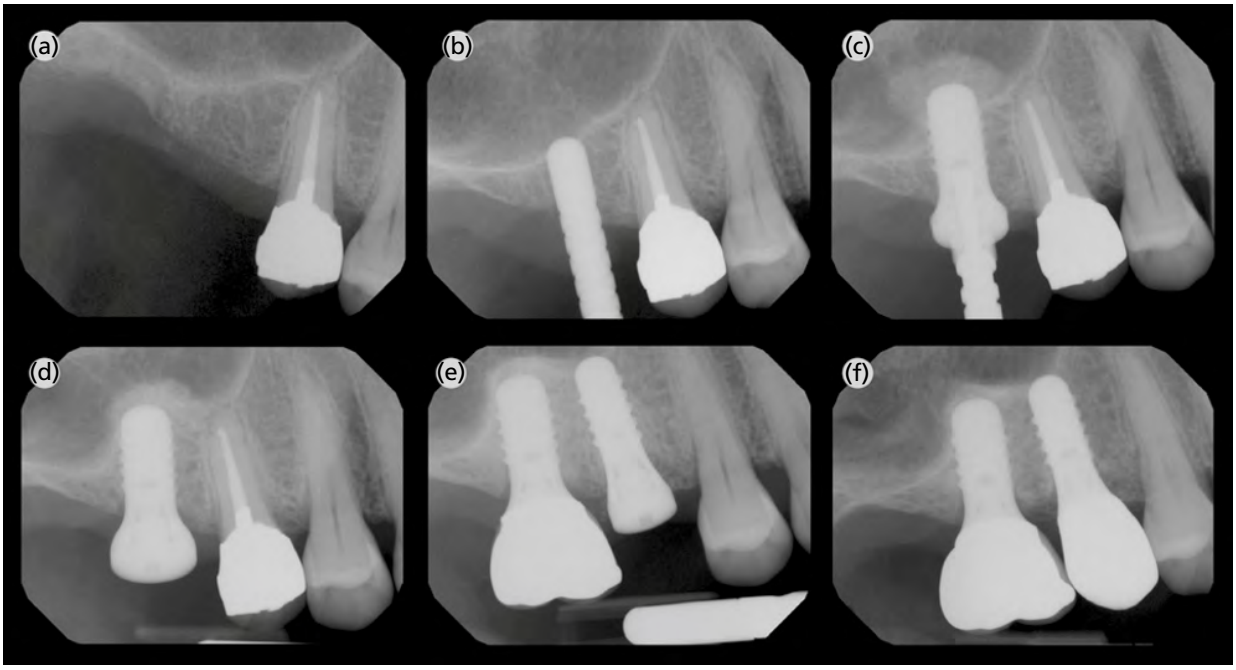

Fig. 42-37 Sequence showing the radiographic outcomes of transalveolar MSFA with simultaneous implant placement to replace a maxillary right first molar. (a) Baseline periapical radiograph. (b) Control radiograph using a radiographic pin after creating a greenstick fracture of the maxillary sinus floor with the final osteotome. (c) Radiograph obtained after grafting the sinus floor with bovine xenograft particles and inserting the implant. (d) Radiograph obtained 4 months later prior to sending the patient to the restorative clinician. (e) Four years after placement of the first implant, an implant was placed to replace the second premolar, which was extracted because of a vertical root fracture. (f) Radiograph obtained at 6 years after placement of the first implant in the molar position. Note the increased radiopacity and consolidation of the grafted area and the stable marginal bone levels around both implants.

of implants placed in sites that exhibited a baseline RBH >5 mm. Moreover, the survival rate of 6-mm implants was only 48%. This clearly demonstrates that the transalveolar MSFA technique was most predictable when placing implants with a length ≥8 mm in sites that presented a baseline RBH ≥5 mm, which is also supported by the findings of other studies, as discussed by Del Fabbro and collaborators in their systematic review on this topic (Del Fabbro *et al*. 2012)

Another systematic review primarily aimed at analyzing the survival rates of implants inserted in combination with transalveolar MSFA included a total of 19 studies reporting on 4338 implants (Tan *et al*. 2008). Meta-analyses of the data extracted from these studies revealed an estimated annual failure rate of 2.48%, which translated to an estimated 3-year survival rate of 92.8% (95% CI 87.4–96.0%). Furthermore, subject-level analyses revealed an annual failure of 3.71%, which translated to at least one implant loss in 10.5% of the subjects over a period of 3 years.

Patient-centered outcome measures (PROMs) have emerged in recent years as a relevant component of clinical research. A previously mentioned prospective comparative study (Pjetursson *et al*. 2009b), represents one of the earliest examples in the field of MSFA research in which PROMs were assessed. Of the 163 patients enrolled in this study, 23% found the surgical experience unpleasant. When asked about other postsurgical complications, 5% of the patients felt their head was tilted too far back during the surgery, and 5% experienced vertigo, nausea, and felt disoriented after the surgical procedure. Nonetheless, 90% of the patients expressed that they would be willing to undergo this treatment again, if necessary.

Summary

Multiple therapeutic options for the rehabilitation of completely or partially edentulous patients presenting posterior tooth loss are available. Maxillary sinus floor augmentation (MSFA) is an implant site development procedure that allows for the simultaneous or delayed insertion of standard-length implants in posterior edentulous segments presenting limited residual bone height (RBH). Different modalities of MSFA have been described in the literature. The most commonly indicated modalities are MSFA with a transcrestal or a lateral window approach. Each modality has different indications, primarily depending on the amount of RBH, horizontal ridge width, and the possibility of achieving implant primary stability, but both have been generally associated with high long-term implant survival rates regardless of the bone grafting material utilized (Jepsen *et al*. 2019). Besides the significance of MSFA as an effective implant site development procedure, it also represents an excellent research model for the study of the healing dynamics associated with different grafting materials or regenerative strategies for the treatment of craniofacial defects (Avila-Ortiz & Galindo-Moreno 2014).

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Part 16: Occlusal and Prosthetic Therapy

Chapter 43

Tooth-Supported Fixed Dental Prostheses

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Clinical symptoms of trauma from occlusion

Angular bony defects

It has been claimed that *angular bony defects* and *increased tooth mobility* are important symptoms of trauma from occlusion (Glickman 1965, 1967). The validity of this suggestion has, however, been questioned (see Chapter 13). Thus, angular bony defects have been found at teeth affected by *trauma from occlusion* as well as at teeth with normal occlusal function (Waerhaug 1979). This means that the presence of angular bony defects *cannot per se* be regarded as an exclusive symptom of trauma from occlusion.

Increased tooth mobility

Increased tooth mobility, determined clinically, is expressed in terms of amplitude of displacement of the crown of the tooth. Increased tooth mobility can, indeed, be observed in conjunction with *trauma from occlusion*. It may, however, also be the result of a reduction of the height of the alveolar bone with or without an accompanying angular bony defect caused by plaque-associated periodontal disease (see Chapter 13). Increased tooth mobility resulting from occlusal interferences may further indicate that the periodontal structures have adapted to an altered functional demand, that is a widened periodontal ligament with a normal tissue composition has become the end result of a previous phase of progressive tooth mobility (see Chapter 13) associated with trauma from occlusion.

Progressive (increasing) tooth mobility

In Chapter 13, it was concluded that the diagnosis of trauma from occlusion should be used solely in situations where a progressive mobility could be observed. Progressive tooth mobility can be identified only through a series of repeated tooth mobility measurements carried out over a period of several days or weeks.

Clinical assessment of tooth mobility (physiologic and pathologic tooth mobility)

If, in the traditional clinical measurement of tooth mobility, a comparatively large force is exerted on the crown of a tooth which is surrounded by a normal

*Deceased.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

periodontium, the tooth will tip within its alveolus until a closer contact has been established between the root and the marginal (or apical) bone tissue. The magnitude of this tipping movement, which is normally assessed using the tip of the crown as a reference point, is referred to as the "*physiologic*" tooth mobility. The term "*physiologic*" implies that "*pathologic*" tooth mobility may also occur. What, then, is "pathologic" tooth mobility?

1. If a similar force is applied to a tooth which is surrounded by a periodontal ligament with an increased width, the excursion of the crown in the horizontal direction will increase; the clinical measurement consequently demonstrates that the tooth has an increased mobility. Should this increased mobility be regarded as "pathologic"?
2. An increased tooth mobility, that is an increased displacement of the crown of the tooth after force application, can also be found in situations where the height of the alveolar bone has been reduced, but the remaining periodontal ligament has a normal width. At sites where this type of bone loss is extensive, the degree of tooth mobility (i.e. excursion of the crown) may be pronounced. Should this increased tooth mobility be regarded as "pathologic"?

   Figure 43-1b shows a tooth which is surrounded by alveolar bone of reduced height. The width of the remaining periodontal ligament, however, is within normal limits. A horizontally directed force applied to the crown of the tooth in this case will result in a larger excursion of the crown than if a similar force is applied to a tooth with normal height of the alveolar bone and normal width of the periodontal ligament (Fig. 43-4a). There are reasons to suggest that the so-called *increased mobility* measured in the case shown in Fig. 43-1b is, indeed, *physiologic*. The validity of this statement can easily be demonstrated if the displacement of the two teeth is assessed not from the crown, but from a point on the root at the level of the bone crest. If a horizontal force is directed to the teeth in Fig. 43-1, the reference points (*) on the root surfaces will be displaced a similar distance in both instances. Obviously, it is not the length of the excursive movement of the crown that is important from a biologic point of view, but the *displacement of the root* within its remaining periodontal ligament.

   In plaque-associated periodontal disease, bone loss is a prominent feature. Another so-called classical symptom of periodontitis is "increased tooth mobility". It is important to realize, however, that in many situations with even or "horizontal" bone loss patterns, the increased crown displacement (tooth mobility) assessed by clinical measurements should, according to the above discussion, also be regarded as physiologic; the movement of the root within the space of its remaining "normal" periodontal ligament is normal.
3. Increased crown displacement (tooth mobility) may also be detected by clinical measurement where a "horizontal" force is applied to teeth with angular bony defects and/or increased width of the periodontal ligament. If this mobility does not increase gradually – from one observation interval to the next – the root is surrounded by a periodontal ligament of increased width but normal composition. This mobility should also be considered *physiologic* since the movement is a function of the height of the alveolar bone and the width of the periodontal ligament.
4. Only *progressively increasing tooth mobility*, which may occur in conjunction with trauma from occlusion, is characterized by active bone resorption (see Chapter 13), and which indicates the presence of inflammatory alterations within the periodontal ligament tissue, may be considered *pathologic*.

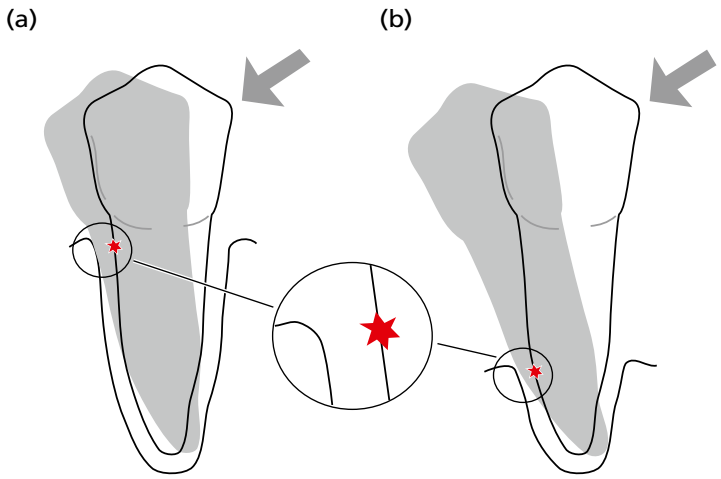

Fig. 43-1 (a) Normal "physiologic" mobility of a tooth with normal height of the alveolar bone and normal width of the periodontal ligament. (b) Mobility of a tooth with reduced height of the alveolar bone. The distance of the horizontal displacement of the reference point (*) on the roots is the same in the two situations (a, b).

Treatment of increased tooth mobility

A number of situations will be described which may call for treatment aimed at reducing an increased tooth mobility.

Situation 1

Increased mobility of a tooth with increased width of the periodontal ligament but normal height of the alveolar bone

If a tooth (e.g. a maxillary premolar) is fitted with an improper filling or crown restoration, occlusal interferences develop and the surrounding periodontal tissues become the seat of inflammatory reactions, that is trauma from occlusion (Fig. 43-2). If the restoration is designed such that the crown of the tooth in occlusion is subjected to undue forces directed in a buccal direction, bone resorption phenomena develop in the buccomarginal and linguoapical pressure zones with a resulting increase of the width of the periodontal ligament in these zones. The tooth becomes hypermobile or moves away from the "traumatizing" position. Since such traumatizing forces in teeth with normal periodontium or overt gingivitis cannot result in pocket formation or loss of connective tissue attachment, the resulting increased mobility of the tooth should be regarded as a physiologic adaptation of the periodontal tissues to the altered functional demands. A proper correction of the anatomy of the occlusal surface of such a tooth, that is occlusal adjustment, will normalize the relationship between the antagonizing teeth in occlusion, thereby eliminating the excessive forces. As a result, apposition of bone will occur in the zones previously exposed to resorption, the width of the periodontal ligament will become normalized, and the tooth stabilized, that is it reassumes its normal mobility (Fig. 43-2). In other words, resorption of alveolar bone which is caused by trauma from occlusion is a reversible process which can be treated by the elimination of occlusal interferences.

The capacity for bone regeneration after resorption following trauma from occlusion has been documented in a number of animal experiments (Waerhaug & Randers-Hansen 1966; Polson *et al*. 1976a; Karring *et al*. 1982; Nyman *et al*. 1982). In such experiments, the induced bone resorption not only involved the bone within the alveolus but also the alveolar bone crest. When the traumatizing forces were removed, bone tissue was deposited not only on the walls of the alveolus, thereby normalizing the width of the periodontal ligament, but also on the bone crest area, whereby the height of the alveolar bone was normalized (Fig. 43-3) (Polson *et al*. 1976a). In the presence of an untreated, plaque-associated lesion in the soft tissue, however, substantial bone regrowth did not always occur (Fig. 43-4) (Polson *et al*. 1976b).

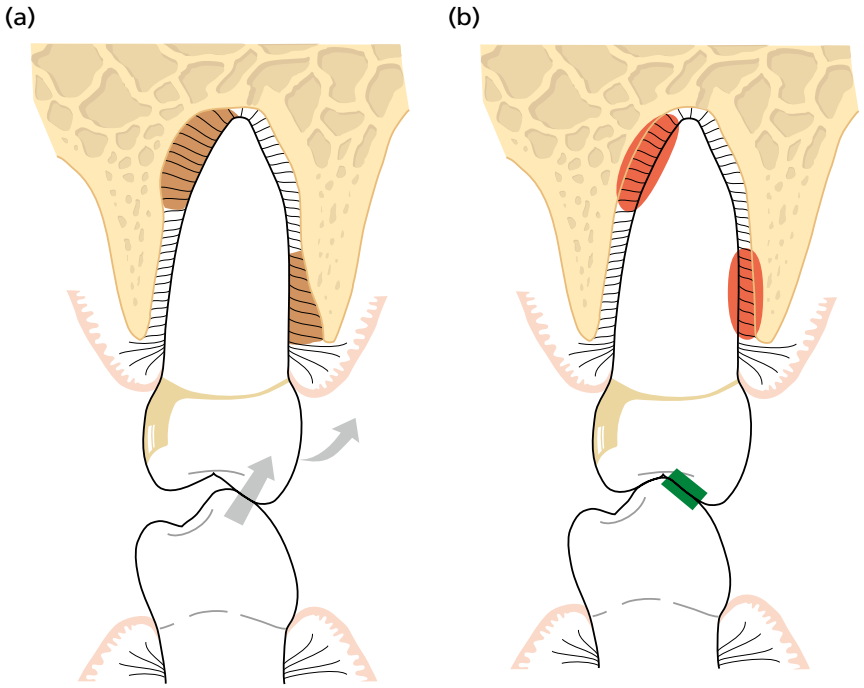

Fig. 43-2 (a) Contact relationship between a mandibular and a maxillary premolar in occlusion. The maxillary premolar is fitted with an artificial restoration with an improperly designed occlusal surface. Occlusion results in horizontally directed forces (arrows) which may produce an undue stress concentration within the "brown" areas of the periodontium of the maxillary tooth. Resorption of the alveolar bone occurs in these areas. A widening of the periodontal ligament can be detected as well as increased mobility of the tooth. (b) Following adjustment of the occlusion, the horizontal forces are reduced. This results in bone apposition ("red areas") and a normalization of the tooth mobility.

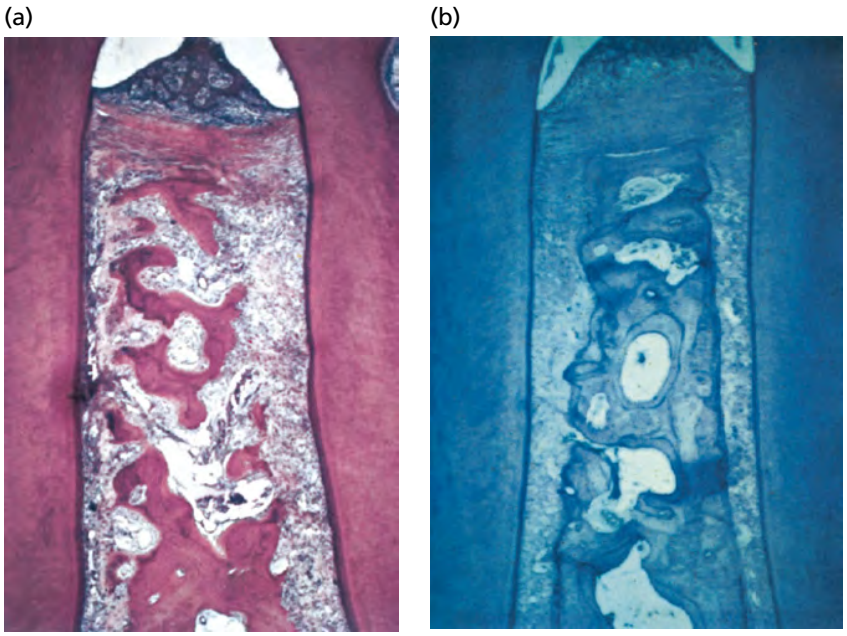

Fig. 43-3 Photomicrographs illustrating the interdental area between two mandibular premolars in the monkey. (a) Two premolars are exposed to jiggling forces. Note the reduction of alveolar bone in the area and the location of the bone crest. Ten weeks after the elimination of the jiggling forces, (b) a considerable regeneration of bone has occurred. Note the increase of the height of the interdental bone and the normalization of the width of the periodontal ligaments. The apical end of the junctional epithelium is located at the cementoenamel junction. (Source: Polson *et al*. 1976a. Reproduced with permission from John Wiley & Sons.)

Situation 2

Increased mobility of a tooth with increased width of the periodontal ligament and reduced height of the alveolar bone

When a dentition has been properly treated for moderate-to-advanced periodontal disease, gingival health is established in areas of the dentition where teeth are surrounded by periodontal structures of reduced height. If a tooth with a reduced periodontal tissue support is exposed to excessive horizontal forces (trauma from occlusion), inflammatory reactions develop in the pressure zones of the periodontal ligament with

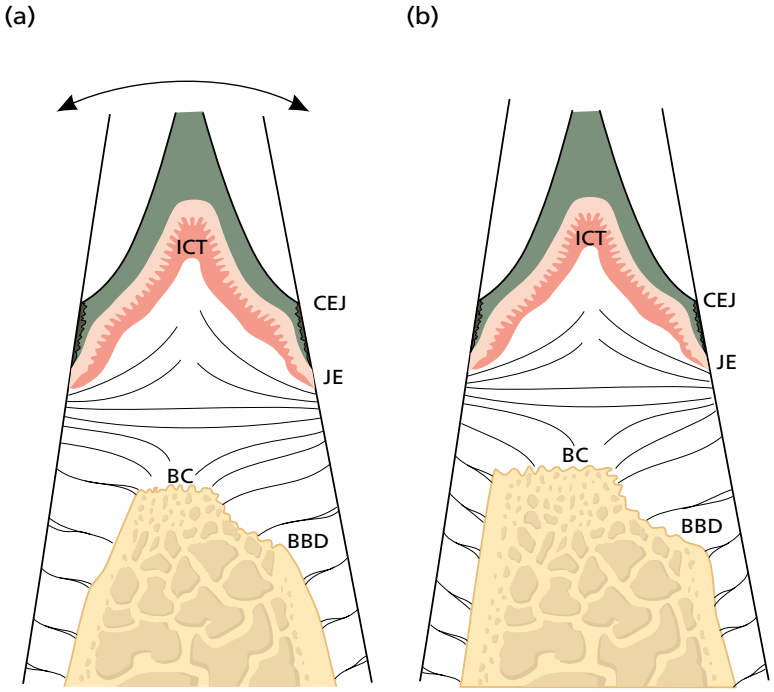

Fig. 43-4 In the presence of an existing marginal inflammation, alveolar bone lost by jiggling trauma (a), will not always regenerate following elimination of the traumatic forces (b). BBD, bottom of angular bony defect; BC, alveolar bone crest; CEJ, cementoenamel junction; ICT, infiltrated connective tissue; JE, apical end of junctional epithelium. (Source: Polson *et al*. 1976b. Reproduced with permission from John Wiley & Sons.)

accompanying bone resorption. These alterations are similar to those which occur around a tooth with supporting structures of a normal height; the alveolar bone is resorbed, the width of the periodontal ligament is increased in the pressure/tension zones, and the tooth becomes hypermobile (Fig. 43-5a). If the excessive forces are reduced or eliminated by occlusal adjustment, bone apposition to the "pre-trauma" level will occur, the periodontal ligament will regain its normal width, and the tooth will become stabilized (Fig. 43-5b).

Conclusion (situations 1 and 2): Occlusal adjustment is an effective therapy against increased tooth mobility when such mobility is caused by an *increased width* of the periodontal ligament.

Situation 3

Increased mobility of a tooth with reduced height of the alveolar bone and normal width of the periodontal ligament

The increased tooth mobility which is the result of a reduction in height of the alveolar bone without a concomitant increase in width of the periodontal membrane cannot be reduced or eliminated by occlusal adjustment. In teeth with normal width of the periodontal ligament, no further bone apposition on the walls of the alveoli can occur. If such an increased tooth mobility does not interfere with the patient's chewing function or comfort, no treatment is required. If the patient experiences the tooth mobility as disturbing, however, the mobility can only be reduced in this situation by splinting, that is by joining the mobile tooth/teeth together with other teeth in the jaw into a fixed unit – a splint.

A splint is "an appliance designed to stabilize mobile teeth" and may be fabricated in the form of joined composite fillings, fixed bridges, removable partial prostheses, etc.

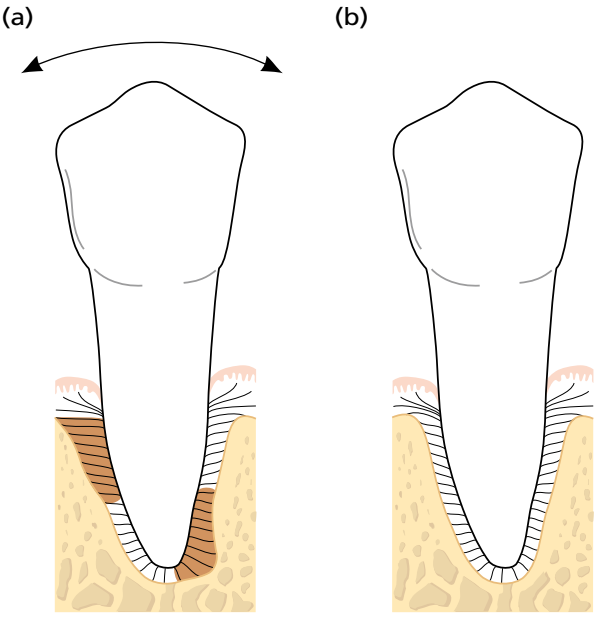

Fig. 43-5 If a tooth with reduced periodontal tissue support (a) has been exposed to excessive horizontal forces, a widened periodontal ligament space ("brown" areas) and increased mobility (arrow) result. (b) Following reduction or elimination of such forces, bone apposition will occur and the tooth will become stabilized.

Example: Case A, 64-year-old male

The periodontal condition of this patient is illustrated by the radiographs from the initial examination (Fig. 43-6). Periodontal disease has progressed to a level where, around the maxillary teeth, only the apical third or less of the roots is invested in supporting alveolar bone. The following discussion relates to the treatment of the maxillary dentition.

In the treatment planning of this case, it was decided that the first premolars (teeth 14 and 24) had to be extracted due to advanced periodontal disease and furcation involvement of degree III. For the same reasons, teeth 17 and 27 were scheduled for extraction. Teeth 16 and 26 were also found to have advanced loss of periodontal tissue support in combination with deep furcation involvements. The most likely *definitive* treatment should include periodontal and adjunctive therapy in the following parts of the dentition: 15 and 25, and 13, 12, 11, 21, 22, 23. For functional and esthetic reasons, teeth 14 and 24 obviously had to be replaced. The question now arose as to whether these two premolars should be replaced by two separate unilateral bridges, using 13, 15 and 23, 25 as abutment teeth, or if the increased mobility of these teeth and also of the anterior teeth (12, 11, 21, 22) (Fig. 43-6) called for a bridge of cross-arch design, with the extension 15–25, to obtain a splinting effect. If teeth 14 and 24 were replaced by two unilateral bridges, each one of these three-unit bridges would exhibit the same degree of mobility in a buccolingual direction as the individual abutment teeth (degree 2) (Fig. 43-6), since a unilateral straight bridge would not have a stabilizing effect on the abutment teeth in this force direction.

From the radiographs it can be seen that the increased mobility observed in the maxillary teeth of this patient is associated mainly with reduced height of the alveolar bone and not with increased width of the periodontal ligaments. This means that the mobility of the individual teeth should be regarded as normal or "physiologic" for teeth with such a reduced height of the supporting tissues. This in turn implies that the increased tooth mobility in the present case does not call for treatment unless it interferes with the chewing comfort or jeopardizes the position of the front teeth. This particular patient had not recognized any functional problems related to the increased mobility of his maxillary teeth. Consequently, there was no reason to install a cross-arch bridge in order to splint the teeth, that is to reduce tooth mobility.

Following proper treatment of the plaque-associated periodontal lesions, two separate

(a)

Periodontal chart

Tooth	Pocket depth M	B	D	L	Furcation involvement	Tooth mobility
~~18~~						
17	6	6	8	8	b2, m2, d1	
16	6	6	8	8	m1, d2	2
15	8	8	6	7		2
14	7	7	7	4	3	2
13	8	4	8	4		2
12	8	4	8	4		2
11	6	4	7	4		1
21	6	4	6	4		1
22	6	5	7			2
23	6		6	4		2
24	7		8		3	2
25	6	8	8	4		2
26	8		6		b2, m2, d2	
27	6	6	10	8	b2, d2	1
~~28~~						
~~48~~						
~~47~~						
46	8	6	6	7	b1, l2	
45	6		7	4		1
44	6		6	4		
43	7	7	6	4		
42	4		4	4		1
41	6	4				1
31	6					1
32	4		6	4		1
33	6		6	6		2
34	4		7	4		
35	7		4	6		2
~~36~~						
37	8	5	6	4	b2, l2	3
~~38~~						

(b)

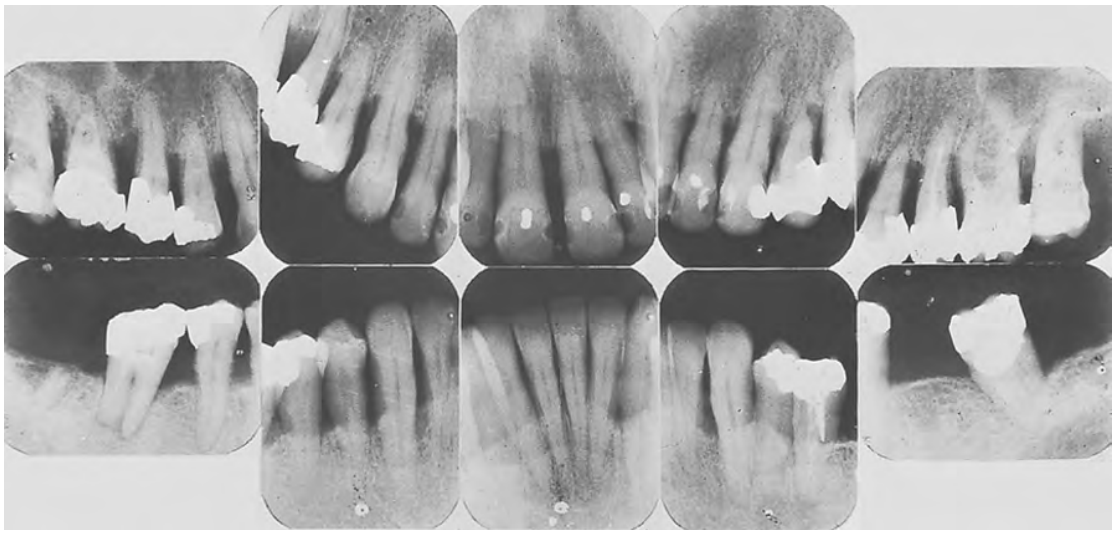

Fig. 43-6 Case A, 64-year-old male. (a) Periodontal chart. (b) Radiographs prior to therapy.

provisional bridges of unilateral design were produced (15, 14, 13; 23, 24, 25, 26 palatal root). The provisional acrylic bridges were used for 6 months during which time the occlusion, the mobility of the two bridges, and the position of the front teeth were all carefully monitored. After 6 months, no change of position of the lateral and central incisors and no increase of the mobility of the two provisional bridges had occurred, and the definitive restorative therapy was performed.

Figure 43-7 shows the radiographs obtained 10 years after initial therapy. The position of the front teeth and the mobility of the incisors and the two bridges had not changed during the course of the maintenance period. There had been no further loss of periodontal tissue support during the 10 years of observation, no further

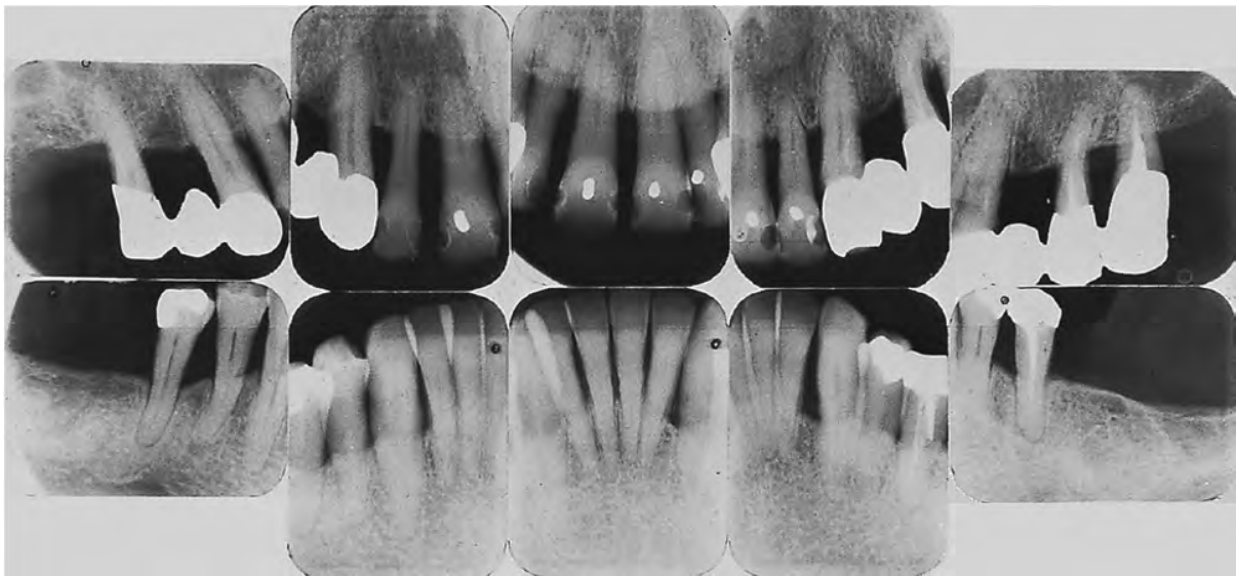

Fig. 43-7 Case A. Radiographs obtained 10 years after periodontal therapy and installation of two unilateral bridges in the maxilla.

spread of the front teeth, and no widening of the periodontal ligaments around the individual teeth, including the abutment teeth for the bridgework.

Conclusion: Increased tooth mobility (or bridge mobility) as a result of reduced height of the alveolar bone can be accepted and splinting avoided, provided the occlusion is stable (no further migration or increasing mobility of individual teeth) and the degree of existing mobility does not disturb the patient's chewing ability or comfort. Consequently, splinting is indicated when the mobility of a tooth or a group of teeth is so increased that chewing ability and/or comfort are disturbed.

Situation 4

Progressive (increasing) mobility of a tooth (teeth) as a result of gradually increasing width of the reduced periodontal ligament

Often in cases of advanced periodontal disease the tissue destruction may have reached a level where extraction of one or several teeth cannot be avoided. In such a dentition, teeth which are still available for periodontal treatment may, after therapy, exhibit such a high degree of mobility, or even signs of progressively increasing mobility, that there is an obvious risk that the forces elicited during function may mechanically disrupt the remaining periodontal ligament components and result in the loss of the teeth.

It will only be possible to maintain such teeth by means of a splint. In such cases, a fixed splint has two objectives: (1) to stabilize hypermobile teeth and (2) to replace missing teeth.

Example: Case B, 26-year-old male

Figure 43-8 shows the radiographs taken prior to therapy and Fig. 43-9 those obtained after periodontal treatment and preparation of the remaining teeth as abutments for two fixed splints. All teeth except 13, 12, and 33 have lost around 75% or more of the alveolar bone and widened periodontal ligaments are a frequent finding. The four distal abutments for the two splints are root-separated molars, the maintained roots being the following: the palatal root of tooth 17, the mesiobuccal root of tooth 26, and the mesial roots of teeth 36 and 47. It should be observed that tooth

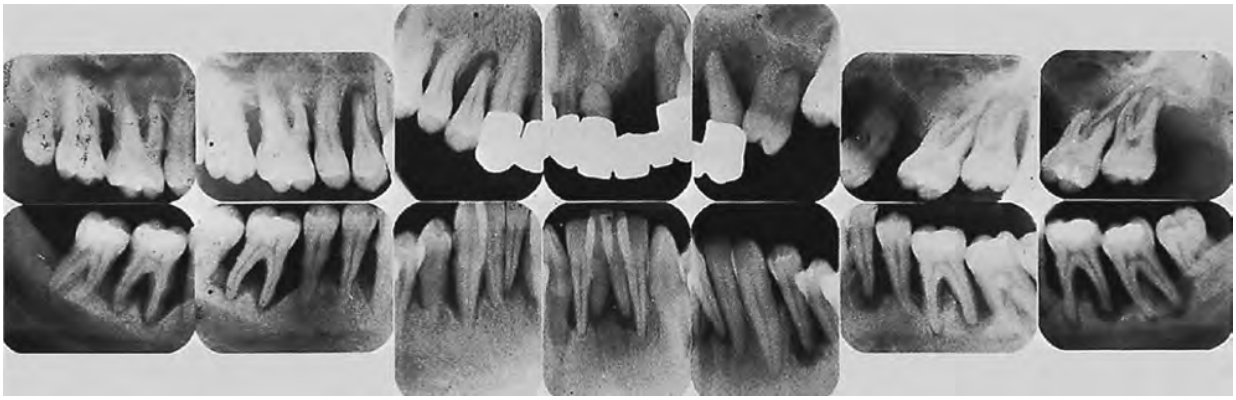

Fig. 43-8 Case B, 26-year-old male. Radiographs showing the periodontal conditions prior to therapy.

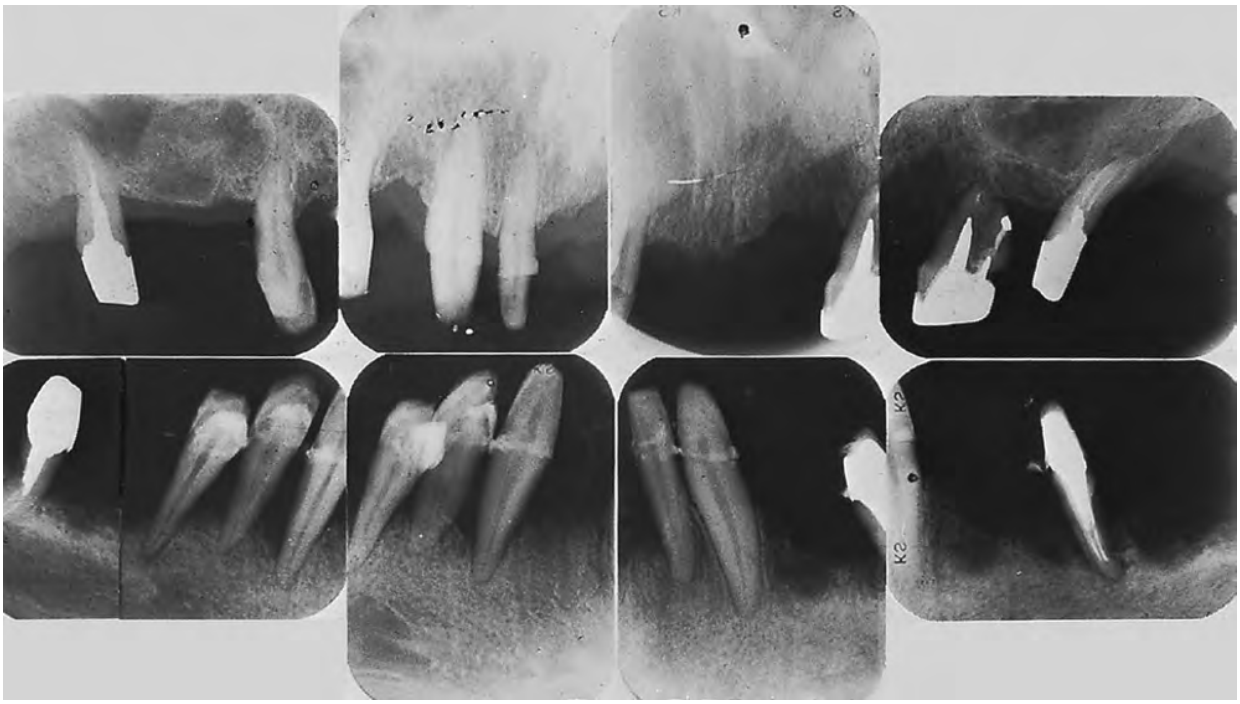

Fig. 43-9 Case B. Radiographs obtained after periodontal treatment and preparation of the abutment teeth for two fixed splints.

24 is root-separated and the palatal root maintained with only minute amounts of periodontium left.

Immediately prior to insertion of the two splints, all teeth except 13, 12, and 33 displayed a mobility varying between degrees 1 and 3. From the radiographs in Fig. 43-9 it can be noted that there is an obvious risk of loss of a number of teeth such as 24, 26, 47, 45, 44, 43, and 36 if the patient is allowed to bite with a normal chewing force without the splints in position.

Despite the high degree of mobility of the individual teeth, the splints were entirely stable after insertion, and maintained their stability during a maintenance period of >12 years. Figure 43-10 shows the clinical status and Fig. 43-11 the radiographs obtained 10 years after therapy. From these radiographs it can be observed (compare with Fig. 43-9) that during the maintenance period there had been no further loss of alveolar bone

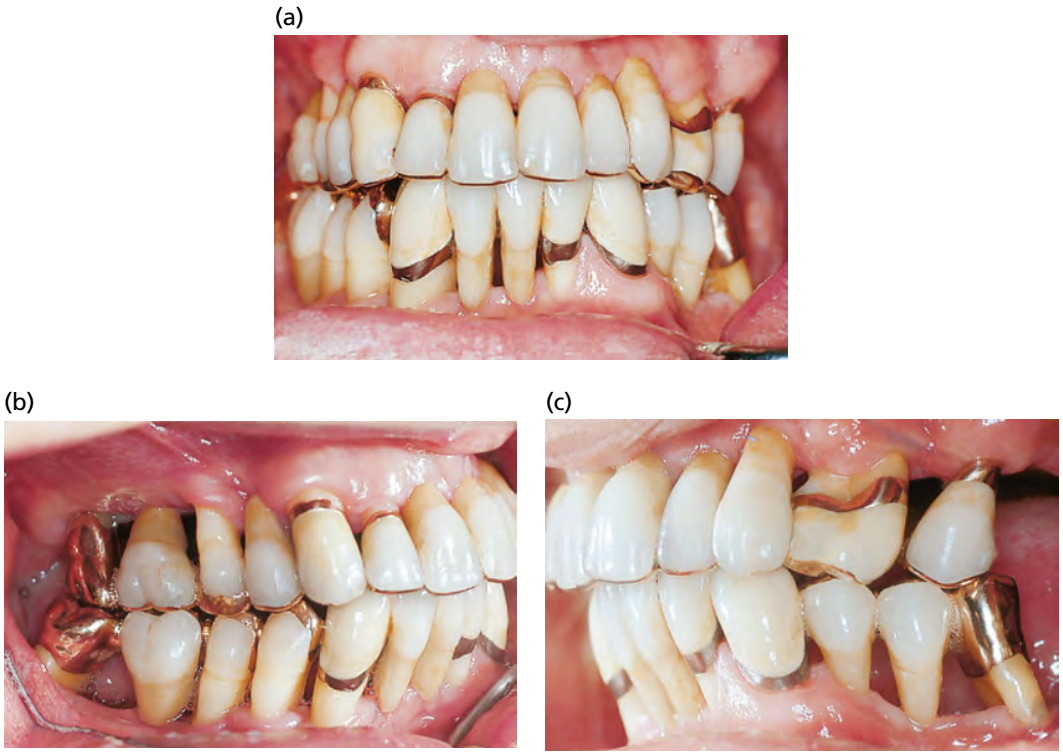

Fig. 43-10 (a–c) Case B. Clinical status 9 years after therapy.

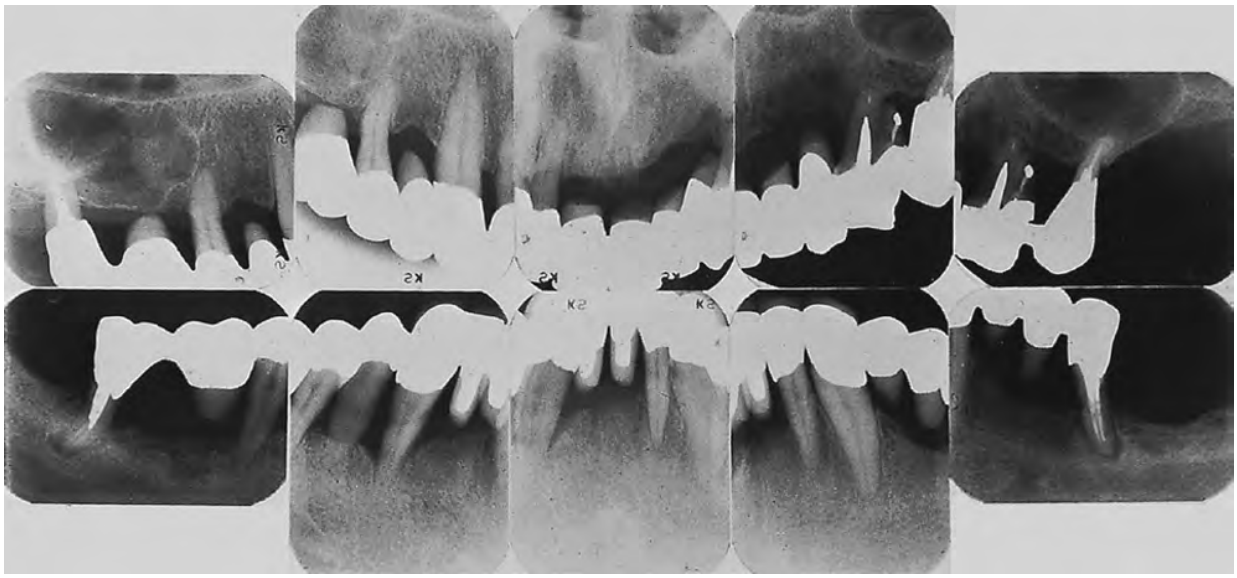

Fig. 43-11 Case B. Radiographs obtained 10 years after therapy.

or widening of the various periodontal ligament spaces.

Conclusion: Splinting is indicated when the periodontal support is so reduced that the mobility of the teeth is progressively increasing, that is when a tooth or a group of teeth are exposed to extraction forces during function.

Situation 5

Increased bridge mobility despite splinting

In patients with advanced periodontal disease, it can often be observed that the destruction of the periodontium has progressed to varying levels around different teeth and tooth surfaces in the dentition. Proper treatment of the plaque-associated lesions often includes multiple extractions. The remaining teeth may display an extreme reduction of the supporting tissues concomitant with increased or progressive tooth mobility. They may also be distributed in the jaw in such a way as to make it difficult, or impossible, to obtain a proper splinting effect even by means of a cross-arch bridge. The entire bridge/splint may exhibit mobility in frontal and/or lateral directions.

It was stated previously (situation 3) that a certain mobility of a tooth or a bridge of unilateral design can be accepted provided this mobility does not interfere with the patient's chewing ability or comfort. This is also valid for a cross-arch bridge/splint. From a biologic point of view, there is no difference between increased tooth mobility on the one hand and increased bridge mobility on the other. However, neither progressive tooth mobility nor progressive bridge mobility are acceptable. In cases of extremely advanced periodontal disease, a cross-arch splint with an increased mobility may be regarded as an acceptable result of rehabilitation. The maintenance of the status quo of the bridge/splint mobility and the prevention of tipping or orthodontic displacement of the total splint, however, requires particular attention regarding the design of the occlusion. Case C is an interesting illustration of this particular clinical problem.

Example: Case C, 52-year-old female

Figure 43-12 shows radiographs obtained at the initial examination. A 12-unit maxillary bridge was installed 10–15 years prior to the present examination using teeth 18, 15, 14, 13, 12, 11, 21, 22, 23, and 24 as abutments. After a detailed clinical examination it was obvious that teeth 15, 14, 22, and 24 could not be maintained because of severe symptoms of caries and periodontal disease. The remaining teeth were subjected to periodontal therapy and maintained as abutments for a new bridge/splint in the maxilla, extending from tooth 18 to the region of tooth 26, that is a cross-arch splint was installed which carried three cantilever units, namely 24, 25, and 26. The mobility of the individual abutment teeth immediately prior to insertion of the splint was the following: degree 1 (tooth 18), degree 0 (tooth 13), degree 2 (teeth 12 and 11), degree 3 (tooth 21), and degree 2 (tooth 23).

Radiographs obtained 5 years after therapy are shown in Fig. 43-13. The bridge/splint had a mobility of degree 1 immediately after its insertion and this mobility was unchanged 5 years later. The radiographs demonstrate that no further widening of the periodontal ligament had occurred around the individual teeth during the maintenance period.

When a cross-arch bridge/splint exhibits increased mobility, the center (fulcrum) of the movement must be identified. In order to prevent further increase in the mobility and/or to prevent displacement of the bridge, it is essential to design the occlusion in such a way that when the bridge/splint is in contact with the teeth of the opposing jaw, it is subjected to a balanced load, that is equal force on each side of the fulcrum.

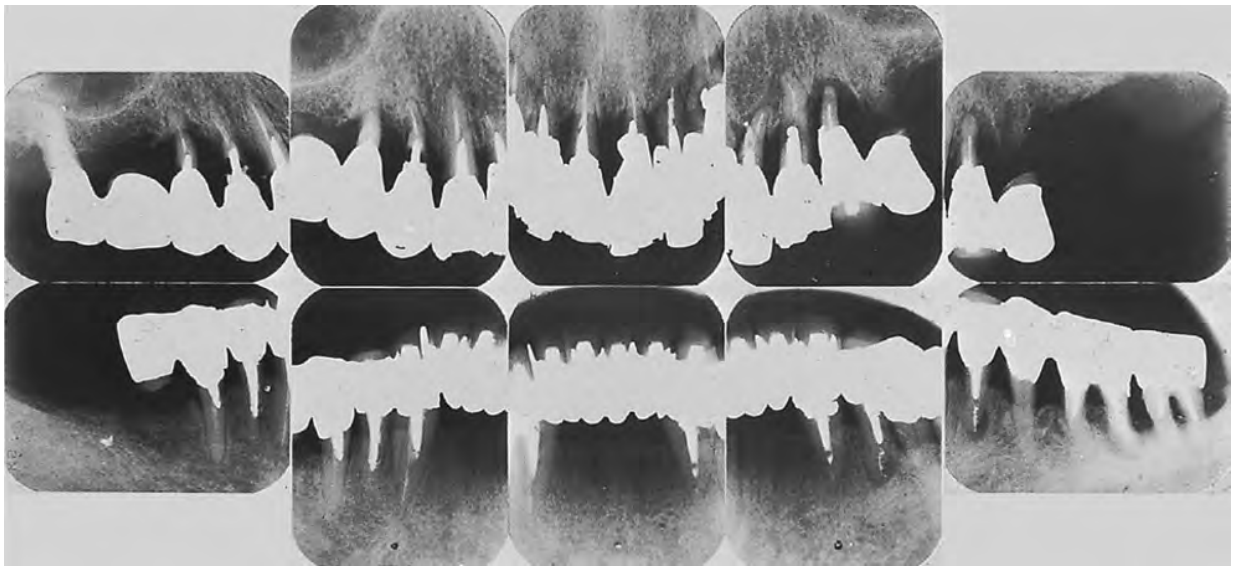

Fig. 43-12 Case C, 52-year-old female. Radiographs obtained at the initial examination.

If this can be achieved, the force to which the bridge is exposed in occlusion can be used to retain the fixed prosthesis in proper balance (thereby preventing a further increase of mobility).

Balanced loading of a mobile bridge/splint has to be established not only in the intercuspal position (IP) and centric occlusion (CP), but also in frontal and lateral excursive movements of the mandible if the bridge shows mobility or a tendency for tipping in the direction of such movements. In other words, a force which tends to displace the bridge in a certain direction has to be counteracted by the introduction of a balancing force on the opposite side of the fulcrum of the movement. If, for instance, a cross-arch splint in the maxilla exhibits mobility in the frontal direction in conjunction with protrusive movements of the mandible, the load applied to the bridge in the frontal region has to be counterbalanced by a load in the distal portions of the splint; this means that there must be a simultaneous and equal contact relationship between the occluding teeth in both the frontal and the posterior regions of the splint. If the splint is mobile in a lateral direction, the force acting on the working side of the jaw must be counteracted by a force established by the introduction of balancing contacts in the non-working side of the jaw. The principle for establishing stability of a *mobile* cross-arch splint is consequently the same as that used to obtain stability in a complete denture. In situations where distal abutment teeth are missing in a cross-arch bridge/splint with increased mobility, balance and functional stability may be obtained by means of cantilever units. It is important in this context to point out that balancing contacts on the non-working side should not be introduced in a bridge/splint in which no increased mobility can be observed.

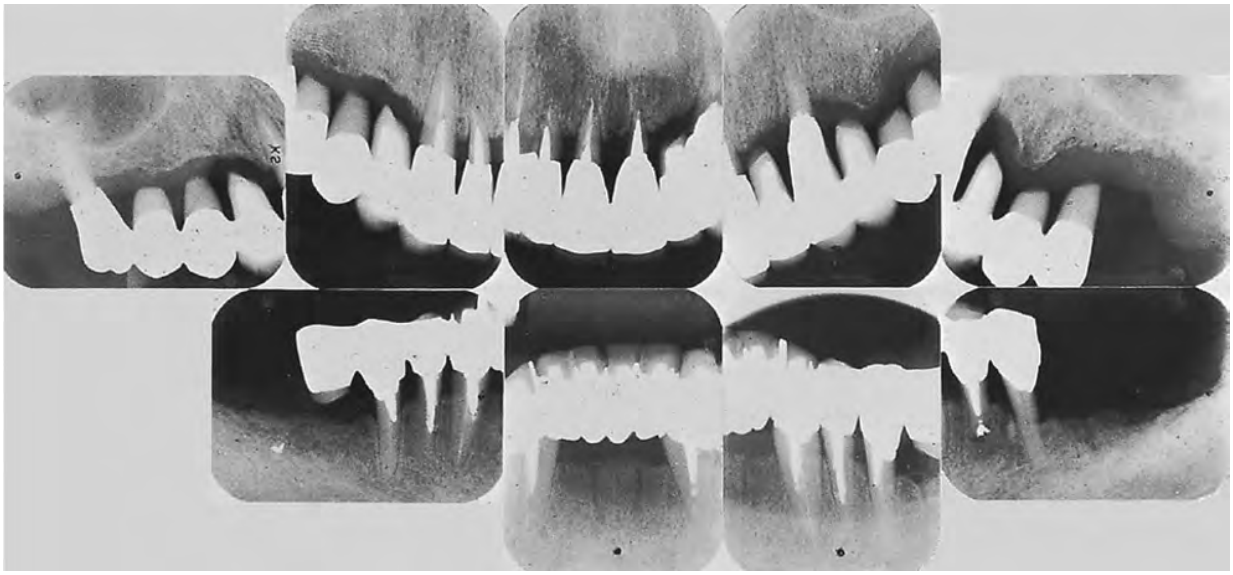

Fig. 43-13 Case C. Radiographs obtained 5 years after therapy.

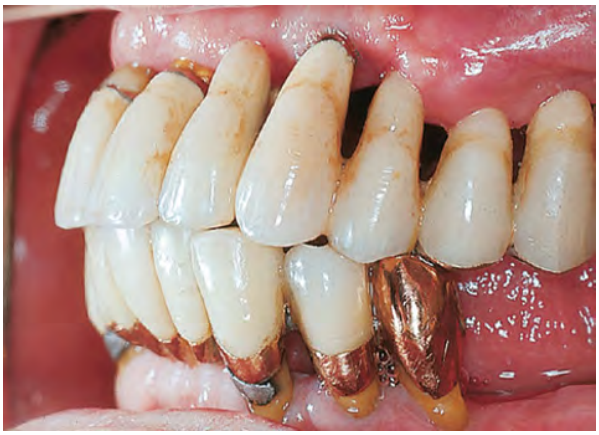

Fig. 43-14 Case C. Cantilever section including teeth 24, 25, and 26.

The maxillary splint in Case C exhibited increased mobility in a frontal direction. Considering the small amount of periodontal support left around the anterior teeth, it is obvious that there would have been a risk of frontal displacement of the total bridge had the bridge terminated at the last abutment tooth (23) on the left side of the jaw. The installation of cantilever units in the 24 and 25 region prevented such a displacement of the bridge/splint by the introduction of a force counteracting the frontally directed forces during protrusive movements of the mandible (Fig. 43-14). In addition, the cantilever units provided bilateral contact relationship towards the mandibular teeth in the intercuspal position, that is bilateral stability of the bridge.

In cases similar to Case C, cantilever units can thus be used to prevent increasing mobility or displacement of a bridge/splint. It should, however, be pointed out that the insertion of cantilever units increases the risk of failures of a technical and biophysical character (fracture of the metal frame, fracture of abutment teeth, loss of retention, etc.).

In cases of severely advanced periodontal disease, it is often impossible to anticipate in the planning phase whether a bridge/splint will show signs of instability and increasing (progressive) mobility after insertion. In such cases, a provisional splint should always be inserted. Any alterations of the mobility of the bridge/splint can be observed over a prolonged period of time and the occlusion continuously adjusted until, after 4–6 months, it is known whether stability (i.e. no further increase of the mobility) can be achieved. The design of the occlusion of the provisional acrylic bridge is then reproduced in the permanent bridge construction. If, on the other hand, stability cannot be obtained, the rehabilitation of the case cannot be achieved with a fixed splint. The alternative treatment then is a complete denture or an implant-supported restoration.

Conclusion: An increased mobility of a cross-arch bridge/splint can be accepted provided the mobility does not disturb chewing ability or comfort and the mobility of the splint is not progressively increasing.

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Chapter 44

Implant-Supported Fixed Dental Prostheses

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Introduction

The overall favorable long-term survival and success rates reported in the literature for osseointegrated implants in the treatment of various types of edentulism (Jung *et al*. 2012; Pjetursson *et al*. 2012; Zhang *et al*. 2019) permit consideration of dental implants as a very reliable therapeutic modality during the establishment of any prosthetic treatment plan. In numerous clinical situations, implants can clearly contribute to a notable simplification of therapy, frequently enabling removable prostheses to be avoided, keeping it less invasive with respect to the remaining tooth structure, or rendering the treatment more versatile (Belser *et al*. 2000).

Beyond any doubt, the advent of osseointegration has had a fundamental impact on the therapeutic approach and strategies implemented today in the field of prosthetic rehabilitation of the compromised posterior dentition. This treatment modality is increasingly applied worldwide, not only by specialists but also more and more by general practitioners, thus having a tremendous influence on traditional prosthodontic attitudes (Buser *et al*. 2017).

Because most of the established dental implant systems today comprise a wide range of mostly screw-type implants with different diameters, dimensions, and designs to replace missing premolars and molars, the versatility of implant therapy in the load-carrying part of the dentition of partially edentulous patients has been significantly enhanced. The use of implants may often significantly reduce the inherent risk of "borderline" conventional tooth-borne fixed dental prostheses (FDPs) (e.g. prostheses based on compromised abutment teeth, long-span FDPs, cantilevers) by implementing the principle of segmentation. It is currently widely accepted that – in comparison with extended splinted prosthetic segments – small units are preferable as they are easier to fabricate, generally provide improved "passive fit" and marginal fidelity, offer better access for the patient's oral hygiene, and ultimately are less complicated to handle where there is need for re-intervention.

In the past decade, various trends, innovations and scientific data shifted implant dentistry from specialists and referral-based clinicians to general dentists (Buser *et al*. 2017). This trend is based on improved

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

diagnostics tools (e.g. cone-beam computed tomographies, digitization), simplified treatment protocols, more options in terms of implant designs, lengths, and diameters as well as the availability of high-strength implant materials and components (Jung *et al*. 2012; Pjetursson *et al*. 2012; Thoma *et al*. 2015; Naenni *et al*. 2018; Roehling *et al*. 2018; Sailer *et al*. 2018b; Schiegnitz *et al*. 2018; Schneider *et al*. 2018; Tahmaseb *et al*. 2018; Avila-Ortiz *et al*. 2019; Cosyn *et al*. 2019).

It is the aim of this chapter to present clinically oriented guidelines and procedures for implant therapy of various types of edentulism in the posterior part of the dentition, addressing the partially dentate patient and focusing on implant-supported FDPs.

Indications for implants in the posterior dentition

Indications for implants in the posterior dentition are related to improve the subjective chewing comfort of partially edentulous patients (Gates *et al*. 2014), or to preserve sound mineralized tooth structure, or to avoid removable partial dentures (RPDs) and conventional FDPs. This includes situations with missing teeth, the distally shortened dental arch, extended edentulous segments, missing "strategic" tooth abutments, and structurally, endodontically, or periodontally compromised potential abutment teeth.

Numerous other indications have been added to the so-called classical indications for the use of implants including severely atrophied edentulous jaws, congenitally missing teeth, or the distally shortened dental arch (particularly when premolars are missing). Among these other indications, one should also mention that all the strategies aim at either reducing the prosthodontic risk in general or rendering the treatment simpler and more cost-effective. Virtually no limits on the placement of implants seem to exist any longer owing, for example, to well-documented bone augmentation (Jepsen *et al*. 2019) techniques comprising horizontal bone augmentation of buccal dehiscence/fenestration defects (Thoma *et al*. 2019), sinus floor elevation (Pjetursson *et al*. 2008; Raghoebar *et al*. 2019) as well as vertical bone augmentation (Rocchietta *et al*. 2008; Urban *et al*. 2019).

The rapid advances in terms of the broad utilization of dental implants are not exclusively based on the associated favorable long-term reports for this treatment modality. Other parameters such as purely "mechanical" advantages and the increasing use of digital technologies (Wismeijer *et al*. 2018) and components, which in turn contribute notably to the simplification of the treatment, also have had a significant impact on current concepts and strategies. Furthermore, clinical decision-making based on prosthetically oriented risk assessment frequently leads to the need for selective placement of dental implants. The objective is to reduce the overall risk (Box 44-1) associated with a given prosthetic solution on the one hand, and to implement the principle of segmenting on the other.

Box 44-1 "High-risk" conventional fixed partial dentures.

- Long-span fixed partial bridges
- Cantilever units (mainly distal extensions)
- Missing "strategic" tooth abutments
- Structurally-/periodontally-/endodontically-compromised tooth abutments

Therefore, the therapeutic strategy should be ideally planned in light of the current clinical evidence and according to the patient needs. In this context, for the posterior zone the following therapeutic concepts have become available in the respective jaws.

Therapeutic concepts at sites with sufficient bone quantity

When sufficient bone is available, placing dental implants in the posterior region of the jaws is a straightforward procedure. Primarily, posterior implants restore the function following the loss of a strategically important tooth. Treatment planning becomes highly involved and extensive reconstructions may result from the loss of such a tooth. Especially in dentitions that have received multiple reconstructions, the loss of one strategic abutment may lead to a time-consuming and costly therapy. By installing oral implants in the strategically correct locations, partial reconstruction of a dentition may become possible. Factors to be considered thereby include gap size, number, dimension (length, diameter) as well as distribution of implants.

Single-unit gap size

Premolar-size single-tooth restorations

In case of a gap size corresponding dimensionally to an average premolar, standard-size screw-form implants are well suited. The implant dimensions, either as a one-piece implant including both the intrabony part and the implant shoulder or as a two-piece implant with the intrabony part only, offer the additional advantage of being mostly compatible with a limited bone volume in an orofacial direction. Whenever feasible, a straightforward low-maintenance restorative design is advocated, normally consisting of a screw-retained porcelain-fused-to-metal (PFM) crown or a hybrid reconstruction with a CAD-CAM all-ceramic crown extraorally cemented to a titanium base, to provide adequate guidance for the cheek and tongue.

As one increasingly strives for the best possible biologic, functional, and esthetic integration of a given implant restoration in the pre-existing dentition, 3D preoperative site analysis is of paramount importance. It is not infrequent that this subsequently calls for a multidisciplinary approach, which may also include presurgical orthodontic therapy rendering a more optimal hard and soft tissue condition for implant therapy.

Optionally, in cases with a limited bucco-oral bone dimension, one might consider the placement of narrow-diameter implants (NDIs). Scientific evidence based on a randomized controlled trial provides favorable results up to 3 years with NDIs (Ioannidis *et al*. 2015). Surgically, NDIs reduce the need for simultaneous bone augmentation procedures and are preferred by clinicians (Benic *et al*. 2013; Jung *et al*. 2018). Nevertheless, from a prosthetic point of view, the reduced dimension of the implant shoulder limits the creation of the emergence profile and implants need to be placed with an increased sink depth.

Molar-size single-tooth restorations

If a given posterior single-tooth gap corresponds to the mesiodistal dimension of a molar, implant systems offer more options. The most often applied concept includes the placement of a standard-diameter implant. Optionally, a wide-diameter implant can be chosen. This approach, however, also requires the appropriate bone volume in an orofacial direction. If this is not the case, implant placement has to be combined with a lateral bone augmentation procedure using a simultaneous approach. This additional effort, risk, and ultimately also cost has to be discussed with the patient, but most often will not be chosen. Similarly, NDIs might be theoretically an option. Limitations apply, however, because of a lack of scientific evidence (in molar sites) and the large dimensional difference between the implant shoulder and the anticipated crown embrasure.

Two-unit gap size

Considering the dimensions of premolars (7 mm) and molars (8 mm) and adequate space for the interdental/interimplant space (4–5 mm), edentulous ridges between existing teeth may be reconstructed and chewing comfort increased without involving adjacent teeth. Obviously, risks can be minimized by reducing the length of bridge spans. Therefore, in combined molar and premolar reconstructions, the surgical positioning of the implants has to be calculated in detail and restoration-driven stents may have to be used in order to create adequate conditions for prosthetic reconstruction.

In the case of two missing occlusal units, one should try as a general rule to select the optimal implant diameter with respect to the total mesiodistal distance of the given edentulous segment. Decisive parameters are the interimplant distance and space between implants and adjacent teeth (if present), as well as the orofacial crest width at the two prospective implant sites. For a total gap diameter of about 14–15 mm (two premolars), two standard-size (Fig. 44-1), one standard-size, and one narrow-diameter or two NDIs are suitable. For an edentulous space of 17–18 mm options include two standard-diameter implants or the combination of one standard and one wide diameter/wide platform implant

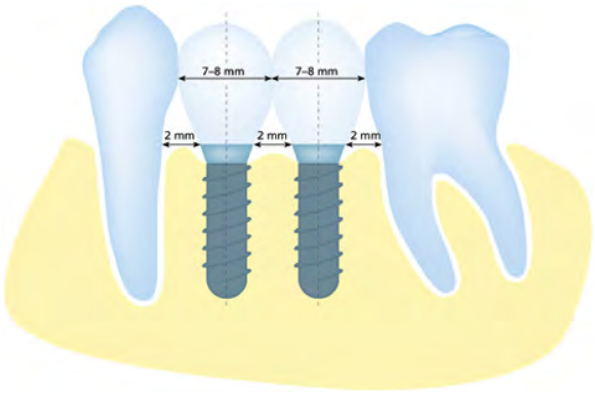


Fig. 44-1 If a given tooth-bound edentulous space only permits the insertion of two adjacent implants, a minimal interimplant distance of 2 mm and a minimal implant-to-tooth distance of 2 mm should be respected.

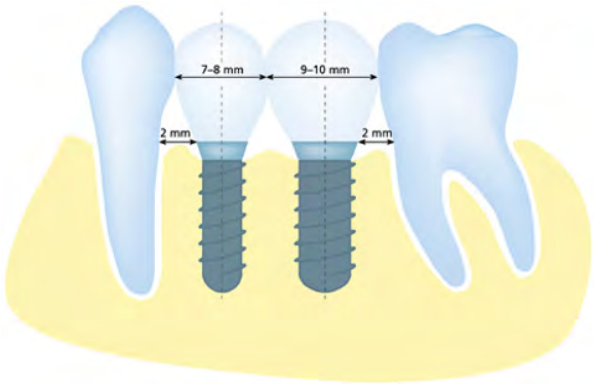


Fig. 44-2 In the presence of a mesiodistal gap width of approximately 17 mm, the combination of a standard and an increased-diameter implant may be considered. The same minimal interimplant and implant-to-tooth distances have to be respected.

(Fig. 44-2). The latter choice, as mentioned above, is rarely selected, mostly because of a reduced bucco-oral ridge width.

These are just the frequently encountered clinical examples, and for the function of other morphology and dimensions of edentulous tooth-bound segments, additional approaches and implant combinations may be envisioned (Fig. 44-3). Such a clinical situation is shown in Fig. 44-4. The gap diameter required the two adjacent implants to be spaced wider than the normally advocated interproximal 2 mm. The laboratory technician compensated for this excess of space with a root-imitation pontic, which in turn provided an excellent guide facilitating the use of an interdental brush (Fig. 44-4a).

Multiunit gap size (≥3 missing teeth to be replaced)

It is still unclear to date how many implants of which dimension and at which location are required to optimally rehabilitate a given edentulous segment in the load-carrying part of the dentition. Several different recommendations and related strategies are currently

in use, mostly derived from traditional prosthodontic experience and attitudes, and based on so-called clinical experience and common sense rather than on solid scientific evidence.

In cases of three or more posterior teeth to be replaced, dental implants are, therefore, strategically placed, and short-span bridges are the preferred treatment option (Fig. 44-3). This therapeutic option offers benefits in terms of costs, efforts to be undertaken, and ease of the surgical and prosthetic procedures compared with the installation of implants at every single-tooth position.

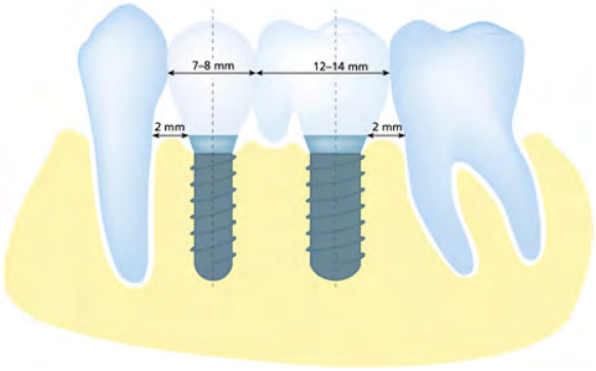


Fig. 44-3 If a posterior mesiodistal gap has a width of approximately 20 mm, a small central pontic should be considered to simplify the cleaning process.

Distribution and number of implants

In a situation where the canine is the most distal remaining tooth of a dental arch, at least five different options can be considered if it is planned that the missing teeth up to the first molar area are to be replaced: (1) replacement of each missing occlusal unit by one implant (Fig. 44-5a); (2) a mesial and a distal implant to support a three-unit FDP with a central pontic (Fig. 44-5b); (3) two distal implants to permit the insertion of a three-unit FDP with a mesial cantilever (Fig. 44-5c); (4) two mesial implants to sustain a three-unit FDP with a distal cantilever (44-5d); and (5) only one distally inserted implant in view of a four-unit FDP combining implant and natural tooth support (Fig. 44-5e).

As far as the recommendation to use premolar-size units for implant-borne posterior FDPs is concerned, it has proven its practical validity in >10 years of clinical experience (Buser *et al*. 1997;

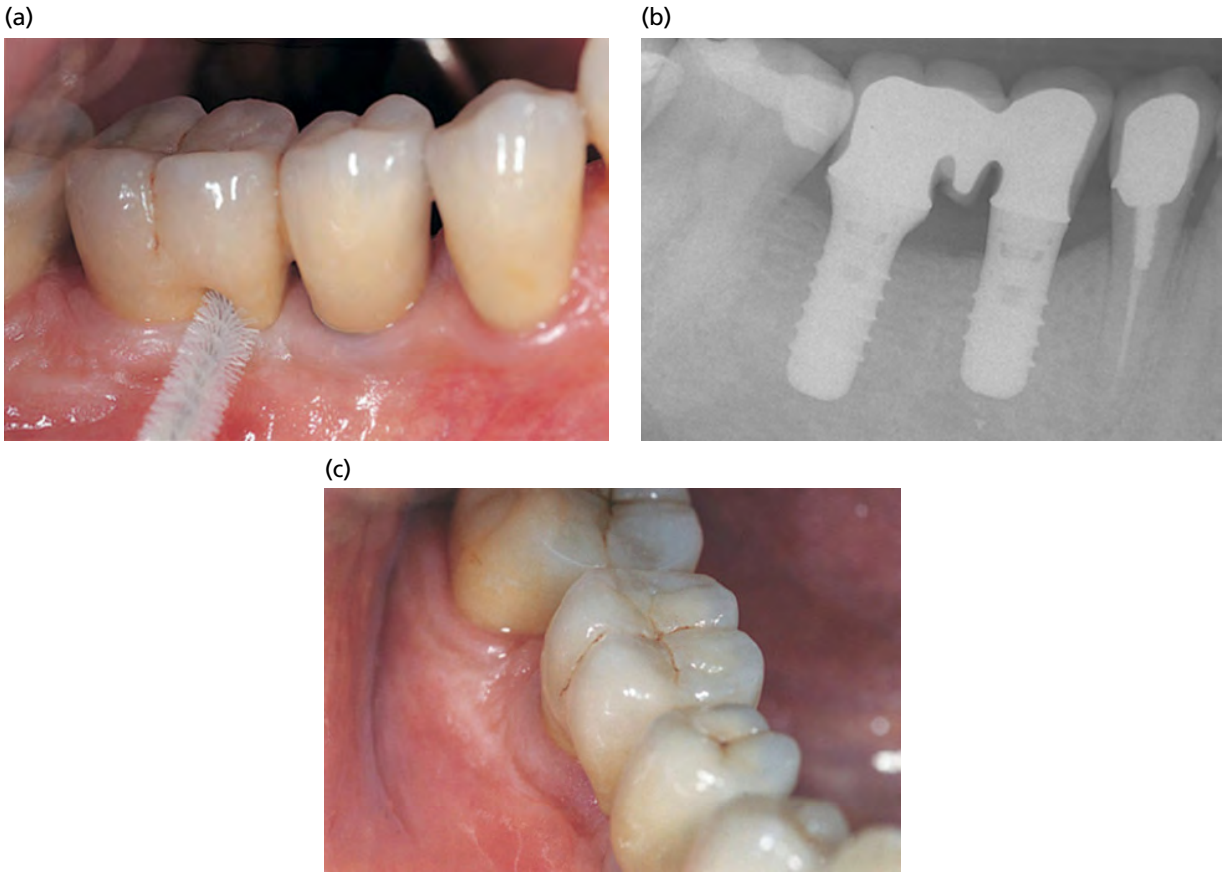


Fig. 44-4 (a) Vestibular aspect of a metal–ceramic restoration supported by two screw-type implants. Due to an excess of mesiodistal space, the implants have been separated by approximately 4 mm. Instead of a traditional pontic, a root imitation has been performed close to the distal implant, providing an adequate guide for an interdental brush in view of an efficient plaque control at the marginal area of the implant restoration. (b) With respect to cleanability, the prosthesis design is clearly visible on the postoperative radiograph. (c) On an oblique view, the vestibular axial profile of the implant restoration becomes visible. Soft tissue (cheek and tongue) support and harmony with adjacent teeth are of paramount importance.

Bernard & Belser 2002). In fact, a crown featuring a mesiodistal diameter of 7–8 mm at its occlusal surface allows the optimal generation of a harmonious axial profile, gradually emerging from the standard-implant shoulder (diameter 4–5 mm on average) to the maximum circumference. Furthermore, and because overloading appears to play little role in late implant failures (Lima *et al*. 2019), clinicians tend to replace molars with molar size reconstructions.

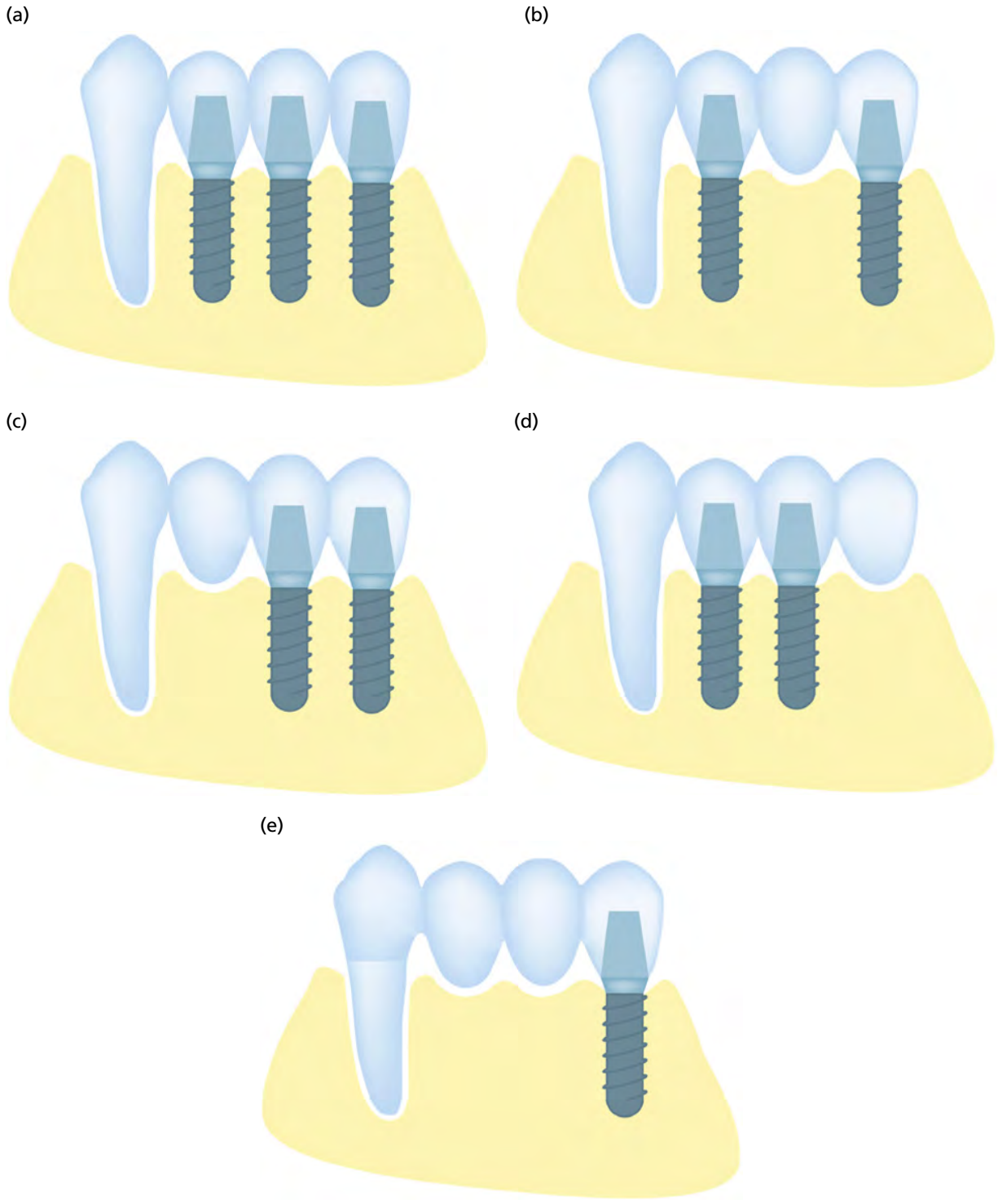


Fig. 44-5 The distally shortened dental arch. (a) One therapeutic option consists of replacing each missing occlusal unit up to the first molar area with an implant. (b) An alternative option would be the replacement of the three missing occlusal units with two implants to support a three-unit suprastructure with a central pontic. (c) In a case of an inadequate bone volume in the area of the missing first premolar, the placement of two distal implants may be considered, leading to a three-unit suprastructure with a mesial cantilever. (d) In a case of an inadequate bone volume in the area of the missing first molar, the placement of two mesial implants may be considered, leading to a three-unit suprastructure with a distal cantilever. (e) In a case of inadequate bone volume in the area of the two missing premolars, the placement of a distal implant may be considered, leading to a four-unit suprastructure with a mixed (tooth and implant) support.

Based on an increasing body of scientific evidence, most clinicians' first choice is the mesial and distal implant and the FDP with the central pontic (Fig. 44-6). Prospective mid- to long-term data (Ioannidis *et al*. 2015; Gamper *et al*. 2017) have confirmed the efficacy and predictability of this specific modality. In fact, it permits the defined treatment objective to be reached with a minimum number of implants and associated costs. Although formal evidence at the level of prospectively documented, randomized clinical trials is still lacking, it appears from clinical experience that the use of two implants to support a four-unit FDP with two central pontics (Fig. 44-7) may be adequate in certain clinical situations. Clinicians tend to use this approach in the presence of favorable bone conditions, permitting standard-size or less frequently wide diameter implants of appropriate length (i.e. ≥8 mm).

Therapeutic concepts at sites with insufficient bone quantity

It is quite common that distally shortened dental arches do not feature an adequate local bone volume at the prospective implant sites. This may refer to bone height, bone width, alveolar bone crest axis, or to the vicinity of noble structures such as the mandibular alveolar nerve canal or the anterior part of the maxillary sinus. Often, a combination of several of the mentioned limitations are encountered. Implant insertion is clearly a three-dimensional surgical and restorative procedure and a "restoration-driven" rather than "bone-driven" implant placement is widely recommended. Therefore, a meticulous presurgical site analysis – based on the envisioned treatment objective – is of primary importance. In order to keep the treatment as easy and cost-effective as possible, one should evaluate comprehensively all

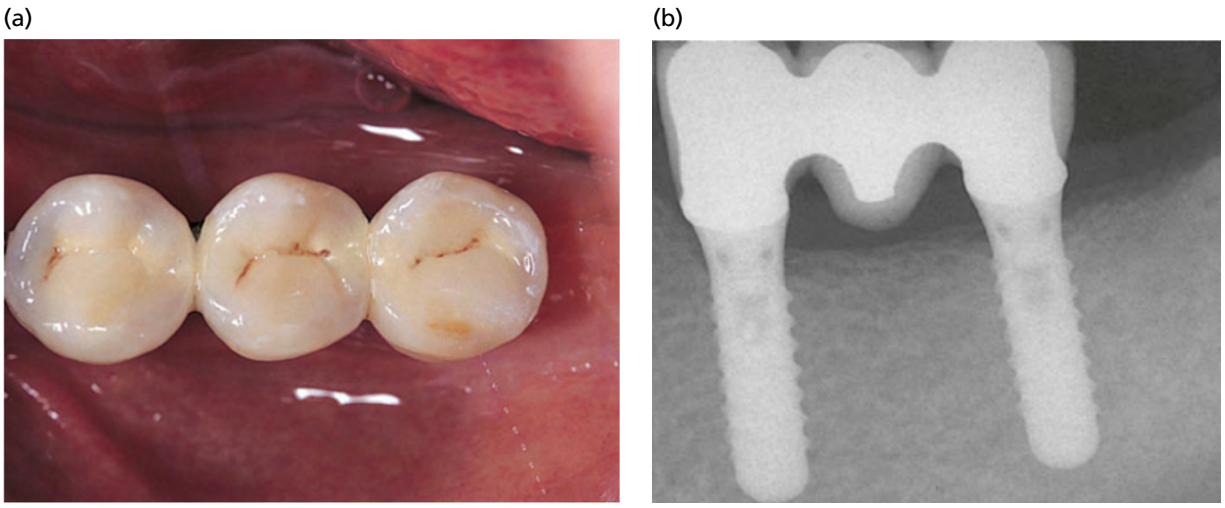


Fig. 44-6 (a) Occlusal view of a cemented three-unit metal–ceramic fixed dental prosthesis, supported by a mesial and a distal implant. (b) Corresponding 3-year follow-up radiograph confirms stable conditions at the implant–bone interface of the two 12-mm solid screw implants.

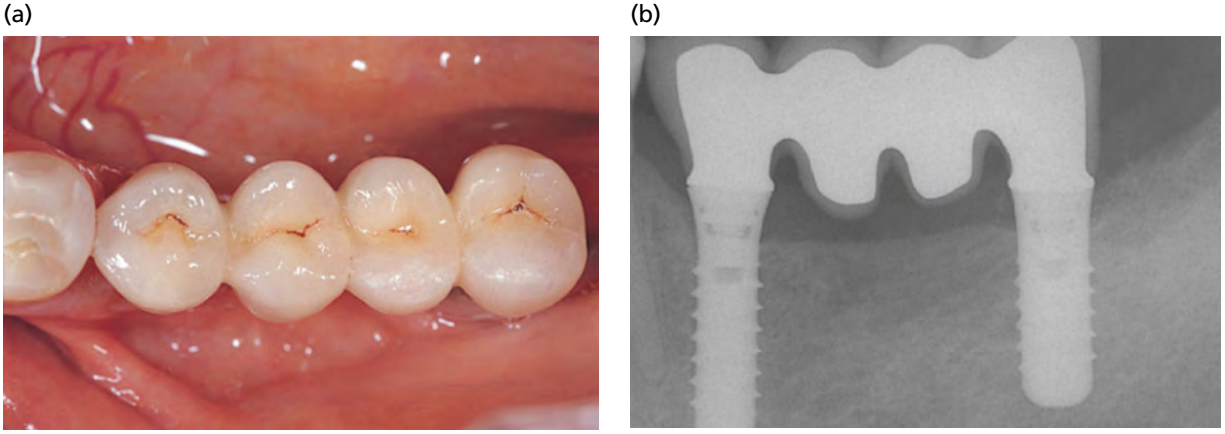


Fig. 44-7 (a) Occlusal view of a cemented four-unit metal–ceramic fixed dental prosthesis supported by a mesial and a distal implant. (b) Corresponding 2-year follow-up radiograph documents that at the distal site a 10-mm solid screw implant with an increased diameter ("wide-body implant") has been used.

available treatment options. Among the options to be considered are: (1) primary (Naenni *et al*. 2019) or simultaneous bone augmentation (Thoma *et al*. 2019) procedures in combination with standard-length implants; (2) use of shorter and NDIs and therefore avoiding extensive bone regenerative procedures (Nisand *et al*. 2015; Thoma *et al*. 2015; Jung *et al*. 2018); (3) insertion of an implant-supported crown with a cantilever (Aglietta *et al*. 2012); (4) the shortened dental arch concept (Kayser 1981); (5) combination of implant and natural tooth support; and (6) even a minor deviation from the ideal implant position (Lin & Eckert 2018) without accepting the risk that this treatment adversely affects predictability, longevity, and/or subjective comfort.

Therapeutic concepts to avoid larger bone augmentation procedures

Shorter dental implants

Clinicians are quite frequently confronted with posterior edentulous jaw segments that present all of the major prerequisites for successful implant, with the exception of a sufficient vertical bone height for the insertion of one or several implants featuring what is broadly accepted as an adequate length of the implants *per se* and also in relation to the prospective height of the suprastructures. The question that arises is whether there is a minimal implant length required in the context of posterior single-unit restorations and whether the ratio between implant length and suprastructure height has an influence on crestal bone resorption and ultimately on the longevity of the entire implant-suprastructure complex (Blanes *et al*. 2007; Quaranta *et al*. 2014; Hammerle *et al*. 2018; Meijer *et al*. 2018; Naenni *et al*. 2018).

Standard-length implants (>8 mm) have been universally recommended for many years, as it was widely accepted that this length was reasonable for a predictable success; the functional forces exerted on the implant were assumed to be distributed over a large surface area throughout the entire length of the implant. Later experimental studies concluded that this stress might not be minimized if the length of the implant is increased (Pierrisnard *et al*. 2003). Hence, it has been claimed that the generated interface stresses are, in fact, concentrated on the crestal bone and not redistributed over the entire length of the implant, and that shorter implants may even be more favorable in terms of peri-implant bone stimulation and resulting bone density (Renouard *et al*. 2006).

In the past 10 years, a high number of clinical studies and eventually systematic reviews broaden the evidence that shorter dental implants are not associated with a higher rate of biological complications (e.g. more marginal bone loss) (Esposito *et al*. 2019) or a lower implant survival rate (Tolentino da Rosa de Souza *et al*. 2018; Chen *et al*. 2019; Esposito *et al*. 2019). This in turn led to a decrease of the mean implant length used for daily clinical practice. At the Clinic of Reconstructive Dentistry at the University of Zürich, Switzerland the mean implant length has decreased by 3–4 mm within the last 10 years (Gamper *et al*. 2017; Ioannidis *et al*. 2019).

Currently, implants that are ≤8 mm long are broadly considered as "short implants". Short dental implants were engineered to avoid interferences with vital anatomic structures (e.g. mandibular nerve canal, maxillary sinus), to reduce surgical trauma and associated risks, to decrease the morbidity involved with advanced grafting/bone augmentation procedures, and to foster "prosthetically-driven" implant positioning (Papaspyridakos *et al*. 2018). As a result, these short dental implants may directly increase patient comfort and compliance (Jung *et al*. 2018), as well as minimize the amount of radiologic investigation and the number of visits, chair-side time, and costs involved.

Clinicians though, might still be afraid of placing shorter dental implants owing to particular limitations such as a slightly higher implant failure rate (Jung *et al*. 2018; Papaspyridakos *et al*. 2018) in direct comparison to standard length implants based on a recently published randomized controlled clinical trial (Naenni *et al*. 2018). Other parameters that have not been studied extensively include the influence of the implant surface and the appropriate implant design of shorter dental implants as well as the influence of the implant diameter. Shorter dental implants are therefore more often proposed in clinical situations where more advanced bone augmentation techniques require more surgical efforts to install the implants (Fig. 44-8) (Jung *et al*. 2018; Papaspyridakos *et al*. 2018).

Narrow-diameter implants

NDIs are recommended in clinical situations with a narrow ridge width or a reduced interdental gap width (Jung *et al*. 2018; Schiegnitz *et al*. 2018). The scientific literature describes various types and designs of NDI, generally with a diameter of ≤3.5 mm. The reported classification by the ITI Consensus Conference in 2018 proposed three categories (Jung *et al*. 2018): Category 1, implants with a diameter of <2.5 mm ("mini-implants"); Category 2, implants with a diameter of 2.5 mm to <3.3 mm; Category 3, implants with a diameter of 3.3–3.5 mm. Based on the current evidence, implants in category 3 are the only ones that can be recommended in posterior regions of the jaws, with a reported survival rate ranging between 91% and 100% after observation periods of 12–109 months (Jung *et al*. 2018). Potential advantages of NDIs include the maintenance of an adequate tooth–implant and interimplant distance in clinical situations with a reduced mesiodistal width, a decrease in the need and complexity of lateral bone augmentation procedures in clinical situations with a reduced bucco-oral ridge width, reduced treatment length by allowing a simultaneous rather

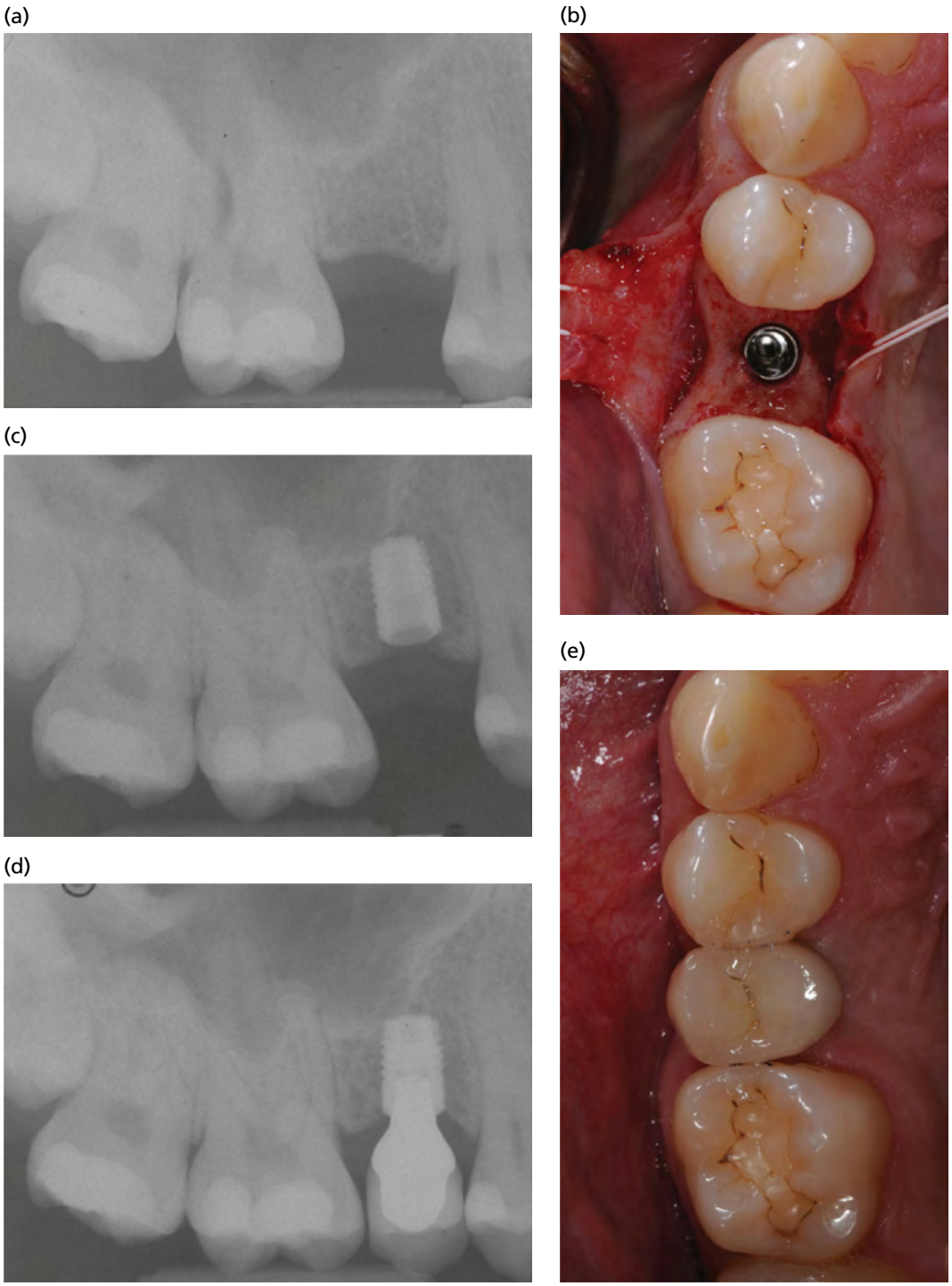


Fig. 44-8 (a) Preoperative radiograph demonstrates a reduced alveolar ridge height (6 mm) in region 15. (b) Occlusal view after implant installation without an additional sinus elevation procedure. (c) Radiograph after implant placement with a 6-mm short implant. (d) Periapical radiograph 1 year after insertion of the final reconstruction. (e) Occlusal view of the final porcelain-fused-to-metal crown after 1 year in function.

than a staged approach of implant placement, and an increased prosthetic flexibility (Benic *et al*. 2013; Jung *et al*. 2018). In an randomized controlled trial, comparing NDI to standard-diameter implants in the esthetic zone including premolars, 3-year data did not demonstrate significant differences in terms of survival and marginal bone level changes (Ioannidis *et al*. 2015). Moreover, at the time of implant placement, NDIs offered advantages by reducing the overall need for bone augmentation procedures and were the preferred choice by the clinicians (Ioannidis *et al*. 2015). Whether or not these results can be transferred to molar sites and short-span bridges (limited to molar sites) remains unclear and currently cannot be recommended.

Given anatomical limitations of the ridge and reduced interimplant/interdental distances, NDIs are a valid treatment option. However, clinicians are advised to consider that NDIs exhibit a lower mechanical stability and a suboptimal prosthetic design for the maintenance of peri-implant health.

Cantilever

The clinical situation with two adjacent missing teeth is often encountered in the posterior area of the jaws. One alternative is the insertion of an implant-supported crown with a cantilever (Fig. 44-9) Apart from being more economical than the placement of two implants, it provides an alternative in cases of unfavorable anatomical conditions of the residual ridge. It has been hypothesized that cantilevers may increase occlusal and functional forces onto the implant leading to a higher rate of biological complications expressed by an increased amount of marginal bone loss. This hypothesis has been investigated in clinical studies for short-span fixed dental prostheses with two implants with a cantilever. The results of these studies, nevertheless, failed to demonstrate a higher marginal bone loss in comparison with non-cantilever FDPs (Wennstrom *et al*. 2004; Halg *et al*. 2008; Aglietta *et al*. 2009). Recently, several studies on single implants with cantilevers have been published (Halg *et al*. 2008; Aglietta *et al*. 2012; Palmer *et al*. 2012; Roccuzzo *et al*. 2020). In these studies, the bone level changes were comparable to those observed at implants without cantilevers. Therefore, implant-supported cantilevers seem to be a viable alternative in cases where the local alveolar bone crest conditions do not allow the insertion of an implant at the most favorable location (Aglietta *et al*. 2009; Freitas da Silva *et al*. 2018). A recent systematic review compared implant-supported fixed prostheses, with and without cantilevers. The authors concluded that the presence of a cantilever does not interfere in the survival of the prosthesis or the marginal bone loss (Freitas da Silva *et al*. 2018). This is supported by other systematic reviews demonstrating a slightly increased rate of technical complications (Torrecillas-Martinez *et al*. 2014), but similar survival rates between implants with and without cantilevers (Van Nimwegen *et al*. 2017; Storelli *et al*. 2018). From a treatment planning point of view, these data may permit consideration of short-span implant-supported FDPs as a valid treatment option for the replacement of missing posterior teeth that avoids the more complex surgical bone augmentation procedures that are necessary for placement of an implant in a traditionally optimal position from a prosthodontic point of view. It has to be underlined in this context, however, that basic prosthodontic design principles, such as increased dimensions of the connectors, have to be respected to avoid mechanical complications.

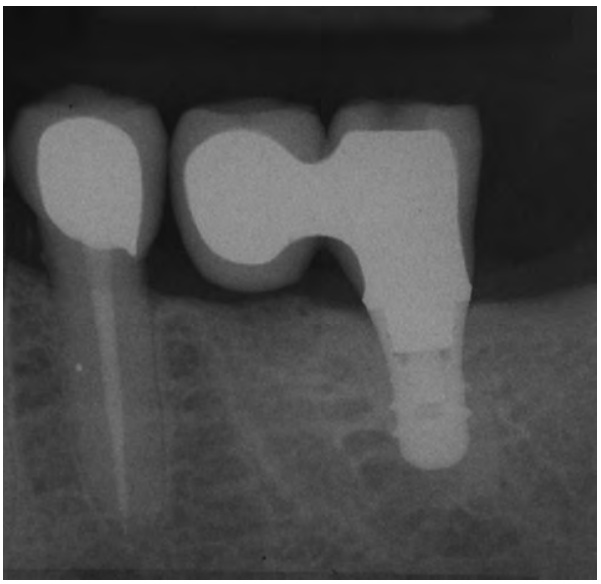


Fig. 44-9 Periapical radiograph of an implant with a mesial cantilever.

Shortened dental arch (SDA) concept

Generally, efforts are made to completely reconstruct a partially edentulous dentition. The question arises whether or not missing teeth have to be replaced at all and to the full extent. Usually, single teeth are replaced because of predominantly esthetic demands, while multiple missing teeth may also affect functionality and chewing capacity and hence, are replaced to improve these aspects. However, it is evident from cross-sectional and longitudinal studies (Kayser 1981; Reissmann *et al*. 2014; Reissmann *et al*. 2019; Walter *et al*. 2020) that not all lost teeth are replaced. The loss of one or more molars especially has been thoroughly studied. Studies on shortened dental arches (SDAs) have shown that dentitions comprising anterior and premolar teeth in general fulfill the requirements of a functional dentition, including patient-assessed oral comfort and chewing ability (Fig. 44-10). A review of the literature on SDAs concluded that the concept deserves serious consideration in treatment planning for partially edentulous patients. However, with ongoing

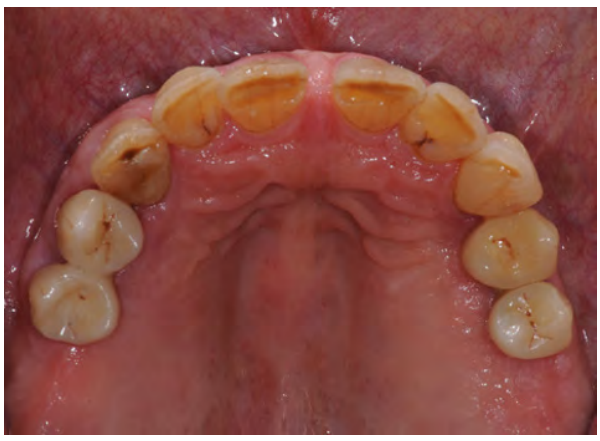


Fig. 44-10 Occlusal view of a patient rehabilitated with implant supported crowns according to the shortened dental arch (SDA) concept.

changes, for example in dental health and economy, the concept requires continuing research, evaluation, and discussion (Fueki & Baba 2017; Manola *et al*. 2017). Special attention has to be given to the patient's own needs and desires for increased chewing capacity when considering the SDA as a limited treatment goal. Clinical observations as well as research findings indicate that elderly patients can function at an acceptable level with a reduced dentition consisting of 10 or even fewer occluding pairs of teeth (Kayser 1981). This is further supported by a more recent review stating that 20 teeth throughout life will assure oral function (Gotfredsen & Walls 2007). The choice of implants as abutments to fulfill individual needs may, therefore, become a welcome treatment option within the concept of a shortened dental arch thereby avoiding additional bone augmentation procedures.

Combination of implant and natural tooth support

Combined tooth- and implant-supported FDPs are a treatment option in clinical situations where bone deficiencies only allow the placement of one implant (e.g. posterior sites) or for patients with limited finances. The potential advantages of combined FDPs are lower patient morbidity and lower treatment cost. Systematic reviews on combined FDPs reported a 5-year FDP survival rate of 90.1% (Lang *et al*. 2004) to 94.7% (Mamalis *et al*. 2012). Similarly, outcomes from a more recent systematic review reported a survival rate of 90.8% at 5 years (von Stein-Lausnitz *et al*. 2019). At 10 years, the survival rates ranged from 77.8% (Mamalis *et al*. 2012) to 82.1% (Lang *et al*. 2004), which are significantly lower than the 10-year survival rates of FDPs supported by implants only (Pjetursson *et al*. 2004). The indications for combined tooth- and implant-supported FDPs are therefore limited due to their relatively low survival rates.

Therapeutic concepts at sites requiring larger bone augmentation procedures

Maxilla–sinus floor elevation procedures

In the posterior regions of the maxilla, the clinician is often confronted with a reduced bone height because of a close relationship to the maxillary sinus. In these cases, different options exist: (1) primary sinus elevation and subsequent implant placement (Raghoebar *et al*. 2019); (2) implant placement with simultaneous sinus elevation (transalveolar approach or lateral window technique) (Pjetursson *et al*. 2008; Tan *et al*. 2008; Raghoebar *et al*. 2019); (3) use of shorter implants to avoid extensive bone augmentation procedures (Thoma *et al*. 2015; Jung *et al*. 2018); and (4) installation of angulated implants (Apaza Alccayhuaman *et al*. 2018) or zygomatic implants. The last of these options is mostly performed in edentulous cases by experienced maxillofacial surgeons (Davo & Pons 2015; Chrcanovic *et al*. 2016).

Sinus floor elevation Primary sinus augmentation procedures are indicated in cases with insufficient implant stability, which are often encountered when the vertical ridge height is <4 mm (Pjetursson *et al*. 2008; Raghoebar *et al*. 2019). This procedure is well documented, predictable, and can lead to high implant survival rates (Pjetursson *et al*. 2008; Jepsen *et al*. 2019; Raghoebar *et al*. 2019). However, the overall treatment time is increased since a healing time of several months (3–12 months depending on the graft material used) is required before implant placement can be performed. In some cases, primary implant stability can be achieved (ridge height 3–6 mm) when standard-length implants are placed simultaneously with either one of the two sinus elevation procedures (transalveolar or lateral window approach) (Pjetursson *et al*. 2009; Raghoebar *et al*. 2019). Simultaneous bone augmentation and implant placement can reduce the overall treatment time and costs and limit the number of surgical interventions. Implant survival rates are reported to be similar for all three sinus elevation procedures (transalveolar approach, lateral window one-stage or two-stage approach) with estimated implant survival rates over 3 years ranging between 88.5% and 98.3% (Pjetursson *et al*. 2008; Tan *et al*. 2008). In cases of the lateral window approach, the implant survival ranges between 88.6% and 100% at 5 years (Raghoebar *et al*. 2019). However, the transalveolar procedure offers benefits in being less invasive and less time-consuming (Tan *et al*. 2008).

Sinus floor elevation versus short implants Compared with standard-length implants in combination with extensive bone grafting procedures, the use of shorter implants potentially provides a variety of benefits: lower risk of damage to adjacent structures (roots, nerves, vessels, sinus), fewer complications, less invasiveness, fewer diagnostic procedures necessary, less diagnostic and surgical skill necessary, shorter treatment time, easier removal in case of failure, and less patient morbidity (Thoma *et al*. 2015; Jung *et al*. 2018).

In order to demonstrate that the use of short implants may result in similar survival rates to those for longer implants with sinus elevation procedures, various studies have been conducted and others are ongoing. In a recent randomized controlled clinical trial, short implants (6 mm) were compared with long implants (11 mm) placed in augmented sinuses (Thoma *et al*. 2018). At 5-years post loading, the results demonstrated similar survival rates for both implant lengths and treatments. However, the use of short implants was associated with a faster and cheaper treatment and less patient morbidity (Thoma *et al*. 2015). These data indicate that the use of short implants in the posterior maxilla may be considered a valuable treatment option (Jung *et al*. 2018) (Fig. 44-8).

Mandible–vertical ridge augmentation

In cases with a reduced ridge height in the mandible, three options exist: (1) primary vertical ridge

augmentation (Urban *et al*. 2019) and subsequent implant installation (Rocchietta *et al*. 2008; Esposito *et al*. 2019); (2) simultaneous implant placement with vertical ridge augmentation (Simion *et al*. 2007); and (3) the use of short implants (Jung *et al*. 2018; Papaspyridakos *et al*. 2018).

Vertical ridge augmentation Primary ridge augmentation procedures that allow the placement of standard-length implants have been proposed to result in smaller crown-to-implant ratios, better esthetics, and better cleanability of the prosthetic reconstruction. An array of different techniques (Urban *et al*. 2019) have been described for primary bone augmentation, including guided bone regeneration (GBR), distraction osteogenesis, and onlay bone grafting. The success rates of these techniques vary quite extensively. In addition, only a limited number of publications are available, and these are from a confined number of surgeons who are able to perform these treatments successfully. Their general use has therefore not been recommended (Rocchietta *et al*. 2008). The main reasons for this lack of recommendation included great variability in outcomes, a high rate of complications (extending up to 75%), and operator sensitivity (Rocchietta *et al*. 2008). However, a recent systematic review concluded that vertical ridge augmentation is a reasonable therapy for the reconstruction of deficient alveolar ridges. Although no technique is superior to others in terms of vertical augmentation (Urban *et al*. 2019), GBR using non-resorbable barrier membranes seems to be the preferable technique due to the low postoperative complication rates.

Vertical ridge augmentation versus short dental implants Similar to the maxilla, the use of shorter implants may avoid extensive bone regenerative procedures in cases with a ridge height exceeding 6 mm (Jung *et al*. 2018). Comparative clinical studies after 5 years of loading demonstrated fewer complications and less marginal bone loss with short implants compared with primary ridge augmentation and longer implants (Esposito *et al*. 2019). Hence, both patients and clinicians may benefit from the use of short implants. However, more comparative clinical studies with documented long-term data need to be provided (Nisand *et al*. 2015).

Diagnostics

Preoperative diagnostics in the posterior dentition

Dental implants are placed to support reconstructions (Esposito *et al*. 1998), and therefore, prosthetically driven implant placement is a prerequisite for the achievement of an ideal biomechanical, functional, and esthetic treatment outcome (Chiapasco & Casentini 2018). Together with anatomical site evaluation and risk assessment, the preoperative prosthetic diagnostics are essential for correct treatment planning in implant dentistry. The larger the span and the higher the complexity of the planned reconstruction, the more important are preoperative diagnostics.

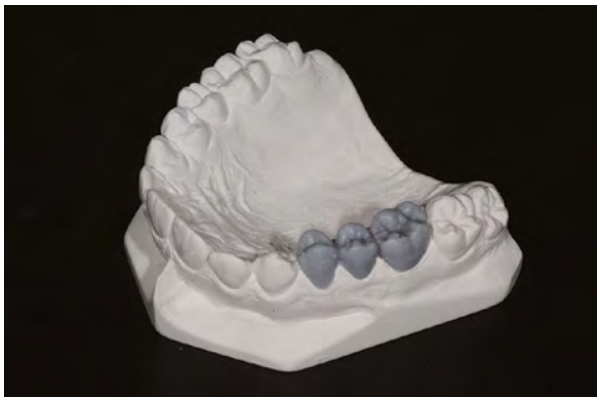


Fig. 44-11 Conventional wax-up on a cast.

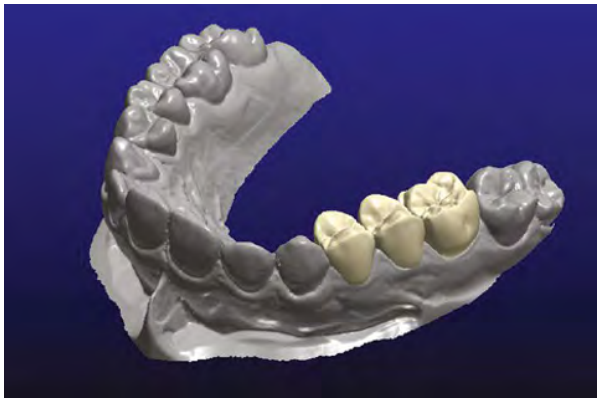


Fig. 44-12 Digital set-up as a screen view.

Prosthetic diagnostics are conventionally performed by means of a diagnostic set-up manufactured on plaster models (Fig. 44-11) as well as digitally using intraoral scans, digital set-ups (Fig. 44-12), and 3D-printed try-in mock-ups. More recently, even augmented reality came into play, allowing patients and professionals to mimic and visualize the final treatment outcome prior to any intervention (Joda *et al*. 2019).

The three-dimensional space available for the reconstruction will have a significant impact on the prosthetic and implant planning. In cases with reduced or excessive mesiodistal or vertical (distance from the prospective restorative margin to the opposing occlusion) space, adjunctive therapies might be necessary to adjust the space to that needed for the planned reconstruction (Fig. 44-13). This may involve orthodontic, surgical, reconstructive, or endodontic treatment procedures. Therefore, such clinical situations will result in an increased complexity of the treatment with dental implants.

Prior to the selection of implant design, length, and diameter, the following prosthetic elements have to be defined:

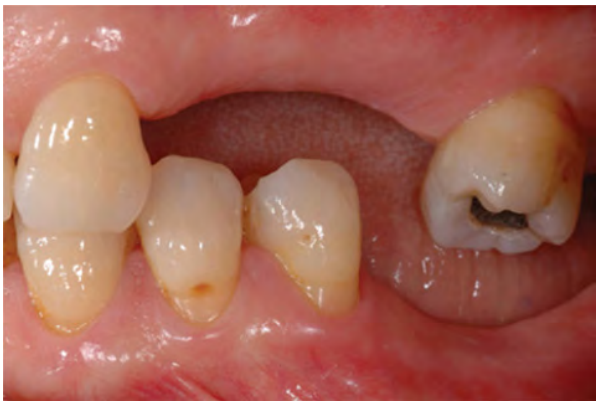


Fig. 44-13 Reduced vertical amount of space in the area of missing teeth 24, 25, and 26 due to elongation of antagonist teeth.

- Reconstruction design and material
- Prospective mucosal margin
- Type of retention
- Occlusal scheme.

Three-dimensional radiographic diagnostics and planning

The introduction of cone-beam computed tomography (CBCT) has allowed the acquisition of 3D images with an adequate quality for dentomaxillofacial examinations at reduced radiation doses compared with conventional multislice computed tomography (CT) (Loubele *et al*. 2009). The radiation burden of CBCT is, however, considerably higher in comparison to conventional two-dimensional (2D) radiography (Tyndall *et al*. 2012). Therefore, cross-sectional imaging should only be undertaken when it gives a justifiable benefit to the patient as a supplementary imaging technique where conventional radiography failed to answer the question for which imaging was required (Tyndall *et al*. 2012).

Computer-assisted implant planning and placement

Several software programs for computer-assisted implant planning based on the data from CBCT scans have been recently developed (Fokas *et al*. 2018; Joda *et al*. 2018; Schneider *et al*. 2018, 2019). A prerequisite for optimal implant planning when using such systems is the combination of the information on bone anatomy with the 3D image of the previously planned prosthetic reconstruction. This can be achieved by means of radio-opaque prosthetic templates or by superimposing a digital set-up on the CBCT image. To transfer the preoperatively planned implant position to the surgical site, intraoperative (static) guidance (Joda *et al*. 2018) or (dynamic) navigation (Aydemir & Arisan 2020) is required. Due to the limitation of computer-assisted implant planning and placement regarding accuracy (Tahmaseb *et al*. 2018; Schneider *et al*. 2019), the clinician should always allow an adequate safety margin for the relevant anatomic structures.

The following clinical situations may benefit from 3D radiographic diagnostics and planning as well as guided surgery (Dula *et al*. 2015; Wismeijer *et al*. 2018):

- In situations with limited vertical or horizontal dimension of the alveolar ridge in which, on the basis of the clinical examination, the two-dimensional X-ray images and the prosthetic diagnosis, a lateral bone augmentation (Fig. 44-14) or sinus elevation with lateral antrostomy is anticipated
- In situations where the two-dimensional X-ray images have failed to identify relevant anatomic structures (Fig. 44-15)
- In cases with unfavorable bone morphology and where there is low tolerance regarding the correct implant position
- If minimally invasive (e.g. flapless) surgery is intended
- When immediate implant restoration is planned, the use of CBCT in combination with guided surgery may be beneficial to obtain sufficient primary implant stability and to prepare the prosthetic reconstruction in advance.

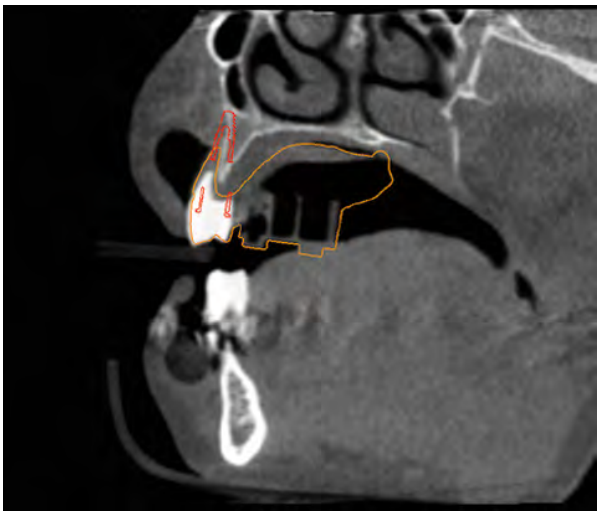


Fig. 44-14 Computer-assisted implant planning by superimposing the cone-beam computed tomography and the stereolithography data obtained from the diagnostic mock-up.

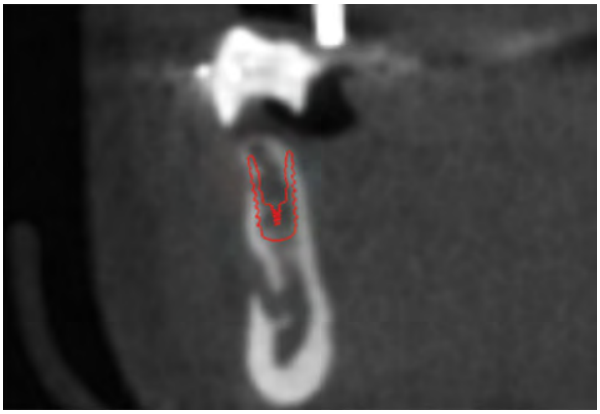


Fig. 44-15 Three-dimensional implant planning in a site with limited bone width.

General considerations and decision-making for implants in the posterior dentition

Decision-making between implant-supported reconstruction and tooth-supported fixed dental prostheses

The decision-making process between implant-supported reconstruction and tooth-supported FDPs and the related decision criteria should be derived essentially from scientific evidence and objective prosthetically oriented risk assessments, as well as patient-related factors, including cost effectiveness and quality of life.

In the clinical situation of a hopeless tooth in the posterior dentition, the therapeutic options are a conventional bridge or an implant-supported single crown (Fig. 44-16). In terms of a hierarchy of decisions, the most important question is whether or not the prognosis of an implant-supported reconstruction is similar to that of a tooth-supported FDP. A systematic review of implant-supported single crowns reported an estimated survival rate of 96.3% after 5 years (Jung *et al*. 2012). These results were similar to the data reported for tooth-supported FDPs, revealing a survival rate of 94.4% after 5 years (Pjetursson *et al*. 2015). From a prognosis point of view, neither of the two treatment modalities appear to be superior to the other. However, it has to be considered that the type of complications seems to be different with each modality. Conventional tooth-supported bridges reveal more biologic complications like caries and loss of abutment vitality, whereas implant-supported single crowns show more technical complications like abutment or occlusal screw loosening. This has an impact on the severity and the invasiveness of the therapeutic intervention during the maintenance phase.

At the next level in the hierarchy for the decision-making process is the clinical and anatomical assessment and the patient's expectations. The clinical analysis comprises the comprehensive evaluation of the neighboring natural abutment teeth, including their structural, restorative, periodontal, and endodontic status. This objective evaluation is of primary importance and represents an ever-increasing challenge to the clinician. This is illustrated by a maxillary posterior segment where both the first premolar and the first molar were missing (Fig. 44-17). The insertion of a five-unit tooth-borne FDP was considered too invasive given the intact canine, and also not suitable because of a slightly questionable status of the endodontically treated second premolar in view of its eventual use as a so-called "peer-abutment". Finally, an implant had been placed at the site of the missing first premolar and subsequently restored with a single-unit restoration. As the proximity of the maxillary sinus at the location of the missing first molar would have required a grafting procedure to make an implant installation possible, a three-unit tooth-supported FDP was ultimately chosen, after having duly discussed the relevant advantages and shortcomings with the patient. Having attributed a "strategic value" to the moderately compromised second premolar by using it as an abutment for a short-span bridge, there was still a difficulty in consistently establishing clinical treatment plans that were fully based on scientific evidence.

Finally, the patient's expectations and requests are very important in the decision-making process. Besides the prognosis and the invasiveness of the reconstruction, the patient will want to know the cost difference and the treatment time difference between implant-supported reconstructions and tooth-supported FDPs. In a retrospective clinical study performed in private practice, 37 patients received 41 conventional FDPs and 52 patients received 59 implant-supported single crowns (Bragger *et al*. 2005). The aim was to assess and compare the economic aspects by recording the number of visits, chair-side time, treatment costs, and costs for implant components and laboratory work. It was reported that the implant treatment required more visits than FDP treatment; however, the total

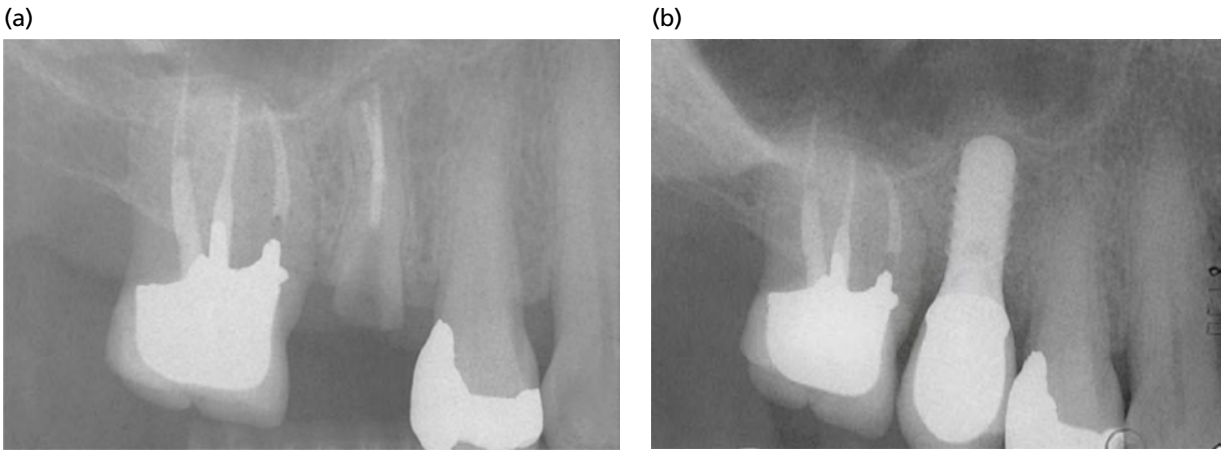


Fig. 44-16 (a) Ad hoc radiograph of the upper right posterior sextant. Note the presence of a structurally greatly compromised second premolar with a periapical pathology. Based on the clinical and radiographic assessment, tooth 15 was considered hopeless. (b) Postoperative radiograph shows that the root of the second premolar was replaced by a single-tooth implant restoration. In particular, the pre-existing metal–ceramic crown on the first molar could be maintained with this approach.

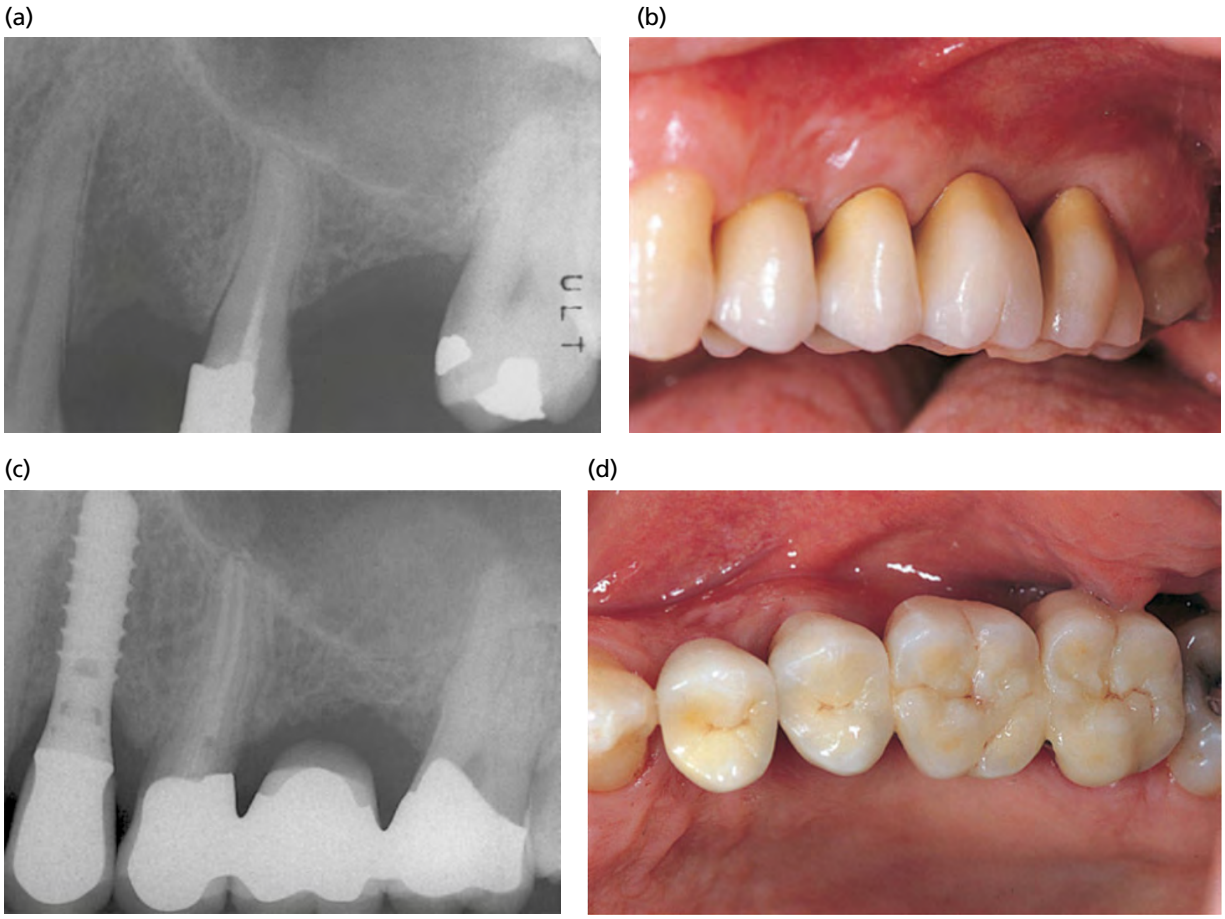


Fig. 44-17 (a) Preoperative radiograph of the left maxilla, revealing two missing dental elements. Note in particular an intact canine, a structurally reduced second premolar, and an extended recessus of the sinus in the area of the missing first molar. (b) Vestibular view of the prosthetic rehabilitation of the maxillary left quadrant: an implant-supported single-tooth restoration on the site of the first premolar, and a three-unit tooth-borne fixed dental prosthesis to replace the missing first molar. (c) Postoperative radiograph documents that an endodontic revision has been performed on the second premolar prior to its restoration with an adhesive carbon-fiber, post-based build-up and a metal–ceramic crown. (d) An identical prosthetic design has been applied for both the implant-supported and the tooth-supported restoration.

treatment time was similar. Regarding the costs, the laboratory costs and the total treatment costs were higher for FDPs than for implant-supported single crowns. Even when considering opportunity costs for each visit, the implant solution was less expensive. It was stated that over a short observation period of 1–4 years, the implant reconstruction demonstrated a more favorable cost-to-effectiveness ratio. Especially in clinical situations with either non- or minimally restored teeth and sufficient bone, the implant reconstruction can be recommended from an economic point of view (Bragger *et al*. 2005). These findings were further confirmed by a more recent systematic review indicating that implant-supported single crowns are more cost-effective than FDP (Beikler & Flemmig 2015).

Conclusion: The decision-making process between implant-supported reconstruction and tooth-supported FDPs should be based on the prognosis and the complication rate, the clinical assessment of the neighboring teeth and the anatomic condition of the edentulous area, and the patient's expectations.

Provisional reconstructions

The period of time between the beginning of therapy and implant loading in implant dentistry may amount to several months. Due to the functional, phonetic, and esthetic impairments during this period, it might be necessary to intermediately restore the edentulous region by means of a provisional reconstruction. Additionally, the provisional reconstruction may be indicated in order to test the ideal design of the final reconstruction, the patient's adaptation to the planned reconstruction, and it represents an important communication instrument between the patient, the dental technician, and the dentist.

The selection of the type of provisional has to be based on the patient's requirements, conditions of

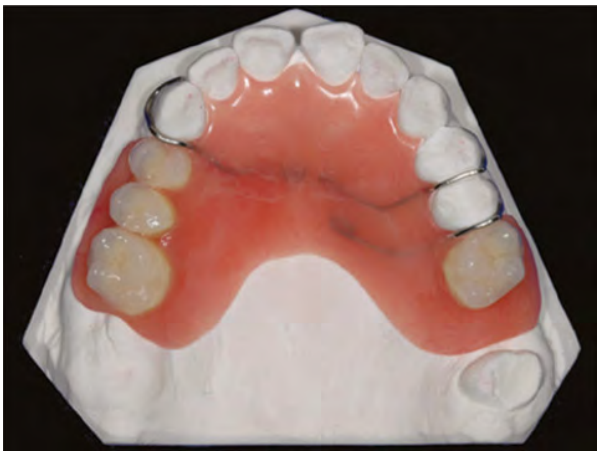


Fig. 44-18 Provisional removable partial denture.

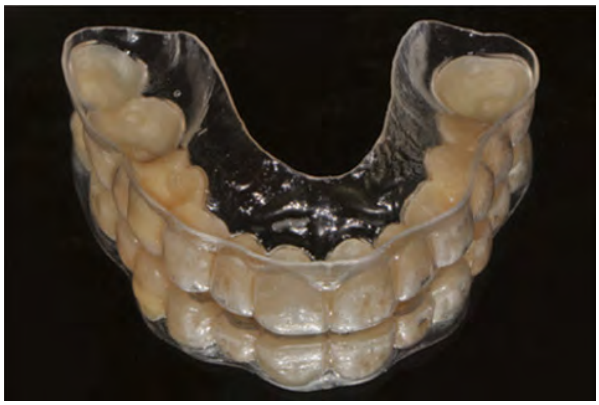


Fig. 44-19 Clear thermoplastic sheet containing pontics of the missing teeth.

the edentulous site, prosthetic requirements of the adjacent teeth, duration of the provisional phase, and financial considerations. The following types of temporary reconstruction are available:

- Removable partial denture (Fig. 44-18)
- Removable thermoplastic sheet containing pontics of missing teeth (Essix provisional) (Fig. 44-19)
- Provisional implant-borne fixed reconstruction with immediate (non-functional) loading
- Fixed partial denture (if full coverage of the adjacent teeth is required)
- Palatal implants (predominantly in patients undergoing simultaneous orthodontic treatment).

Resin-bonded partial dentures are generally unfavorable for the provisionalization of the posterior dentition due to the risk of debonding and fractures and significantly lower survival compared with resin-bonded bridges in the anterior zone (Thoma *et al*. 2017).

A correctly designed provisional should include the ability to accommodate changes of the underlying soft tissue and avoid uncontrolled pressure on healing implants and augmented regions.

Loading concepts

Loading concepts in implant dentistry have been widely discussed in the literature. Initially, healing phases of 3 months in the mandible and 6 months in the maxilla were recommended (Branemark *et al*. 1977). In order to meet the patients demands for earlier prosthetic rehabilitation, shortened healing periods between implant installation and loading were introduced. A variety of influencing factors, like initial implant stability, implant surface characteristics, bone quantity, bone healing, interim prosthesis design, and occlusal pattern during the healing phase, have been identified for successful osseointegration with modified loading protocols (Gallucci *et al*. 2018). Based on improvements primarily related to developments of the implant design (resulting in a higher primary stability) and surface modifications (resulting in an accelerated osseointegration), earlier time-points including immediate loading have been well documented (Gallucci *et al*. 2018).

Over time, the terminology for timing of loading has changed a few times. The most recent reference refers to the following terminology: "immediate loading or type A" is defined as a prosthesis in occlusion with the opposing arch within 7 days following implant placement; "immediate restoration or also type A" as a prosthesis held out of occlusion with the opposing arch within 7 days following implant placement; "early loading or type B" as a prosthesis being connected between 1 week and 2 months after implant placement; "conventional loading or type C" as a prostheses connected >2 months after implant placement allowing a longer healing period (Table 44.1) (Gallucci *et al*. 2018; Morton *et al*. 2018).

Concepts for partially edentulous patients

In patients with partially edentulous segments, various studies have confirmed high implant survival of immediately or early loaded compared with conventionally loaded implants. The respective mean survival rates range between 96% and 98.4% (Gallucci *et al*. 2018). These survival rates, however, do not take into account the considerable influence of the timing of implant placement as well as the fact that the majority of the studies on immediate and early loading were performed in the esthetic zone or using full-arch reconstructions. Thus, a more conservative approach combining late implant placement with early or delayed loading or immediate/early/

Table 44.1 Implant loading protocols. (Sources: Gallucci *et al*. 2018; Morton *et al*. 2018. Reproduced with permission of John Wiley & Sons.)

Loading protocol	
Type A	Immediate restoration/loading
Type B	Early loading
Type C	Conventional loading

late placement with conventional loading appears to be reasonable since these combinations are clinically well documented (Gallucci *et al*. 2018; Morton *et al*. 2018). Contributing factors in the posterior maxilla and mandible include cases of low implant stability including a complete lack of primary stability, extensive bone augmentation, or patient-related risk factors (e.g. parafunction, bruxism). In these cases, a conventional loading is recommended (Gallucci *et al*. 2018) (Table 44.1).

Loading concepts for single-tooth replacements

The load-bearing region of the maxilla and mandible present a higher risk and the decision on the timing of loading appears to be critical. The scientific evidence based on clinical studies applying immediate and early implant loading concepts for the posterior maxilla and mandible is increasing immensely, however (Ganeles *et al*. 2008; Nicolau *et al*. 2013). This is predominantly based on modifications of the implant design, surface, and the drilling protocol, ensuring a higher primary stability and a faster osseointegration.

Based on a clinical study, the comparison between immediate and early loading of implants in the posterior region did not demonstrate differences in terms of implant survival (Ganeles *et al*. 2008). Similar outcomes were reported for single implants in the posterior mandible with survival rates amounting to 97.4% (immediate) and to 96.7% (early) at 3 years post loading (Nicolau *et al*. 2013). Given this more recent clinical evidence, traditional loading concepts appear to be changing and at least the early loading concept might soon be considered as a standard of care.

It is important, however, to point out that the scientific documentation is almost exclusively based on studies with implants placed in sites with sufficient bone and without concomitant bone augmentation techniques. Therefore, little scientific documentation exists on outcomes of implants placed with simultaneous GBR procedures (Salvi *et al*. 2018). Depending on the size of the bone defect, it might be advisable to allow for longer healing periods after implant placement in conjunction with GBR (Jung *et al*. 2015) or sinus elevation procedures (Raghoebar *et al*. 2019). Human histologic data show a marked increase of bone in grafted sites between 6 and 8 months after augmentation (Cordaro *et al*. 2008). Clinical data for the augmented sinus recommend conventional loading protocols for dental implants placed with a lateral window or a transalveolar approach (Raghoebar *et al*. 2019). In clinical practice, loading of implants 3–6 months after placement together with GBR procedures has been documented to be a successful concept after 3–5 years of observation (Jung *et al*. 2015; Basler *et al*. 2018).

In general, immediate or early loading can be considered in patients with a high primary implant stability and without systemic risk factors or significant peri-implant bone defects. Splinted fixed reconstructions are favored over removable or single crown reconstructions in the posterior segments (Jung *et al*. 2018). Moreover, when considering immediate or early loading, reconstructions can be fabricated free from occlusal load as described earlier (Gallucci *et al*. 2018).

Splinted versus single-unit restorations of multiple adjacent posterior implants

In situations with multiple adjacent implants, the dentist faces the decision between fabricating either splinted or unsplinted implant crowns. The rationale for splinting implants is to evenly distribute loading forces on all the implants in order to minimize the stress on the marginal bone, implants, and prosthetic components. Dentists usually give the following reasons for splinting adjacent implants:

- Poor bone quality or major bone augmentation procedures (e.g. sinus floor elevation)
- Short implants or reduced diameter implants
- Anticipation of high occlusal forces (e.g. bruxism)
- Easier handling for the dentist (no adjustment of interproximal contacts is necessary).

The main arguments against splinting are:

- Perfect framework fit is more difficult to achieve with a multiunit FDP
- Interproximal hygiene is more demanding (if the use of interdental brushes or floss is hampered by the connector)
- Re-intervention is more complicated for multi- than single-unit FDPs (especially for cemented FDPs).

In the literature, the issue of splinting adjacent implants is controversial (Grossmann *et al*. 2005). Clinical studies directly addressing the issue reported no difference in survival rate or marginal bone loss between splinted and unsplinted implants (Clelland *et al*. 2016). Unsplinted implants nevertheless exhibited more technical complications such as screw loosening. More recently, a systematic review with meta-analysis assessed the marginal bone loss, implant survival rate, and prosthetic complications of splinted and unsplinted implant restorations. The study concluded that there were no differences in the marginal bone loss and prosthetic complications between splinted and unsplinted implant restorations. However, splinted restorations were associated with a decreased implant failure (de Souza Batista *et al*. 2019). The concept of splinting adjacent implants is also challenged by the evidence for high survival and success rates of unsplinted short implants particularly at the posterior region of the mandible (Ravida *et al*. 2019). It might be advisable, nonetheless, to splint restorations involving adjacent short implants (Jung *et al*. 2018). In general, there is no evidence that overloading of osseointegrated implants

is a phenomenon that occurs under standard clinical conditions (Lima *et al*. 2019). Thus, there is probably no need to distribute loading forces over several implants and no need to splint implants of standard diameter and length in sufficient bone quality and in patients without parafunctional habits.

Type of reconstruction(s)

When it comes to the prosthetic reconstruction of implants in the posterior region, the clinician has to decide on the type of retention and the material of the reconstruction. The decision is based on both general and clinical considerations:

- Does the implant angulation allow for screw-retention?
- How thick is the mucosa and how important are esthetics?
- What kind of reconstruction is planned: single unit/cantilever FDP/multiunit FDP (≥3 units).

Type of retention

The major advantages of screw-retained prostheses include retrievability and accessibility, facilitating replacement and maintenance of the reconstruction (Wittneben *et al*. 2017b). In addition, it is easier to shape the emergence profile with screw-retained implant provisionals and to transfer the contour to the master cast. Screw-retained restorations, nevertheless, usually involve more complex and more expensive laboratory procedures and can suffer from inherent mechanical complications such as screw loosening and fractures (Wittneben *et al*. 2017b). The presence of a screw access hole may impede the occlusal morphology and thus, interfere with the occlusion. Furthermore, the ceramic layer is thereby discontinued, which could have an impact on the stability of the ceramics in the long-term (Fig. 44-20).

In contrast to the screw-retained restorations, where the ideal implant axis is a prerequisite, a cemented reconstruction offers the option to better compensate for a suboptimal implant position (Wittneben *et al*. 2017b). The restoration of inadequately positioned implants is facilitated through cementation and the esthetics of the restoration can be enhanced since the screw access hole is not visible (Wittneben *et al*. 2014). One of the major advantages of cement-retained restorations therefore is the absence of a screw opening (Fig. 44-21). As well as the abovementioned advantageous esthetics, an optimal occlusal morphology and a sound ceramic layer are enabled (Hebel *et al*. 1997). Nonetheless, a variety of disadvantages for cemented reconstructions have been reported, including the difficulty of removing cement and thereby a higher risk of peri-implant disease, a more complex retrievability of the reconstruction, and the possibility of crown loosening due to loss of retention (Wittneben *et al*. 2017b; Monje *et al*. 2019).

Clinically, the choice between using screw-retained or cemented reconstructions is controversial and mostly depends on the preference of the clinician (Sailer *et al*. 2012; Wittneben *et al*. 2017b).

With regard to the survival of implants and restorations, no differences were reported based on systematic reviews focusing on the comparison of the

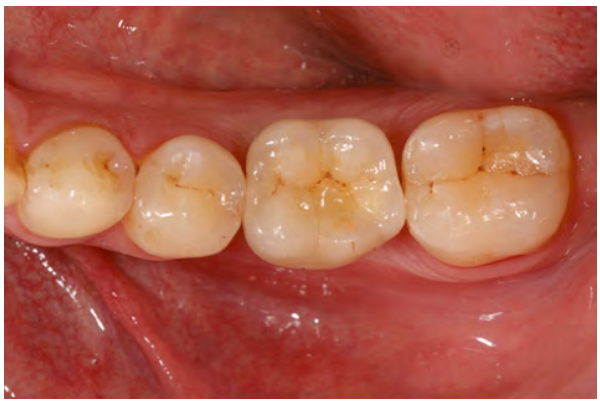
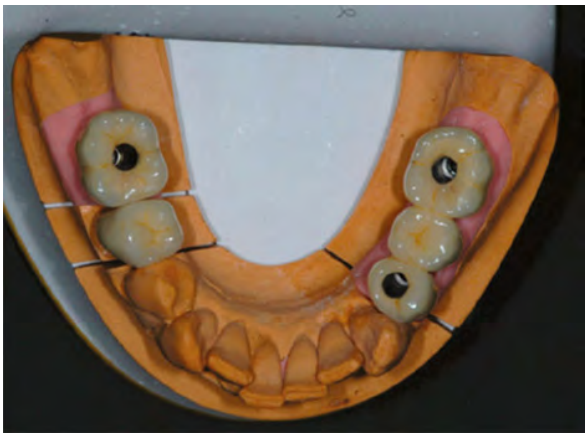


Fig. 44-21 Cement-retained implant supported crown at site 36.

(a)



(b)

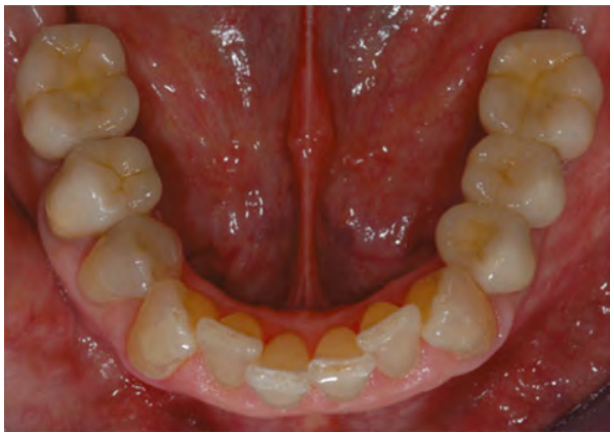


Fig. 44-20 Missing teeth (46, 34, 35, 36) in the posterior mandible. (a) The final screw-retained reconstruction on the master cast. (b) Screw-retained reconstruction with single implant crown (46) and screw-retained fixed dental prosthesis (35 × 37) after closing the screw-access holes.

two treatment modalities with survival rates being reported to range between 89.3% and 96.5% (single crowns) and between 96.9% and 98% for multiunit reconstructions (Sailer *et al*. 2012). Major differences, however, are reported in terms of the rate of complications. Screw-retained reconstructions predominantly suffer from technical complications, whereas cemented reconstructions are associated with a higher rate of major biological complications (Sailer *et al*. 2012).

Conclusion: On the basis of the existing scientific evidence, the decision to cement or screw-retain an implant restoration can rest on a clinician's personal preference when the implants are placed in a manner that allows both options (implant placement enabling optimal location of the screw access hole at screw-retained restorations). Ideally, the choice should depend on each particular patient situation, including anatomic, economic, and esthetic factors. However, from a clinical point and bearing in mind that technical rather than major biological is the "preferred" type of complications, screw-retention should be chosen whenever possible (Sailer *et al*. 2012; Wittneben *et al*. 2017b).

Selection criteria for choice of reconstruction materials

The posterior region of the jaw being the most load-bearing area mainly requires mechanically stable and biocompatible materials for the reconstructions. Today, a large variety of biocompatible materials is available due to the widespread use of CAD-CAM technology. Different factors are crucial to making the right decision between the optimal material and the reconstruction type for the posterior region (Muhlemann *et al*. 2018).

In general, a choice can be made between two kinds of abutments: prefabricated and customized. The decision-making process should be based on a variety of clinical, technical, and biologic factors. For implant reconstructions (irrespective of their location), an adequate emergence profile is a prerequisite for healthy soft (biologic width) (Sculean *et al*. 2014; Araujo & Lindhe 2018) and hard tissue integration, as well as ease of cleaning for the patient and a natural appearance. Prefabricated abutments have long been the treatment of choice due to the ease of use, decreased costs and a limited availability of individualized options. More esthetic concerns associated with a one-piece dental implant being placed deeper and an increased use of two-piece dental implants resulted in greater distances between the implant shoulder and the mucosal margin. This considerably increases the risk of cement excess (Monje *et al*. 2019). Therefore, the number of standardized abutments is decreasing and can only be proposed in clinical situations where the implant shoulder is close to the mucosal margin (Agar *et al*. 1997; Sancho-Puchades *et al*. 2017).

In addition, in molar areas, a large deviation between implant and crown diameters can often be found. In these situations, customized abutments in conjunction with the ideal emergence profile allow the crown margin to follow the present mucosal outline (Marchack 1996). Further conditions, like a limited vertical distance between the crown and the surrounding bone, a prosthetically inadequate implant position, and a thin highly scalloped mucosa, require customization of abutments even in posterior regions (Wittneben *et al*. 2017b).

A large variety of materials is available both for abutments (e.g. gold, titanium, alumina, and zirconia) and crowns (e.g. PFM) (Fenner *et al*. 2016), veneered zirconia (Heierle *et al*. 2019), veneered lithium-disilicate (Simeone & Gracis 2015), monolithic zirconia (Lerner *et al*. 2020), and lithium-disilicate (Joda *et al*. 2017). Metal abutments offer excellent material stability and exhibit superior clinical outcomes (Jung *et al*. 2012). For a long time they were considered to be the "gold standard" (Jung *et al*. 2008). Today, high strength ceramics are competing with the well-documented metal materials. Clinical mid- to long-term data are encouraging when used for single-tooth implants in the esthetic zone (Wittneben *et al*. 2017a; Heierle *et al*. 2019). However, it remains controversial whether or not use of the former in posterior regions is acceptable. Based on more recent systematic reviews, all-ceramic reconstructions based on one-piece abutments were associated with significantly higher fracture rates compared with metal-based treatment options (Pjetursson *et al*. 2018; Sailer *et al*. 2018c). Therefore, a more conservative approach applying metal-based reconstructions appears to be advisable in the posterior zone (Zarauz *et al*. 2020).

In order to overcome the abovementioned mechanical issues of one-piece zirconia abutments, so-called hybrid abutments were introduced. Hybrid abutments consist of a standardized titanium base. CAD-CAM-fabricated all-ceramic monolithic crowns can be extraorally cemented allowing these reconstructions to be screw-retained intraorally (Fig. 44-22) (Kurbad & Kurbad 2013). These reconstructions are widely used because of decreased costs, extensive availability for many implant systems, and the option of using various all-ceramic reconstruction materials. Based on *in vitro* experiments, hybrid abutments offer a strength comparable to that of metal abutments while still providing esthetic benefits of all-ceramic reconstructions (Sailer *et al*. 2018a). Unfortunately, clinical data exceeding 3 years and the lack of randomized controlled clinical trials limit to some extent a general recommendation for that kind of reconstruction (Joda *et al*. 2017; Asgeirsson *et al*. 2019). Scientific data on cantilever and multiunit FDPs using hybrid abutments and monolithic reconstructions are scarce but appear to offer the same benefits as single-unit hybrid abutments. Clinically, this type of reconstruction is increasingly being applied predominantly in the posterior region of the jaw.

Conclusion: Metal-based reconstructions are still considered to be the gold standard for the load-bearing zone of the jaw. Depending on the clinical situation, the anatomy and the position of the implant(s), screw-retained or cemented reconstruction are chosen. The

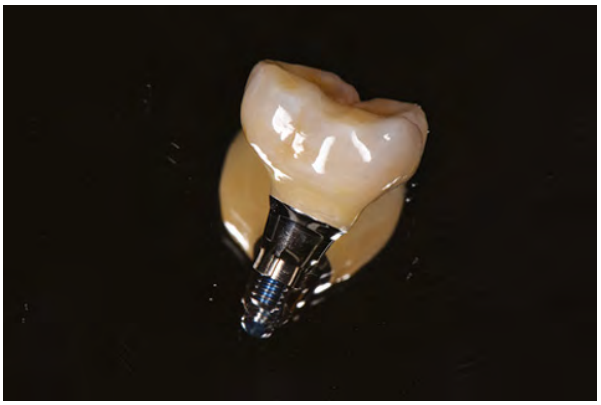


Fig. 44-22 All-ceramic zirconia crown cemented to a hybrid abutment with a titanium base.

use of monolithic hybrid reconstructions is increasing for single- and multiunit reconstructions offering two main advantages: decreased costs and high mechanical stability, thereby reducing the risk of chipping.

Decision tree

The clinical decision tree involves three steps:

1. Does the implant angulation allow for screw retention?
2. What kind of reconstruction is planned: single unit/cantilever FDP/multiunit FDP (≥3 units)
3. How thick is the mucosa and how important are esthetics?.

Figures 44-23 and 44-24 illustrate the decision tree for the selection of the type of retention, the type of reconstruction, and the type of material.

Applied clinical concepts

Therapeutic concepts at sites with sufficient bone quantity

Single-unit gap size

Premolar-size single-tooth restorations

All-ceramic tooth reconstruction on titanium implant A 65-year-old woman was referred from the endodontist because of a vertical root fracture on tooth 14. The patient requested a fixed reconstruction at site 14. The patient did not smoke and was without any underlying health conditions. After explaining and discussing the different treatment alternatives, the patient chose an implant-supported reconstruction to replace the missing tooth (Fig. 44-25).

All-ceramic reconstruction on a one-piece zirconia implant A 73-year-old woman was referred by her general dentist after endodontic failure of tooth 24. Tooth 24 was extracted 5 months prior to implant placement with a simultaneous ridge preservation procedure. The patient formerly smoked and was without any underlying health conditions. She requested a fixed reconstruction at position 24. Furthermore, the patient asked for a metal-free implant solution. After discussing the possible

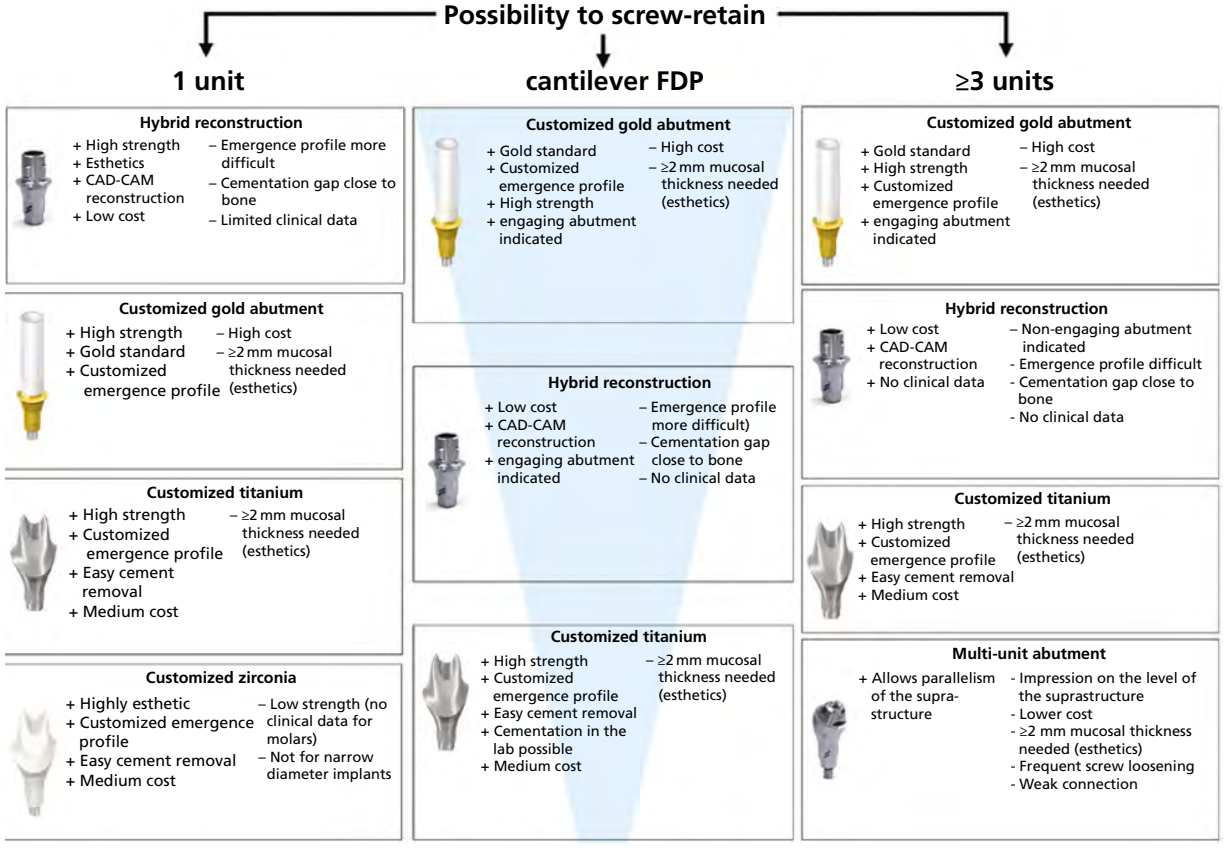


Fig. 44-23 Screw-retained decision tree.

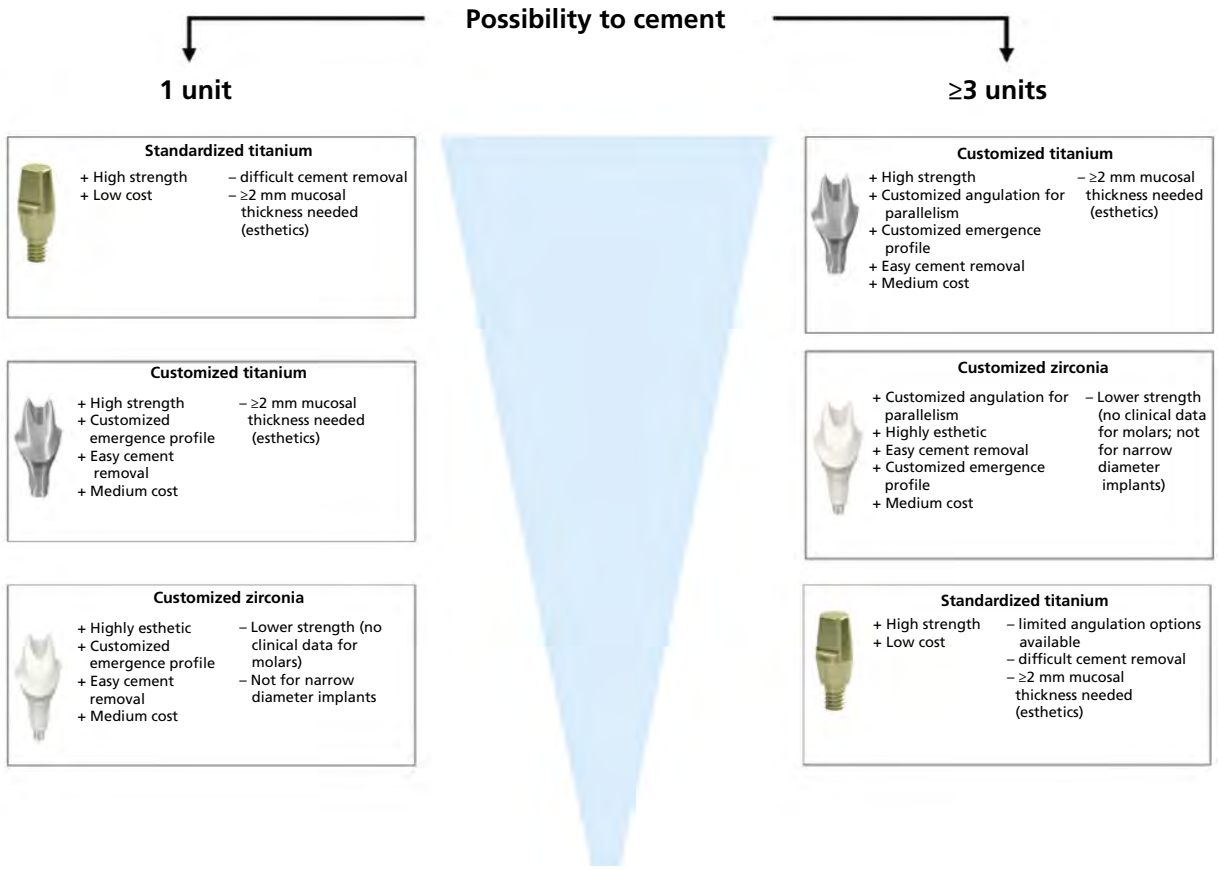


Fig. 44-24 Cement-retained decision tree.

treatment alternatives, an implant-supported crown using a zirconia implant was chosen. The patient was thoroughly informed about the advantages and disadvantages of zirconia implants in comparison with titanium implants. In addition, the patient was informed about the differences between one-piece and two-piece zirconia implants. Based on greater scientific evidence the patient chose a one-piece zirconia implant (Fig. 44-26).

Molar-size single-tooth restorations

A 69-year-old woman was referred by her general dentist for a restoration of a single-tooth gap at region 36. Tooth 36 was extracted due to a vertical fracture. The patient smoked fewer then 10 cigarettes a day and was systemically healthy. After having duly discussed the relevant advantages and shortcomings of implants with the patient, a standard titanium implant was chosen (Fig. 44-27).

Two-unit gap size

Two implants

A 73-year-old man was referred by his general dentist due to a vertical fracture of tooth 24 which supported a conventional tooth bridge (24–26). The patient did not smoke, was systemically healthy and requested a fixed and esthetic solution. After a thorough examination and discussion with the patient about the different treatment alternatives along with considering the good prognosis of the distal abutment tooth, it was decided to replace the two-unit gap size with two single implants (Fig. 44-28).

One implant with a cantilever

A 67-year-old woman was referred by her periodontist for a prosthetic rehabilitation at region 24–25. The patient, originally diagnosed with severe periodontitis, demonstrated a high standard of self-performed plaque control and all lesions in the periodontal tissues had been resolved. The patient wanted to increase her chewing comfort and therefore there was a need for a prosthetic rehabilitation in the posterior region of the maxilla. Furthermore, the patient, if possible, preferred to have fixed prosthetic reconstructions. After discussing the different alternatives with the patient along with considering her expectations, the morbidity, and particularly the costs, a single-tooth implant reconstruction with a mesial cantilever was chosen. The patient was informed that the treatment with a cantilever encounters a higher risk of technical complications compared with two implants with two single implant crowns (Halg *et al*. 2008) (Fig. 44-29).

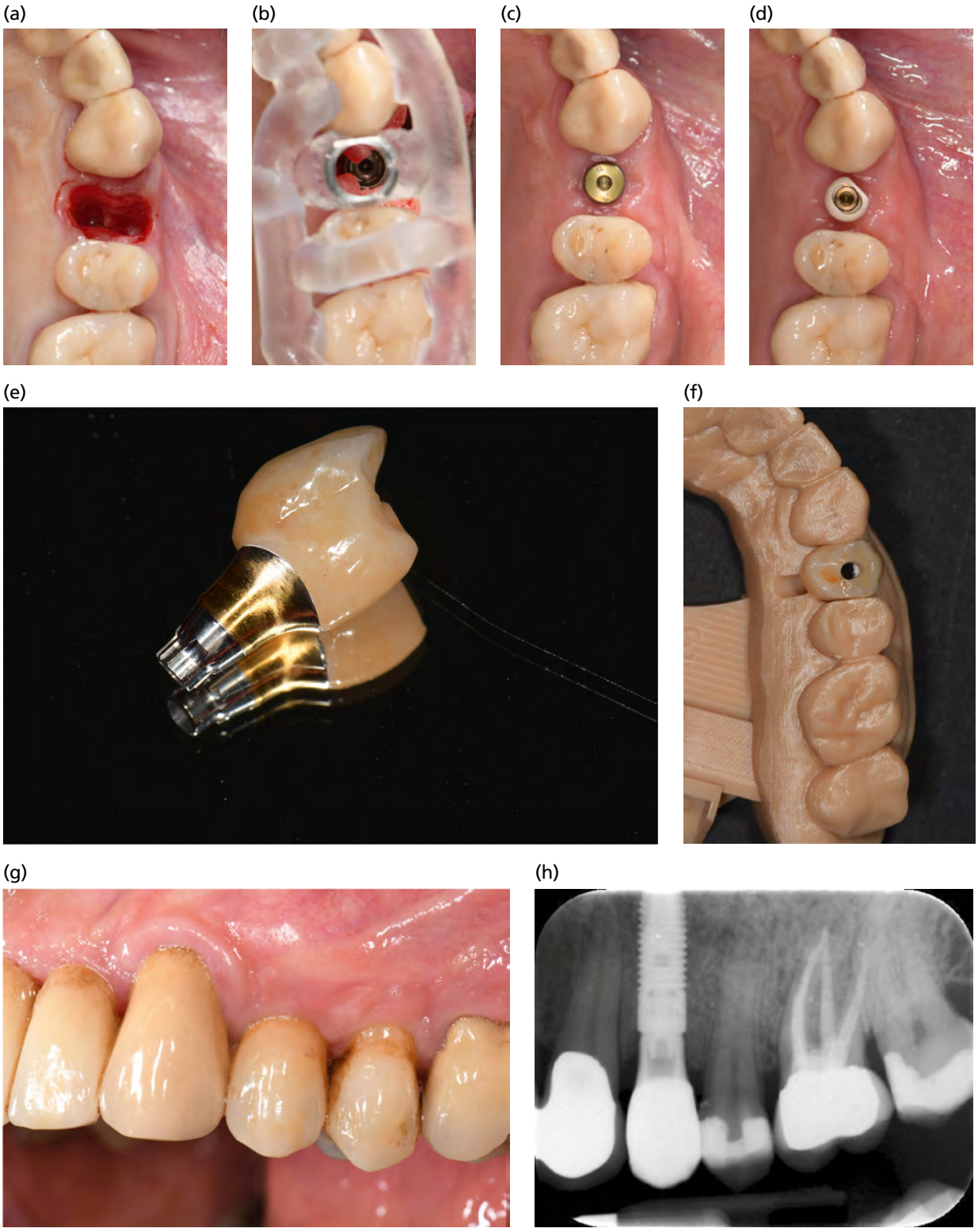


Fig. 44-25 (a) Clinical situation immediately after tooth extraction of tooth 24. The occlusal view reveals favorable soft and hard tissue conditions with an intact buccal bone plate. (b) Implant placement using a computer-assisted implant planning and placement (CAIPP) protocol. A 3D-printed surgical stent was placed to foster a prosthetically driven implant positioning. (c) Transmucosal healing 2 weeks after implant insertion with a healthy mucosa and a sufficient width of keratinized tissue. (d) Scan body mounted onto the implant serving as a digital reference for the digital impression by using an intraoral scanner. (e) For the screw-retained implant reconstruction a customized CAD-CAM-processed titanium abutment with an all-ceramic zirconia crown was fabricated. The veneered zirconia crown had been cemented to the titanium CAD-CAM abutment in the dental laboratory. (f) Screw-retained reconstruction fitted on the printed model. (g) Two weeks after all-ceramic crown delivery, showing healthy soft tissues and a sufficient amount of keratinized tissue. (h) Periapical radiograph reveals optimal osseointegration at the 1-year follow-up.

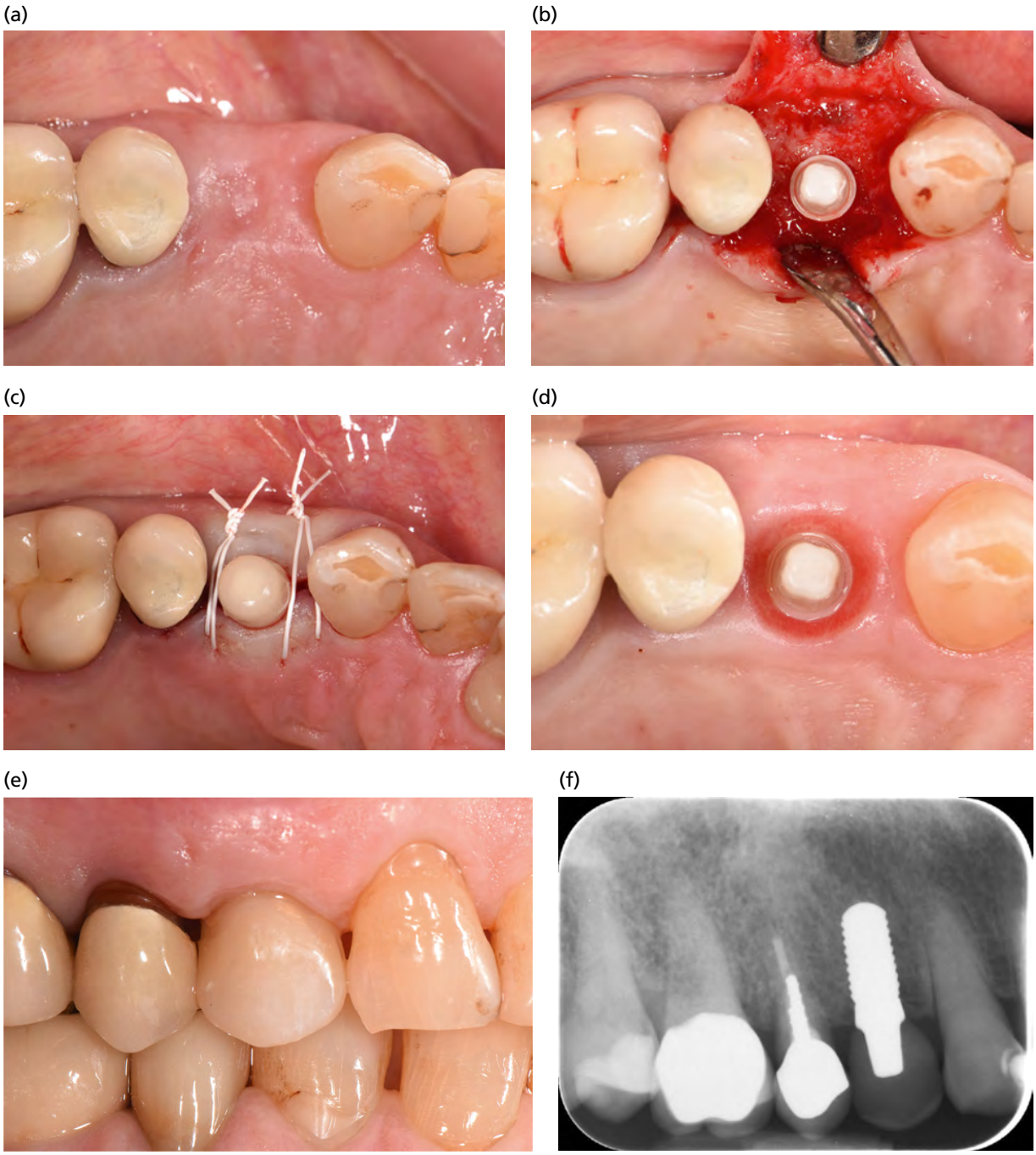


Fig. 44-26 (a) Preoperative single-tooth gap in the area of 14, with sufficient horizontal bone volume and sufficient keratinized mucosa. (b) Intraoperative situation after moderate flap elevation and the insertion of a one-piece zirconia implant. The implant shoulder was placed about 1.5 mm above the bone crest. (c) A temporary cap has been placed on the one-piece implant. Subsequently, the flap was adapted around the neck of the implant with two non-resorbable ePTFE sutures for transmucosal healing. (d) After 3 months of transmucosal healing, the zirconia implant is surrounded by healthy peri-implant tissues. At this time-point an implant impression was performed to initiate the prosthetic treatment. (e) Cemented zirconia implant crown at the 1-year follow-up with healthy and stable peri-implant soft and hard tissues. (f) Periapical radiograph reveals an optimal osseointegration of the one-piece zirconia implant with stable marginal bone levels after 5 years in function.

Multiunit gap size (≥3 missing teeth to be replaced)

Three-unit bridge

A 65-year-old patient was referred by her general dentist for a fixed reconstruction at region 35–37. Due to the presence of extensive caries and the poor prognosis of those teeth, a tooth-supported fixed dental prosthesis was not reasonable. After discussing the different alternatives with the patient along with considering her expectations and costs, a three-unit implant-supported bridge was chosen (Fig. 44-30).

Two implants with a cantilever

A 77-year-old woman presented to the dental clinic with a large edentulous area at region 13–17. The patient previously smoked, was systemically healthy,

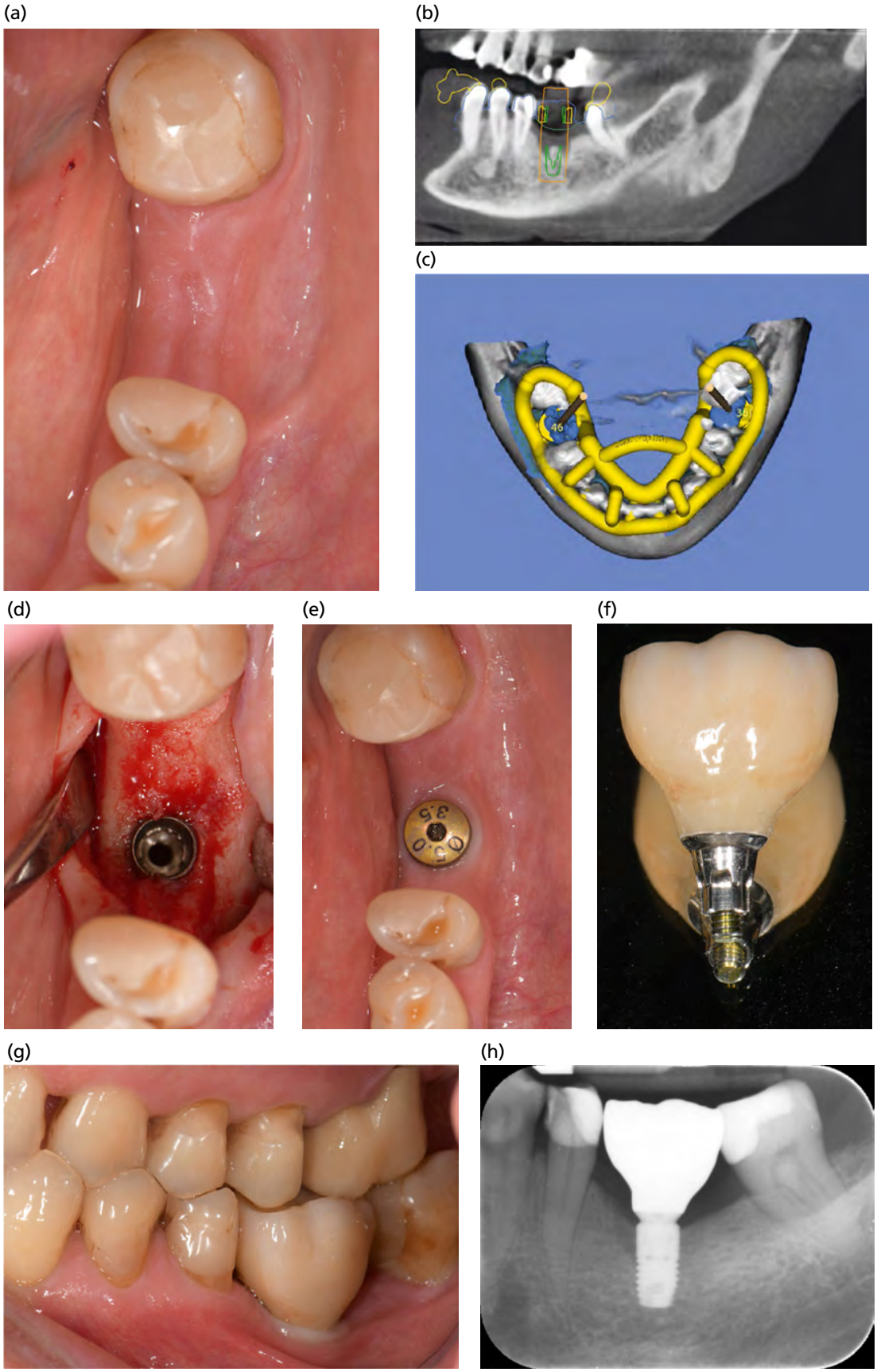


Fig. 44-27 (a) Preoperative single-tooth gap in the area of 36, with sufficient horizontal bone volume and sufficient keratinized mucosa. (b) Computer-assisted implant planning based on cone-beam tomography data. (c) 3D surgical guide based on the integration of the three-dimensional computer-tomography and the stereolithography data obtained from the diagnostic mock-up. The surgical 3D-printed guide allows for a prosthetically driven implant placement. (d) Intraoperative situation following flap elevation and implant insertion in a prosthetically driven position. (e) Clinical situation after 3 months of healing showing healthy peri-implant tissues and sufficient keratinized mucosa. (f) For the screw-retained CAD-CAM implant reconstruction a stock hybrid abutment with a titanium base was used. The CAD-CAM crown made out of zirconia had been cemented to the hybrid abutment in the dental laboratory. Alternatively, and in case a higher translucency is required, a monolithic lithium disilicate (LDS) crown can be fabricated (see Fig. 44.34h). (g) All-ceramic crown at region 36 right after crown insertion revealing an ischemic zone at the marginal gingiva. (h) Periapical radiograph showing the titanium implant with stable marginal bone levels at the 1-year follow-up.

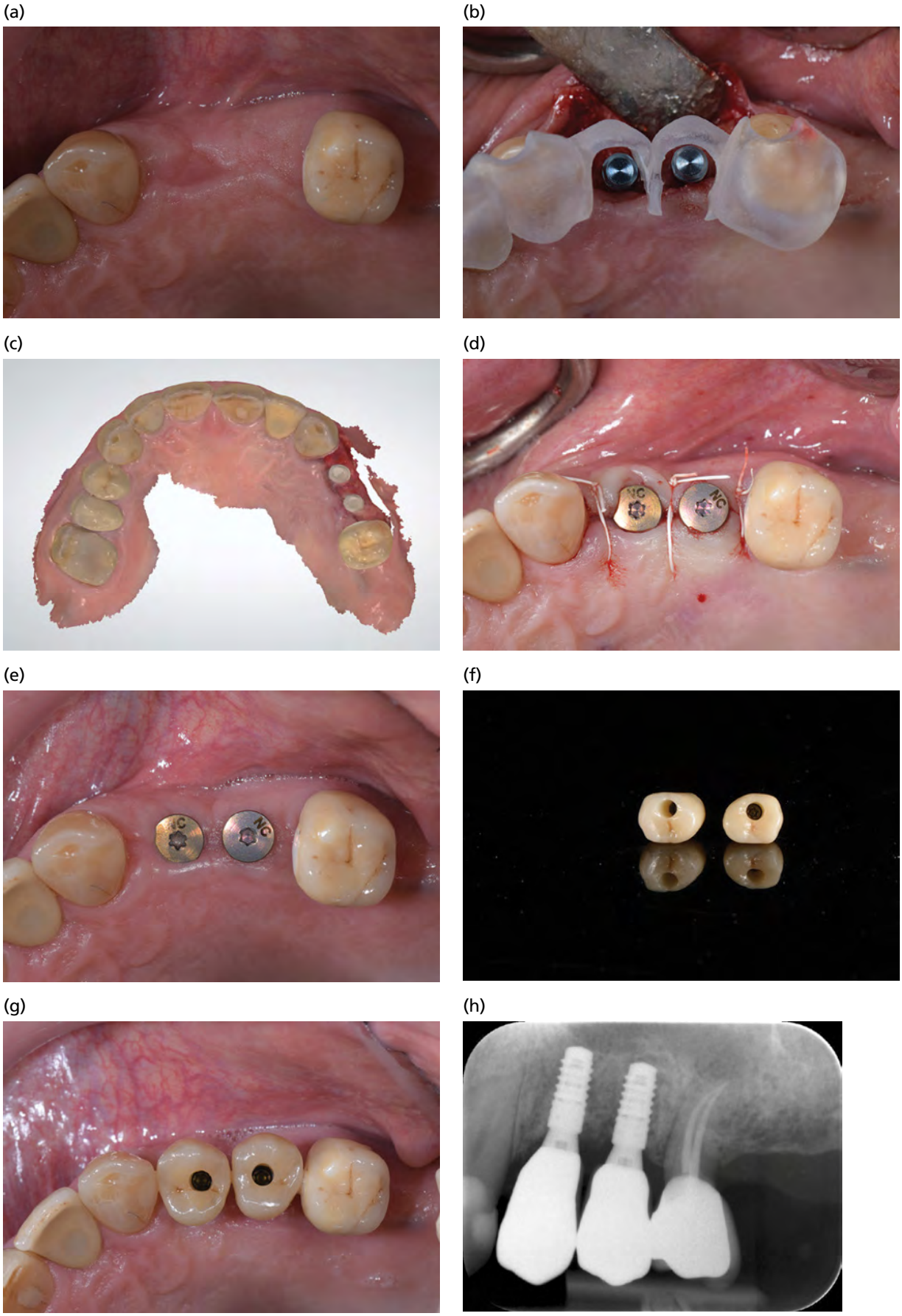


Fig. 44-28 (a) Preoperative two-unit gap size in the area of 24 and 25 showing sufficient horizontal bone volume and sufficient keratinized mucosa. (b) Intraoperative situation following flap elevation and implant insertion in a prosthetically driven position. (c) Digital impression taken with an intraoral scanner (IOS). The scan bodies had been mounted onto the implants serving as a digital reference. (d) Flap closure and adaptation around the healing abutment with two non-resorbable ePTFE sutures for transmucosal healing. (e) Clinical situation after 4 months of healing showing healthy peri-implant tissues and sufficient keratinized mucosa. (f) Screw-retained CAD-CAM implant reconstructions using a stock hybrid abutment with a titanium base. The CAD-CAM crowns were made out of monolithic zirconia and had been cemented to the hybrid abutment extraorally. (g) All-ceramic crowns at region 24 and 25 right after crown insertion. (h) Periapical radiograph revealing an optimal osseointegration of both implants at the crown delivery.

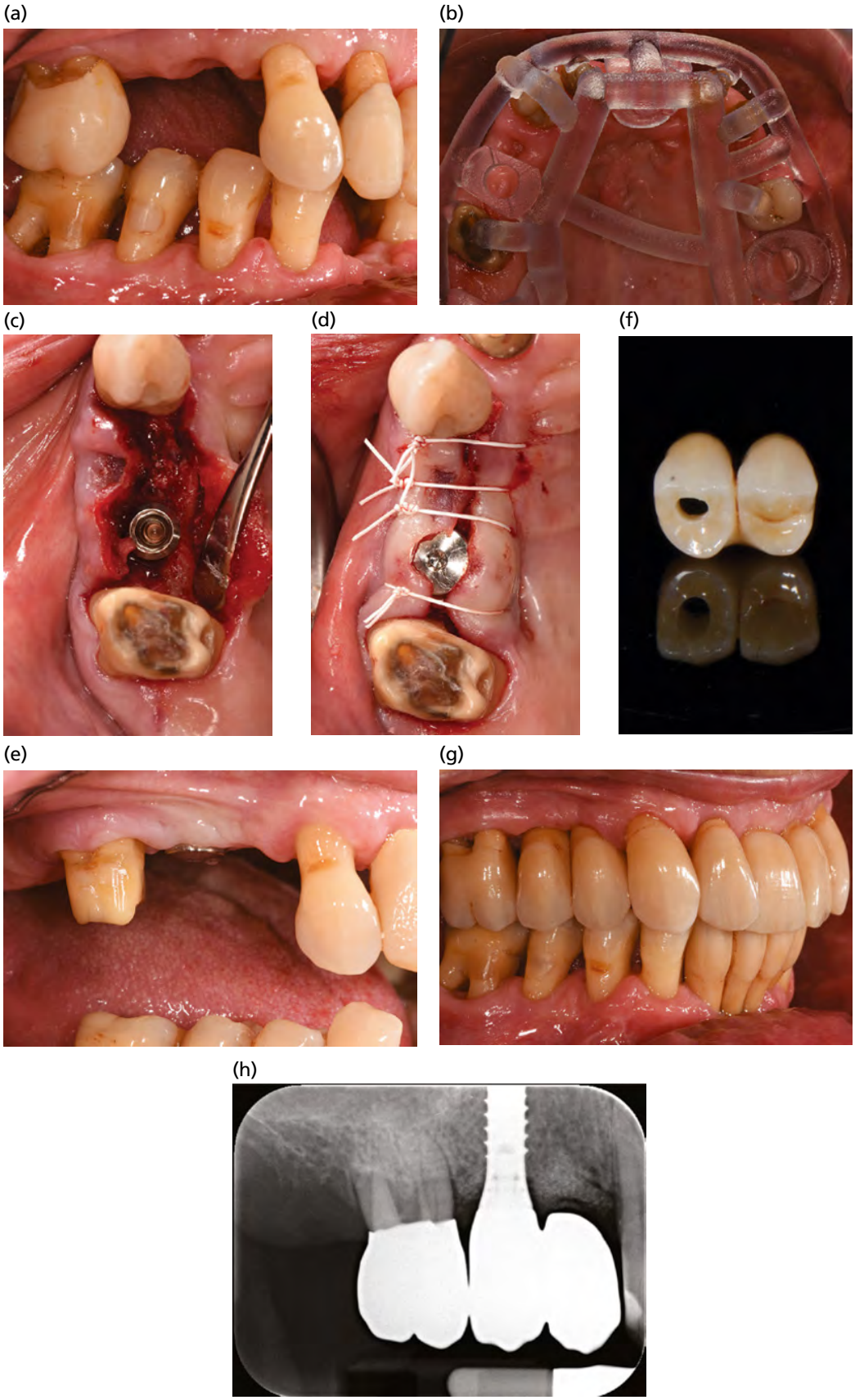


Fig. 44-29 (a) Preoperative clinical situation with a two-unit tooth gap in the area of 15 and 14 with sufficient horizontal bone volume and sufficient keratinized mucosa. (b) 3D-printed surgical stent based on the superimposition of the cone-beam computed tomography and the stereolithography data obtained from the diagnostic mock-up. (c) Intraoperative situation following flap elevation and implant insertion in a prosthetically driven position. In addition, an osteoplasty had been performed in order to level the alveolar ridge. (d) Flap closure and adaptation around the healing abutment with two non-resorbable ePTFE sutures for transmucosal healing. (e) Clinical situation after 3 months of healing exhibiting healthy conditions around the implant including a sufficient width of keratinized tissue. (f) For the screw-retained crown and the mesial cantilever a reconstruction made out of zirconia was chosen. The zirconia reconstruction was buccally veneered and was subsequently cemented extraorally to a stock hybrid abutment with a titanium base. (g) All-ceramic reconstruction delivery at region 15 with the mesial cantilever, showing healthy peri-implant tissue conditions along with sufficient keratinized tissue. (h) Periapical radiograph implant-supported reconstruction with the mesial cantilever revealing optimal osseointegration and stability of the marginal bone levels at 6-month follow-up.

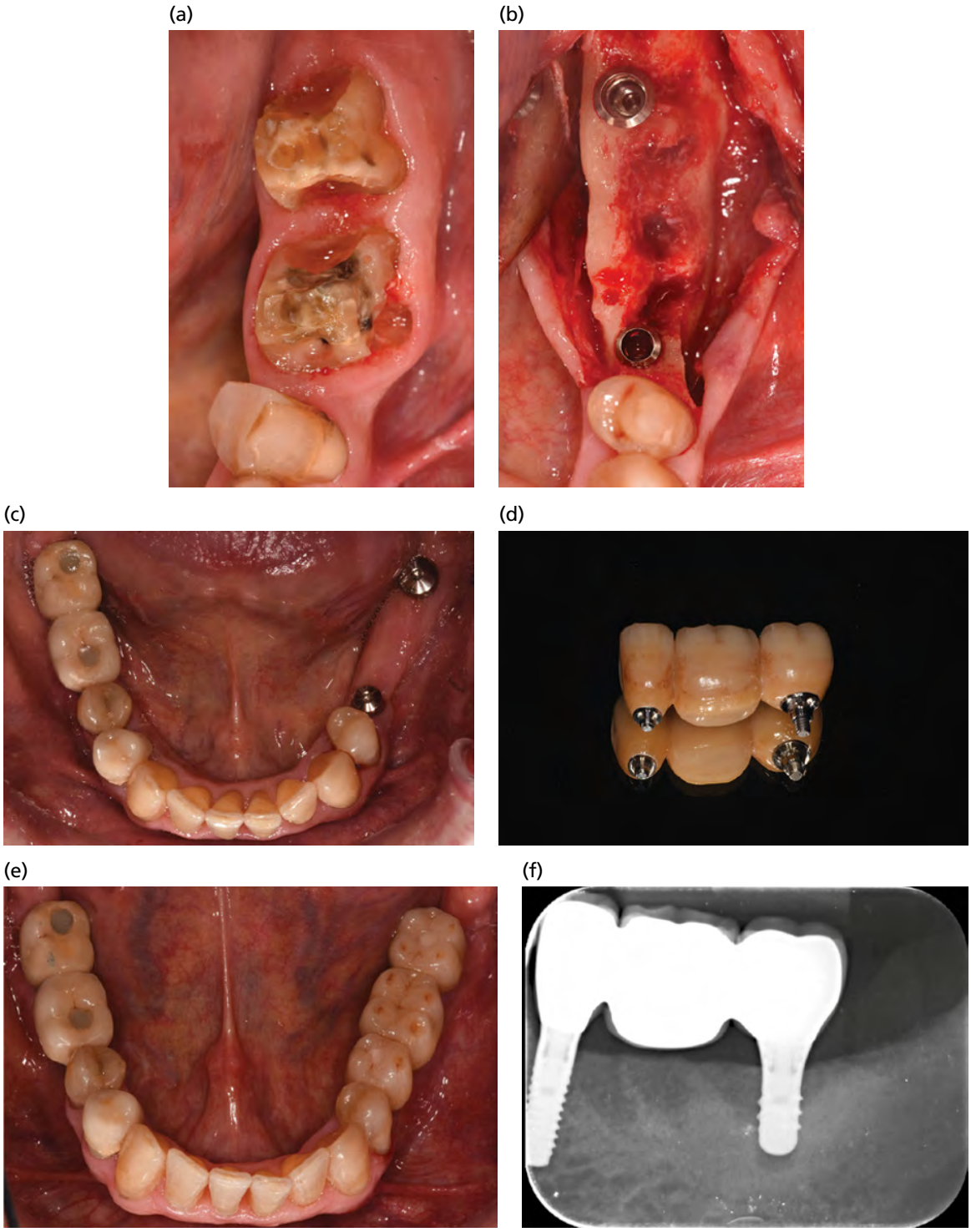


Fig. 44-30 (a) Clinical situation after the removal of metal–ceramic crowns and caries. The caries lesions surrounded the natural teeth abutments and extended into the root canal therefore the extraction of teeth 36 and 37 was indicated. (b) Intraoperative situation after the placement of two one-piece implants, one at region 35 and one at region 37. In addition, an osteoplasty was performed in order to level the alveolar ridge. The tooth extraction had been performed 2 months before implant placement. (c) Clinical situation after 3 months of transmucosal healing showing healthy peri-implant tissues and sufficient keratinized mucosa. (d) Screw-retained implant reconstruction made out of zirconia cemented extraorally to a titanium base. (e) All-ceramic 3-unit implant-supported bridge following insertion. (f) Periapical radiograph of the 3-unit implant-supported bridge at 6-month follow-up exhibiting stable marginal bone levels.

and her chief complaint was reduced chewing comfort. The patient also wanted to improve the esthetic appearance and, if it was possible, requested fixed prosthetic reconstruction. Furthermore, she stressed that she wanted as few surgeries as possible. After discussing the different alternatives with the patient, considering her expectations, the costs, and particularly the morbidity of the treatment, two single implants with a distal cantilever with a flapless approach was selected (Fig. 44-31).

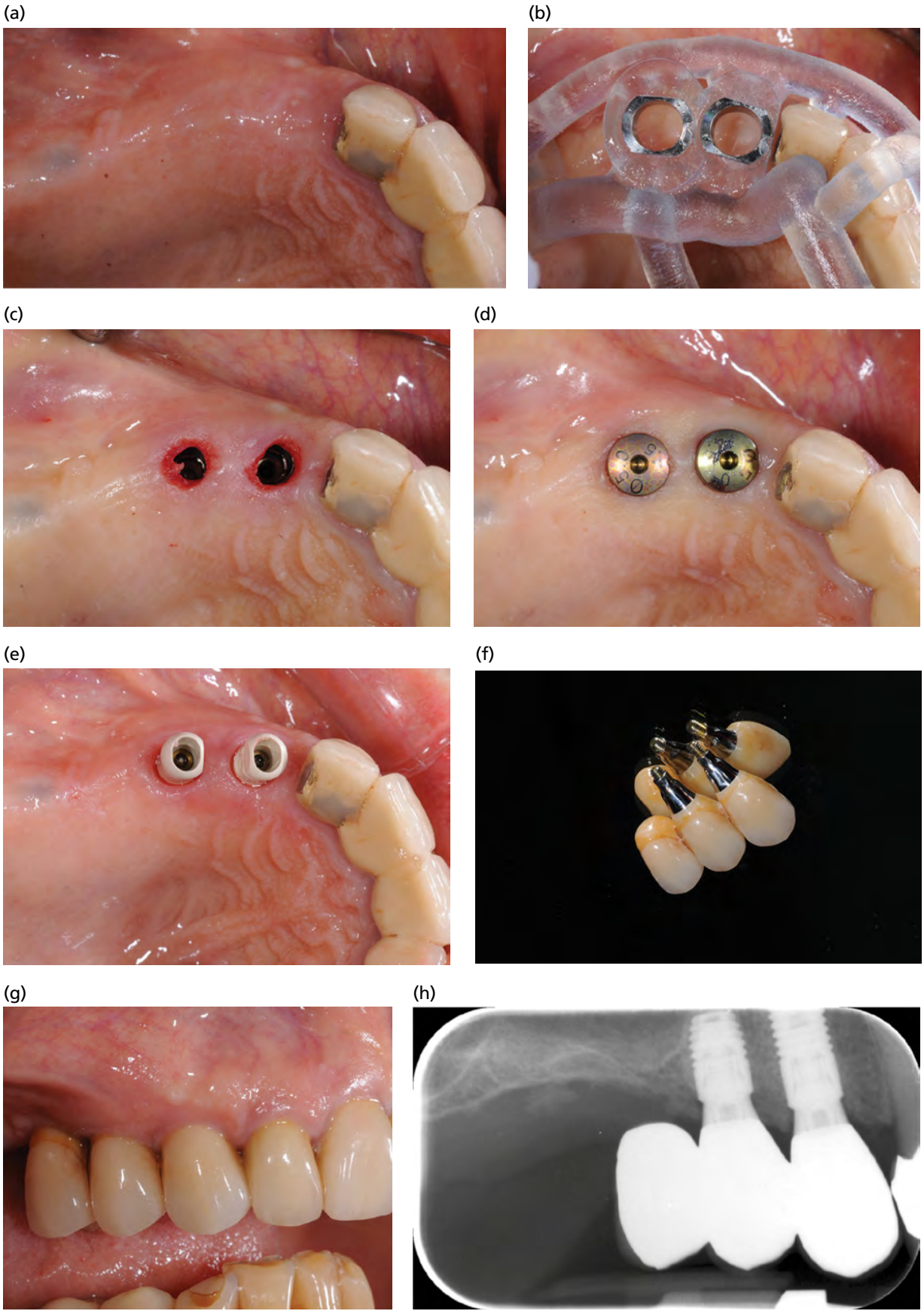


Fig. 44-31 (a) Preoperative clinical situation with a large edentulous area at region 13–17 with sufficient horizontal bone volume and sufficient keratinized mucosa. (b) Flapless implant surgery using a computer-assisted implant planning and placement (CAIPP) protocol. A 3D printed surgical stent was placed to foster a prosthetically driven implant positioning. (c) Clinical situation following implant placement. (d) Following implant placement, two healing abutments are placed for transmucosal healing. (e) After a healing period of 3 months, scan bodies are mounted onto the implants to serve as a digital reference for the digital impression with an intraoral scanner. (f) Splinted screw-retained implant crowns made out of zirconia cemented extraorally to a stock titanium abutment with titanium base. (g) All-ceramic reconstruction following insertion exhibiting healthy peri-implant soft tissues and satisfactory esthetics. (h) Periapical radiograph revealing optimal osseointegration following the insertion of the 3-unit final reconstruction.

Therapeutic concepts at sites with insufficient bone quantity

Short dental implants

A 50-year-old woman presented to the dental clinic with a single-tooth gap at region 16. The patient did not smoke and had no underlying health conditions. The chief complaint was the absence of tooth 16. The patient requested, if it was possible, a fixed reconstruction without many surgeries. Considering the patient's expectations, particularly regarding morbidity, and after discussing the different alternatives, a short single implant was finally chosen (Fig. 44-32).

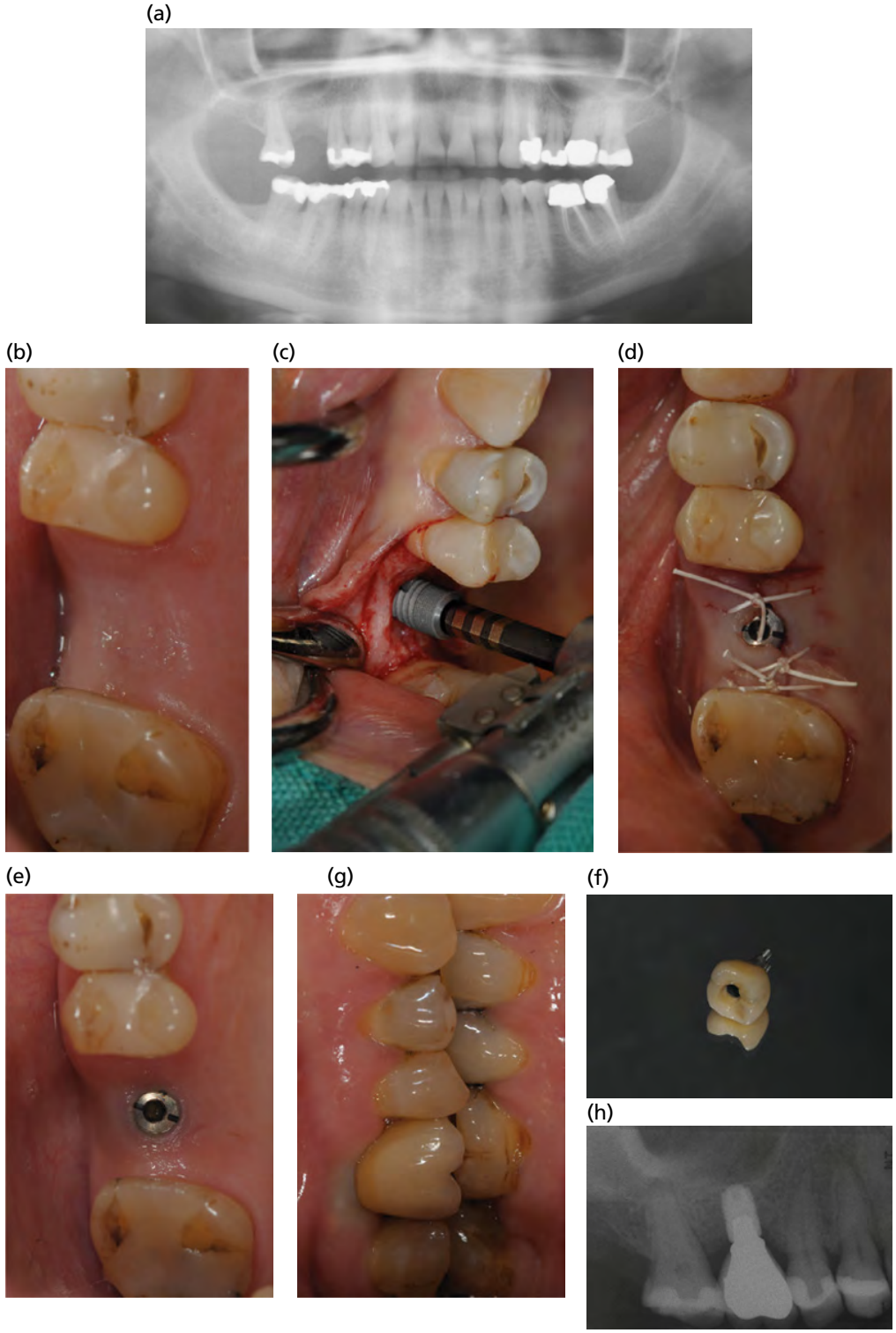


Fig. 44-32 (a) Panoramic radiograph evaluation revealing the proximity of site 16 to the sinus floor precluding implant placement of a regular length implant without sinus floor elevation. (b) Preoperative clinical situation of the single-tooth gap with sufficient keratinized tissue and an optimal amount of space for a single implant. (c) Implant insertion following flap elevation. (d) Flap closure and adaptation around the healing abutment with non-resorbable ePTFE sutures for transmucosal healing. (e) Three months after implant placement revealing healthy peri-implant tissues. (f) Screw-retained reconstruction based on a porcelain-fused-to-metal crown. (g) Clinical situation right after crown insertion showing an ischemic zone at the marginal gingiva. (h) Periapical radiograph at 6-year follow-up revealing an optimal osseointegration and stability of marginal bone level.

Narrow-diameter implants

A 56-year-old patient was referred by the orthodontist to replace the single-tooth gap at region 45. The orthodontist recommended distributing spaces, closing the diastemata, and uprighting the mesially tilted molars in order to create enough space for a fixed reconstruction at region 45. The patient was systemically healthy and did not smoke. Considering the healthy condition of the neighboring teeth, the site region (premolar area), the patient's expectations, and especially the limited mesiodistal amount of space, an implant-supported crown using NDIs made out of titanium-zirconium was chosen (Fig. 44-33).

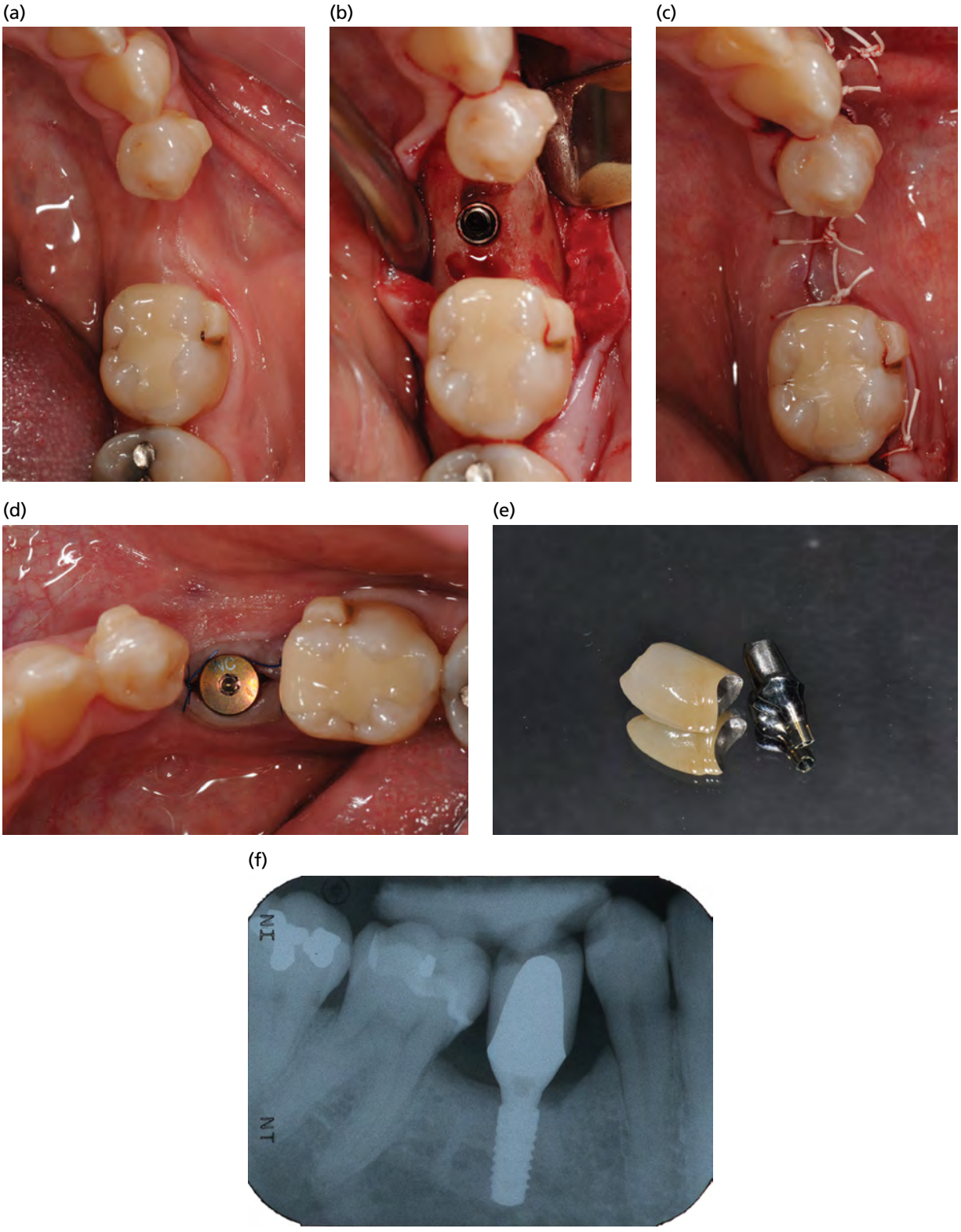


Fig. 44-33 (a) Preoperative clinical situation of a single tooth gap with reduced bucco-oral bone dimension and limited mesiodistal amount of space. (b) Intraoperative situation following flap elevation and insertion of a 3.3 mm titanium-zirconium implant in a prosthetically driven position. (c) Flap closure with ePTFE sutures for submerged healing. (d) Abutment connection after 3 months of submerged healing showing healthy peri-implant tissues and sufficient keratinized mucosa. (e) Screw-retained reconstruction made out of a porcelain-fused-to-metal crown. (f) Periapical radiograph of the one-piece narrow-diameter implant at 3-year follow-up revealing an optimal osseointegration and stability of the marginal bone level.

Maxilla–sinus floor elevation procedures

A 65-year-old patient was referred to replace the single-tooth gap at region 26. The patient wanted to increase his chewing comfort and if possible, preferred to have a fixed prosthetic reconstruction. The patient did not smoke and was systemically healthy. Considering the patient's expectations along with the healthy condition of the neighboring teeth an implant fixed reconstruction was chosen. In order to examine the bone height and volume at the implant region a CBCT was indicated. The results of the CBCT revealed insufficient bone height precluding a regular implant placement or an implant placement with minor sinus floor elevation using the osteotome technique. Therefore, a maxillary sinus floor elevation at region 26 using the lateral approach was chosen (Fig. 44-34).

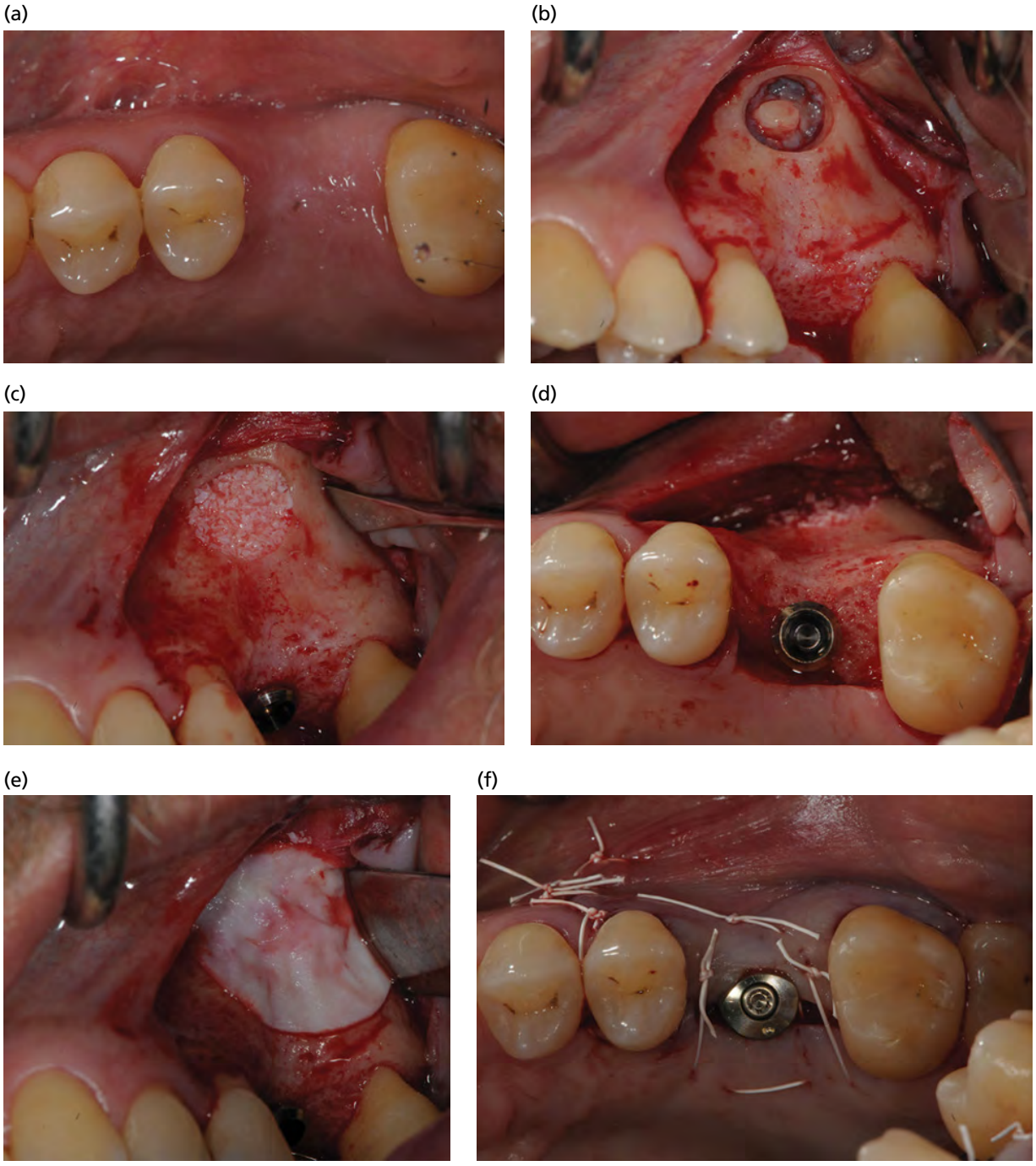


Fig. 44-34 (a) Preoperative clinical situation with a single-tooth gap with sufficient keratinized mucosa. (b) Outline of the small lateral window revealing the bluish hue of the sinus membrane. (c) After removing the buccal bone, the Schneiderian was carefully elevated to obtain access to the sinus floor. Thereafter, the implants were placed and subsequently the sinus compartment was filled with deproteinized bovine bone materials. (d) Intraoperative situation following sinus floor elevation and implant insertion of a one-piece implant in a prosthetically driven position. (e) Lateral window covered with a resorbable collagen membrane. (f) Flap closure and adaptation around the healing abutment with non-resorbable ePTFE sutures for transmucosal healing.

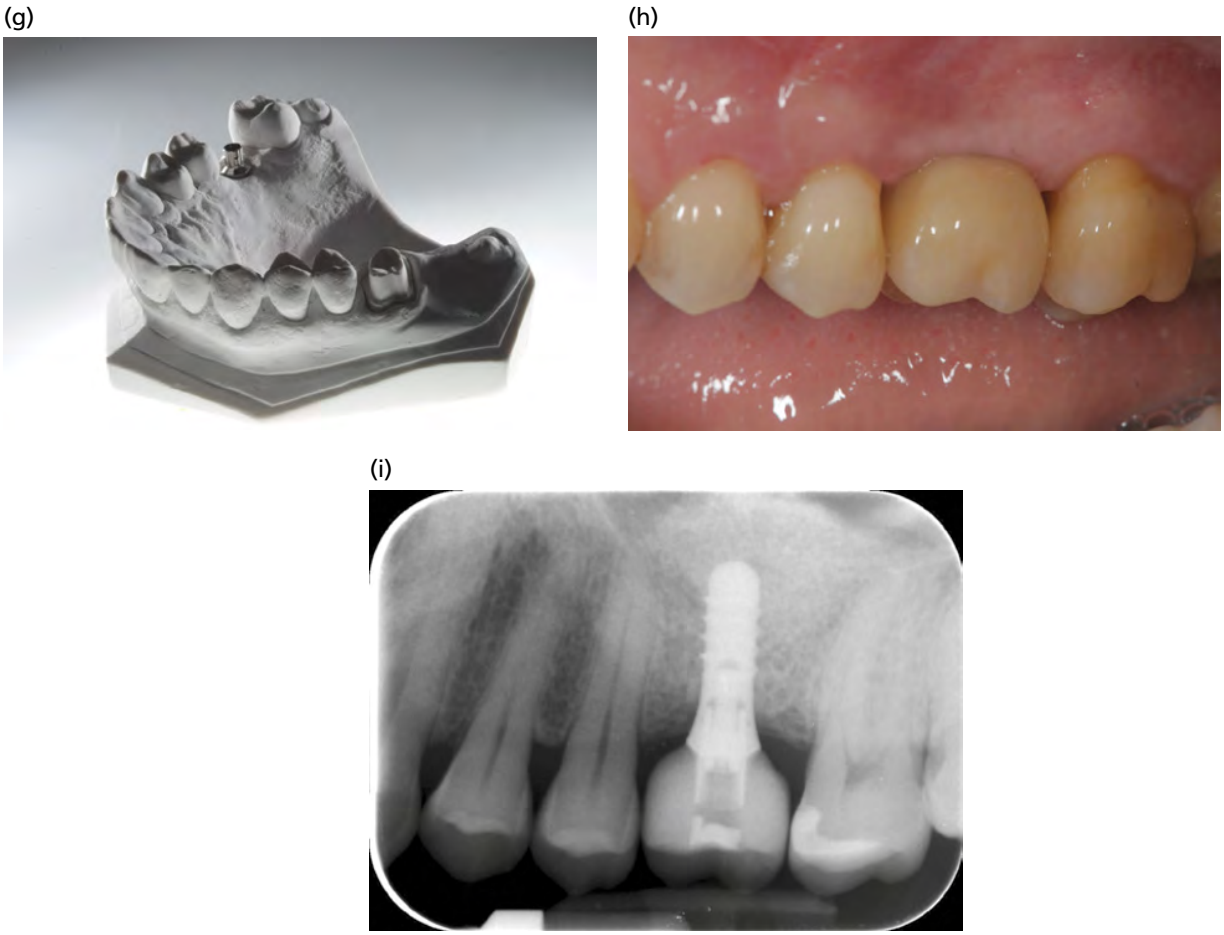


Fig. 44-34 (*Continued*) (g) For the screw-retained CAD-CAM implant reconstruction a stock hybrid abutment with titanium base was used. (h) Final implant supported crown made out of monolithic lithium disilicate (LDS) that was extraorally cemented to the hybrid abutment. (i) Periapical radiograph revealing an optimal osseointegration and a new inferior border of the maxillary sinus with a stable graft volume at the 2-year follow-up.

Acknowledgment

The authors gratefully acknowledge the help of the Drs. Ásgeir Ásgeirsson, Alexis Ioannidis, Roman Schellenberg, Lukas Stucki, and Prisca Walter (Clinic of Reconstructive Dentistry, University of Zurich, Switzerland) for their clinical contribution and their help in preparing the clinical cases for this chapter.

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Chapter 45

Implants in the Zone of Esthetic Priority

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Introduction

Today, in modern reconstructive dentistry, nobody would doubt the importance of esthetics as a primary outcome variable in the prosthetic rehabilitation of missing teeth. The loss of one or more teeth in the zone of esthetic priority may impair the esthetic appearance of the patient and, therefore, any treatment modality for reconstruction of the lost tissues must address both functional and esthetic outcomes.

In the last decade, much has been published concerning the promising esthetic results of prosthetic restorations supported by endosseous implants (Belser *et al*. 2009; Chen & Buser 2014; Hartlev *et al*. 2014; Slagter *et al*. 2014). Additionally, the main etiological factors for adverse outcomes have been described (Hammerle & Tarnow 2018). Despite scientific efforts to shed light on the causative aspects of esthetic failures, the many congresses and courses focusing on esthetics and implants, and publications aimed at educating clinicians, altered esthetic results

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

after placement of implant-supported reconstructions in the upper anterior area, with and without malpractice claims, still occur (Bordonaba-Leiva *et al*. 2019).

How can this chapter contribute to reducing errors in treatment planning and clinical execution so that performance and consistency is improved? The answer is complex and it seems naïve to believe that just summarizing the available scientific evidence in the specific subject area is enough to achieve the aforementioned goals. The chapter in the previous edition of this book on implant restorations in the zone of esthetic priority was written based on the principles of evidence-based dentistry (EBD) and the cited articles were strictly selected accordingly. However, despite the considerable benefits of EBD, it has since been realized that there have also been unintended consequences with an adverse impact on health care in general, and individual patient care in particular (Greenhalgh *et al*. 2014).

Implant dentistry is a part of oral health care that is influenced by several interconnected organizations such as oral health care-related industries, health authorities, universities, political organizations, and others. There is no doubt that the complex interactions between these players with individual interests have an effect on the quality of evidence informing person-centered health care. First discussed in the mid-1990s, EBM became central to research, teaching, writing, and administrative management in the majority of medical specialties and was described as "a new paradigm for medical practice". It quickly became an energetic intellectual community committed to making clinical practice more scientific and empirically grounded and thereby achieving safer, more consistent, and more cost-effective care (Pope 2003).

The first problem is that the evidence-based "quality mark" has been misappropriated and distorted by vested interests (Greenhalgh *et al*. 2014). In particular, the medical devices and biomedical products industries increasingly set the research agenda (Popelut *et al*. 2010; Probst *et al*. 2016). Secondly, many dentists did not learn how to interpret and use scientific evidence in their daily practice and how to amalgamate it with their clinical experience and expertise as a basis for good clinical decisions in each individual patient. Even if evidence does exist, very often patients and clinicians act according to their social roles, and not based on evidence. And last but not least, for many clinical problems there is simply not enough practice-related evidence available.

The fact that implant-supported restorations can give esthetically appealing results is documented by many cases in dental magazines and at implant congresses. However, the efficacy of the treatment and the quality of the decisions taken by the clinician cannot be determined from the result. Only too often, we assume that a decision that led to a good clinical result was a good decision. Rarely do we review whether the initial prognosis was correct.

It is the goal of this chapter to provide interested clinicians with an overview of the current knowledge in the specialty, to support them in clinical decision making, and thus help them to improve performance and to reduce errors. These goals cannot be achieved by simply summarizing the evidence-based literature concerning implant dentistry and related fields. Too many important questions would remain unanswered using this approach.

The operating room is a hugely complex environment that requires considerable interaction between various team members (Undre *et al*. 2007). An array of non-technical skills is required of a surgeon, which influences the quality of the surgical results. Although the importance of non-technical skills is being increasingly recognized, there is currently little integration of its teaching and assessment with technical skills training. To comply with these requirements, we have revised this chapter considering technical and non-technical skills, the latter consisting of cognitive (decision making) and social skills (communication, leadership, and teamwork) and the personal resource factors (personality traits, ability to cope with psychological stress).

Implant restorations in the zone of esthetic priority have developed and broadened considerably in recent years. It is now more than 20 years since this chapter first appeared; it has been extensively revised to include a section on non-technical skills, an analysis of the mechanisms of clinical decision making, and an examination of the clinician as a risk factor for esthetic implant failures. With reference to shared decision making in implant dentistry, we examine the relationship between patients and health professionals, viewed as one of the most complex interpersonal relationships, and attempt to identify ways of implementing shared decision making in daily practice in order to avoid unrealistic expectations by patients.

The sections on diagnostics and risk assessment have been updated. A description of the newly available digital technologies and software for planning and visualization of prospective prosthetic results has been included.

The main clinical sections describing the surgical and prosthetic concepts have been shortened, updated, and illustrated with new clinical cases. A new section concerning immediate implant placement has been added, including a discussion of the risks and benefits of such a treatment modality.

The final section, which describes the strategies for retreatment of esthetic failures, has been completely revised, based on recently available knowledge and scientific findings.

Patient safety first: how to protect patients from avoidable harm?

Understanding benefits and harms of implant treatments

In implantology and many other surgical specialties, patient safety and professional liability are

major concerns worldwide. Based on the results of the Harvard Medical Practice Studies (Brennan *et al*. 1991; Leape *et al*. 1991), including 30 121 reviews from randomly selected records from 51 randomly selected hospitals, the US Institute of Medicine (IOM) published a landmark report, entitled "To Err is Human: Building a Safer Health System" (Kohn *et al*. 2000). The report concluded that adverse events do occur, causing a substantial amount of injury to patients. Depending on the discipline, the prevalence of adverse events varied substantially, being highest for surgeries requiring fine motor skills. Of course, adverse events do not necessarily signal poor-quality care; nor does their absence necessarily indicate good-quality care. But interestingly, most of the adverse events resulted from substandard care, and, independent of the medical specialty, in all categories, negligence was the main causative factor. Regarding the type of error, performance errors ranked highest with 46.4%, followed by prevention errors (26.0%), diagnostic errors (17.5%), and drug treatment errors (10.1%).

The report brought the issues of medical error and patient safety to the forefront of international concern and as it described that errors were not rare or isolated, the WHO (World Health Organization) adopted a resolution that urged member states to pay the closest possible attention to the problem of patient safety and the systems of monitoring (WHO 2002).

An interim assessment, published by Harvard Medical Practice Studies (Leape *et al*. 2009), eight years after the IOM report, concluded that efforts to improve patient safety had been insufficient and progress toward improvement frustratingly slow. They claimed that medical education should be restructured to reduce its almost exclusive focus on the acquisition of scientific and clinical facts and to emphasize the development of skills, behaviors, and attitudes needed by practicing clinicians. These include the ability to manage information, understanding of the basic concepts of human interaction, patient safety, and health care quality.

A progress report was published by Gandhi *et al*. (2018), documenting that some existing gaps could be closed. Increasing volumes of data and information are collected from patient experience surveys at the service or clinician level and compelling evidence confirms that sharing data, successes, and failures can markedly accelerate learning and improvement (Lee 2017). However, the report also emphasized the many remaining challenges. There is still a lack of transparency between patients and clinicians regarding communication before treatment and in the aftermath of adverse events (McGaffigan *et al*. 2017; Wu *et al*. 2017) and current evidence documents that the prevalence and the severity of treatment errors do not primarily depend on the complexity of the medical problems but rather on the errors in diagnosis and improper performances of the clinicians (Graber 2013).

When considering implant treatments in the zone of esthetic priority, almost all procedures are scheduled, non-urgent surgical events. A review of malpractice claims in oral and maxillofacial surgery confirmed that 95% of patients were treated with implants as elective interventions (Bordonaba-Leiva *et al*. 2019). Because most cases did not involve a medical emergency, it is surprising that the most frequently claimed events in oral and maxillofacial surgery (30.5% of the total claims) were implant failures and diseases. In addition, a much higher risk for claims of malpractice was found when implants had to be placed in the anterior zone of the upper jaw, where the esthetic perception of the patient has the most impact.

When implant installations associated with an esthetic component lead to a higher risk of disappointed patients, compared with implant restorations in the posterior area, communication problems between the clinician and the patient may be the cause, with the latter having too high expectations regarding the esthetic appearance of the implant-supported prosthesis. On the other hand, considering that the majority of technical errors involve fully trained and experienced surgeons, operating within their area of expertise and in routine operations (Regenbogen *et al*. 2007), the causative origin of the adverse events might be based on the clinician's overconfidence, underestimating the technical sensitivity of the surgical procedure (Berner & Graber 2008). Whatever the cause, it is valuable to examine why esthetic treatment errors occur and how they can be prevented.

The patient

Efficient health care requires informed doctors and patients. After doctors and friends, the media such as television, magazines, or newspapers are the most frequented sources of health information in European countries. In a recent survey, 43% stated that they relied on TV reports frequently. However, when it came to understanding the benefits of the treatment, those patients who relied more on TV, radio, magazines, or daily newspapers were not better informed than those who did not consume information from the media (Gigerenzer *et al*. 2009).

In recent years, studies concerning the quality and accuracy of health and medical information available on the internet or from leaflets have shown that many sources provide inadequate information (Muhlhauser & Oser 2008). In implantology, a major cause of non-transparent risk communication is a conflict of interest concerning those communicating health statistics (Edelmayer *et al*. 2016). Websites and leaflets regarding oral implants, illustrated with decorative images, focus on the description of treatment and advantages with less information about risks of complications, adverse esthetic outcomes, and disadvantages (Ali *et al*. 2014; Barber *et al*. 2015). Additionally, a fundamental aspect of

patient information is the importance of making patients aware of the different treatment alternatives for missing single or multiple teeth in the zone of esthetic priority (Edelmayer *et al*. 2016). As each discipline and specialty in health care brings its own perspective to treatment and management, described as the specialty bias (Seshia *et al*. 2014), current evidence confirms an omission of information transfer between doctors and patients regarding alternative treatment options (Sherman *et al*. 2013).

In health care, non-transparent framing of information seems to be the rule rather than the exception, which is why patients have difficulties finding reliable information. The problem is aggravated when benefits and harms of treatment options must be evaluated (Gaissmaier & Gigerenzer 2011). To make informed health decisions, patients need to understand that in the first place, there is no such thing as certainty. The term "illusion of certainty" refers to an emotional need for certainty when none exists. This is true for both patients and doctors. However, although health care providers may not be sure about the probability of negative side effects of a particular treatment, studies indicate that they rarely communicate the uncertainties about risks and benefits of treatments to patients (Braddock *et al*. 1999). This might be a consequence of a conflict of interest for the clinician – and financial conflicts of interests are not the only source of conflicting interests for doctors – or caused by the fact that the results of studies were not correctly understood by the health professional.

The clinician

Gaissmaier and Gigerenzer (2011) suggested three basic competencies for health professionals in the twenty-first century. The first is health literacy, including basic knowledge about diseases, diagnostics, prevention, and treatment, as well as the ways to acquire reliable knowledge in further education. The World Health Organization recognized that social competencies and skills are essential additional components and defined health literacy as "cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good (oral) health" (Sorensen *et al*. 2012). The so-called critical health literacy originates from this new concept and contains competencies that enhance the autonomy of the consumer (doctor and patient), combining evidence-based medicine or dentistry, evidence-based health care, and health literacy (Steckelberg *et al*. 2009; Steckelberg *et al*. 2009). People who are health literate are able to request missing information and question the knowledge source and its bias. They are suspicious when a brochure specifies the benefit of, for example, implant restoration in the anterior area of the upper jaw, but neglects to list possible harms or the merits of alternative routes of action.

The second competency that was suggested is health system literacy, which is important not only for clinicians, to assist in making informed treatment decisions, but for all citizens. To know which medical treatment will be best in each individual case, clinicians must be aware of the organization of the system and the incentives within it, such as, for example, collective agreements or political prioritization of a prevention system. The inclusion of implant restorations in the service spectrum of compulsory health insurances, or the country-specific variabilities in quality and number of dental schools, which may produce a surplus of practitioners, illustrates the importance of knowledge concerning the interconnectedness of health systems and their effect on health care quality.

The third competency refers statistical literacy, that is, a basic understanding of numerical information in order to grasp benefits and harms of treatment options and understand test results (Fig. 45-1). It is commonly assumed that only patients have problems with health statistics. However, doctors themselves might not understand medical evidence (Reyna & Brainerd 2007; Smith 2011). Several studies investigating the statistical literacy of doctors in different specialties have shown that most clinicians do not understand medical statistics (Hoffrage *et al*. 2000; Welch *et al*. 2000; Young *et al*. 2002; Muhlhauser *et al*. 2006; Gigerenzer *et al*. 2007; Wegwarth *et al*. 2011). Such a lack of statistical literacy makes clinicians dependent on biased information contained in poor quality specialty journals or continuing education organized by the industry.

To understand benefits and harms of implant restorations in the zone of esthetic priority, it is crucial to understand the complexity of modern implantology, on the one hand offering unique and reliable treatment options, which are well investigated and scientifically proven. On the other hand, as complexity characterizes a system whose components interact in multiple ways and follow local rules, health care professionals and patients must be aware of the many incentives, the cognitive biases, conflicts of interest and ethical violations that are inherent in the system at individual and organization level, subverting the evidence that informs person-centered health care (Seshia *et al*. 2014). At this stage, it must be emphasized that a health system, branches of the industry, health professionals, or single doctors must be not be criticized, but the *whole system* should be analyzed which – by understanding the interconnectedness of its variables – helps us to improve the quality of clinical decision making when implant restorations in the anterior zone of the upper jaw are one of the options.

The gap between scientific evidence and what happens

Expertise in implantology requires mastery of a diversity of knowledge from different areas such as structural biology, material sciences, ethics, and

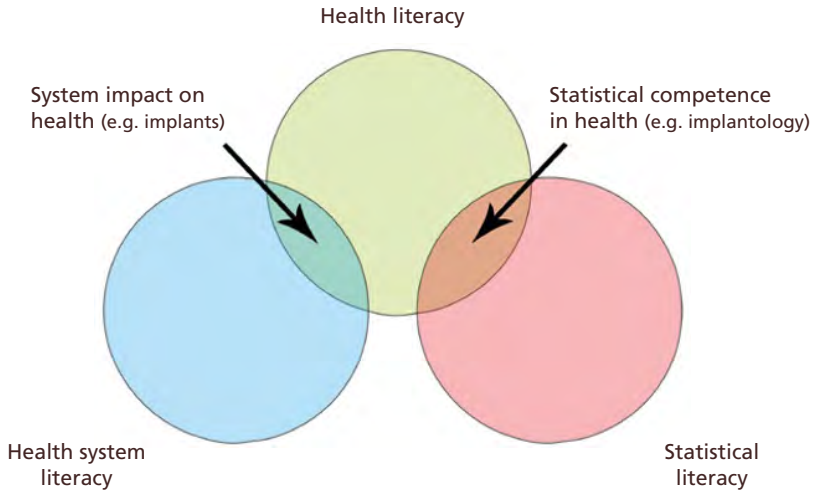


Fig. 45-1 Basic competencies for clinicians and patients for informed treatment decisions in implantology. Health system literacy entails basic knowledge about the organization of a system and the incentives within it. Health literacy comprises factual knowledge about diseases, diagnostics, prevention and treatment, and ways to acquire reliable knowledge. Statistical literacy involves the ability to understand uncertain evidence, including concepts such as false positive rates or differences between statistical significance and clinical relevance. (Source: Adapted from Gigerenzer & Gray.)

psychology. Clinical practice guidelines based on the principles of EBD build the foundations for teaching and implementing this knowledge into clinical workflows. In the last decade, much research has been performed in the specialty of oral implantology to increase patient safety and ensure that the esthetic outcome is more predictable and consistent. Critical voices and personal observations confirm that a significant gap exists between research recommendations, scientific evidence, and clinical practice guidelines, on the one hand, and actual clinical practice on the other (Cochrane *et al*. 2007). One of the major barriers to using current research evidence is the time, effort, and skill needed to access the right information from a considerable volume of research. For example, around 3000 new articles concerning the specialty of oral implantology are indexed each year in Medline.

A growing field of research on how to disseminate and implement scientific findings into clinical practice reveals the slow acceptance of practice guidelines by health care professionals in general, and doctors in particular (Bero *et al*. 1998; Wensing & Grol 2019; Wudrich *et al*. 2020). These transfer processes are summarized in the field of knowledge translation and aim to improve health care practice and make it more effective, thus leading to better care and outcomes for patients. Ultimately, research on knowledge implementation enhances the use and usefulness of all research efforts in medicine and dentistry.

Correctly applied, EBD aims to provide clinicians and patients with choices about the most effective treatment. These choices must be carefully considered, allowing for the specific circumstances, and the needs and expectations of the patient. For patients, this is a natural expectation, but studies document that practitioners rarely implement evidence in the decision-making process and they hardly ever change because of a change in evidence (Armstrong *et al*. 1996; Curran *et al*. 2011; Harding *et al*. 2014).

The lack of knowledge dissemination and implementation and the fact that clinicians do not apply the available evidence in their clinical treatment planning has also been documented for oral surgeons and dentists (van der Sanden *et al*. 2005). A study about the effectiveness of a dental clinical practice guideline on the management of asymptomatic impacted lower third molars clearly showed that the guidelines derived from systematic reviews only improved the dentist's knowledge but did not change their clinical performance by establishing a relevant improvement of their clinical decision-making skills.

Two pioneers of EBM provided a very helpful analysis to understand why there is a leakage of the possible efficiency in the pathway from research to practice (Glasziou & Haynes 2005). They argued that the translation of knowledge has to pass through several steps before it is implemented in everyday practice. By conservative estimation, in each step approximately 20% of evidence leaks and fails to proceed to the next step (Fig. 45-2). In the first three steps, clinicians are aware of evidence and that they should do something different from their daily routine. In general, they find it difficult to be aware of all the relevant, valid evidence. A central problem is that clinicians may be persuaded by many means other than unbiased evidence, such as the marketing techniques of advertising, authority, social validation (acceptance by peers), and friendship/personal relationships (Glasziou & Haynes 2005).

In the following two steps, the practitioner has internalized the evidence and now the patient must be brought into the discussion. Many patients may have their own ideas about treatment priorities and the restoration of their missing teeth. The opinions might deviate from the recommendations of their

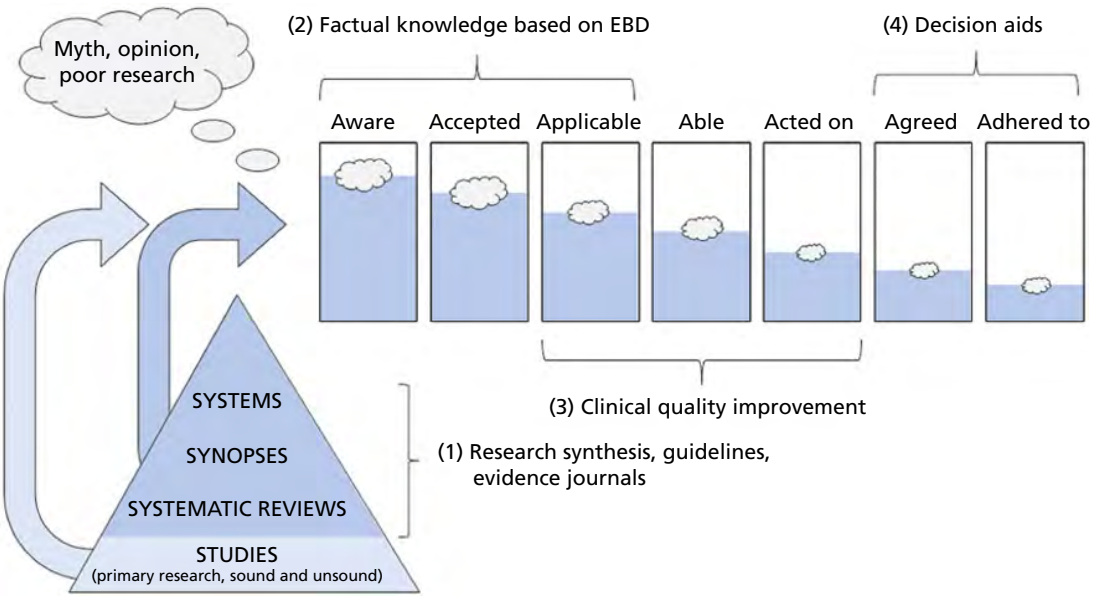


Fig. 45-2 Pathway from research to practice. At each step, approximately 20% of scientific evidence "leaks" and fails to proceed to the next step. This results in only 21% of scientific evidence being incorporated into patient care. EBD, evidence-based dentistry. (Source: Adapted from Glasziou & Haynes 2005.)

dentists. This failure to act is particularly common with preventive interventions such as oral hygiene programs prior to implant placement. Frequently, these important measures are not urgent for patients, and as a consequence, by respecting the patients' wishes, doctors skip the important steps to establish and maintain periodontal health. The gap between what we know and what we do is characterized by three different problems, namely misuse, overuse, and omission (National Academy of Medicine 2001), the latter perfectly describing the leakage of evidence in steps "able" and "acted on" and illustrated in the abovementioned example (Fig. 45-2).

The final two steps aim to match the values of the patients and of the clinicians, which might differ substantially. Patients may have their own interpretation of evidence and decline an intervention for reasons such as unwillingness to accept the pain or the inconvenience after a surgery. Even though clinicians prefer a certain therapy due to its evidence-based benefits, to successfully transfer evidence into clinical practice, patients must adhere to it, meaning that they must quit smoking, change their tooth brushing habits, or take their drugs as prescribed.

The reasons for the gap between scientific evidence and what is performed in clinical practice are manifold. Beyond the described loss of evidence in the knowledge transfer process, we must be aware that there is a bias already prevalent in many implant studies because much of the research in this field is of low quality and/or relevance (Masood *et al*. 2011; Tomasi & Derks 2012). The randomized trials that are published about implants and biomaterials might be biased in favor of the products owned by the company funding the trial (Popelut *et al*. 2010). Clinicians who do not interpret statistics correctly or only read low quality journals may have a very distorted view of the world.

Being aware of the described problems, which may have much more impact on the quality of esthetic outcomes of implant therapies than widely recognized, is a first step in engaging in an analytical process for critical self-reflection, in restructuring reasoning, and in changing ways of thinking (Croskerry *et al*. 2013a, b). Confidence in the procedure does not increase the suitability of the choice of therapy. The psychologic literature has well documented that, objectively, doctors are not good at assessing what they really know and generally tend to be overconfident in their judgments (Kruger & Dunning 1999; Saposnik *et al*. 2016; Burkhardt *et al*. 2019). Cognitive biases are specific systematic patterns of judgment or decision making that result in thoughts and behaviors deviating from what might generally be believed to be rational or optimal. They are hazardous because they are hardwired in our thinking, are strongly influenced by emotions, and are processed unconsciously. To counteract overconfidence and to detect the need for debiasing begins with becoming aware of the different types of cognitive errors which, mostly unconsciously, substantially influence clinical decision making and treatment planning (Croskerry & Norman 2008; Croskerry *et al*. 2013a, b). This means that those who are "unconsciously incompetent" do not even know how incompetent they are. One has to become consciously incompetent and ultimately unconsciously competent to take good clinical decisions and to provide the best benefit for each individual patient (Smith 2011).

Once the hurdles discussed above are cleared and the clinician has prepared a treatment plan to restore a missing central incisor with an implant, based on the

best available evidence, the idea has to be processed to the patient. However, the patient might have different expectations and be unwilling to accept the plan. In fact, the scenario that a clinician is processing the evidence unilaterally to the patient seems rather outdated. In a true clinician–patient partnership, the two will process the evidence together (Smith 2011).

Transparent risk communication and shared decision-making programs

The WHO defined oral health as a state of being free from any diseases and disorders that limit an individual's capacity in biting, chewing, smiling, speaking, and psychosocial well-being (WHO 2003). Considering the many site-specific variables which can affect the esthetic appearance of an implant restoration, it is obvious that an unfavorable result in the zone of esthetic priority may impair the smiling and psychosocial well-being of a patient and thus negatively affect his or her oral health. There are different scenarios which may lead to such an undesired result, but it is in almost all situations based on a discrepancy between expectations and outcome.

In one scenario, even if the clinician carefully communicated all possible benefits and harms of the therapy, it is probable that the patient did not or could not understand the explanations. A study on prosthodontic patients by Wolfart *et al*. (2006) evaluated general well-being with self-assessment of their dental appearance, and measured distinct esthetic concerns and psychosocial consequences of esthetic impairment. By using a psychometric test, the pretreatment mood of the patients, from euphoric to depressive, was diagnosed and placed in relation to the final satisfaction with prosthetic appearance. The patients in a depressive state were highly significantly more dissatisfied with their dental appearance than patients with normal well-being. Independent of the quality of the preoperative information, the psychological disposition of the patient may have an impact on the self-perceived esthetic appearance of the implant-supported crown or bridge.

In another scenario, the cause of the imbalance between expectations regarding esthetics and outcome may be based on the clinician not understanding the available evidence, not explaining it well, or being overconfident and providing the patient with a far too positive prognosis.

Whatever the reason, the communication between patient and clinician is essential and contributes substantially to mutual understanding and finally to a good overall clinical result.

Shared decision making is much more than the patient selecting one option from a given menu set. It was already part of the EBM movement of the 1980s and 1990s and has been defined as "involvement of both the patient and the doctor, a sharing of information by both parties, both parties taking steps to build a consensus about the preferred treatment, and reaching an agreement about which treatment to implement" (Charles *et al*. 1997). How much a patient needs to be involved in the process of decision making depends on their willingness and interest to participate. Many patients do not seek out information, feeling this is the doctor's job. More important than the dominance of the responsibility for the decision in the doctor–patient relationship is the patient's engagement in discussion about the nature of their problems (Bugge *et al*. 2006), the question about who defines the question set (Wirtz *et al*. 2006), and the facilitation of the patient's contribution to the delivery of the choice of therapy (Entwistle & Watt 2006). Independent of the benefits of task-related information, the feeling that patients are well cared for as individuals and respected as part of the team is crucial for a good patient–doctor relationship (Wright *et al*. 2004). Frequently, the underlying cause of the patient's unhappiness with the appearance of the restored teeth and the smile is not the medical problem itself but the lack of self-confidence and the pressure of a highly competitive society. Clinicians who believe that they can solve such psychological issues with medical technologies, without a detailed conversation with their patient, cannot genuinely be interested in the patient's well-being (Maio 2007). It is proven by systematic reviews that the involvement of patients in the decision-making process and a thorough presurgical conversation results in better quality of care, increased patient satisfaction, and improved self-esteem (Crawford *et al*. 2002).

The field of shared decision making has evolved in the last two decades and is closely related to concepts such as EBM, informed decision making, and patients' autonomy, in the medical context, describing patients making use of their right of self-determination when dealing with health subjects. In 2020 more than 10 000 related articles were indexed in Medline, but only a handful dealt with shared decision making in dentistry (Bauer & Chiappelli 2010) and implantology (Alzahrani & Gibson 2018). In general, the involvement, needs, and perceptions of dental patients have not yet been sufficiently assessed (Reissmann *et al*. 2019). The few available studies in dentistry are in accordance with those from the medical context and confirm that the majority of patients prefer to actively participate in the decision process (Singh *et al*. 2010). The preference for a more active role in decisions seems to correlate with the invasiveness of the intervention and the long-term effects (e.g. treatments concerning the various stages of tooth loss and the replacement of teeth).

In the whole process of shared decision making, the communication of risks and the manner of sharing uncertainty is an essential part, which is difficult to achieve but contributes substantially to the quality of shared informed decisions. Firstly, uncertainty exists on a professional collective level, which suggests that additional and better quality research is required. Secondly, uncertainty relates to the

individual clinician and depends on his or her professional education. Thirdly, effective risk communication about harms and benefits of different treatments or care options is important and is known as stochastic uncertainty (Edwards *et al*. 2002). Factors such as ensuring credibility of the source, competing interests, previous experiences, understanding patients' values and maximizing the clarity of the message are important to determine the quality of risk communication (Poortinga & Pidgeon 2004). Besides the cognitive aspects of risk perception and communication, the method and preferred format of information delivery, ensuring that the information has been understood by the patient, and monitoring the reactions triggered by the information are also important and contribute to make evidence part of the patient choices. Risk communication on the collective level and open declaration of one's own uncertainty (individual uncertainty), once it is realized by critical self-reflection ("does this work in my hands?"), should remind the patients that virtually all treatment options are associated with some possibility of risk. Practical strategies and helpful guidelines for clinicians have been described elsewhere (Paling 2003).

Compared with other medical domains, the role of shared decision making and risk communication in implantology is not yet well investigated and, in regular practice, contrasts between patient preferred and perceived roles in decision making may occur (Reissmann *et al*. 2019). On the other hand, it is documented by some scientific evidence from other surgical specialties that the application of the principles of shared decision making and the use of decision aids result in much higher patient satisfaction (Sepucha *et al*. 2019). In particular, when decisions have to be taken for elective surgeries and patients have been informed on the basis of shared decision-making programs, it is evident that the willingness to undergo the intervention decreases, but for the patients who, nevertheless, decided in favor of the surgery, the patient-reported outcome, the satisfaction, and overall happiness with the intervention, on short- and long-term evaluation, is much better (Bozic *et al*. 2013; Martinez-Gonzalez *et al*. 2019). It is hoped that shared decision-making programs will be implemented in oral implantology in the near future. This would help to reduce biological and esthetic adverse outcomes and provide patients with the best individual benefit from the chosen treatment.

Preoperative diagnostics

Clinical measurements

Preoperative diagnostics in the zone of esthetic priority do not differ fundamentally from those in other areas of the upper and lower jaw. The precise evaluation of the three-dimensional loss of tissue in the edentulous area and the periodontal condition of the neighboring teeth are the center of attention. From the latter, the periodontal attachment level at the tooth, adjacent to the site where an implant has to be placed, is of utmost importance as the complete embrasure fill between an implant restoration and the neighboring tooth is correlated with the integrity of the periodontal ligament (Roccuzzo *et al*. 2018). Preoperative interproximal probing on the adjacent teeth, combined with recordings of the gingival recessions, reduce the risks for adverse esthetic outcomes. Other parameters that reflect the oral hygiene status and compliance of the patients have to be evaluated routinely before starting treatment and while monitoring implant reconstructions over a lifetime (Mombelli *et al*. 1987). Besides the well-known negative effects of poor oral hygiene habits on implant complications and survival (Heitz-Mayfield & Salvi 2018; Schwarz *et al*. 2018), an inflamed mucosa cannot be manipulated with the same precision as a healthy one, and primary wound closures are more difficult to achieve as inflamed soft tissues are ambiguous and at higher risk for soft tissue dehiscences during the early healing phases.

Another factor that may influence the esthetic success of an implant reconstruction in the anterior area and, therefore, needs to be recorded presurgically, is the soft tissue phenotype (Cortellini & Bissada 2018) or according to the nomenclature, the phenotype (Caton *et al*. 2018). Even if numerous studies on humans show that a thin phenotype is more friable, less vascularized, and accompanied by thinner underlying bone and seems to be more susceptible to mucosal dehiscences (Linkevicius *et al*. 2009; Linkevicius *et al*. 2010), actual data confirm that thin mucosal phenotypes may be compensated by the use of connective tissue grafts, at least when implants are placed immediately after tooth extractions, and thus, level out the clinical differences between thick and thin phenotypes and the range of transitional categories in between (Tatum *et al*. 2020).

The extent of an edentulous space in the arch can best be described based on the number of missing teeth. The defects have been classified based on their morphologic characteristics (Wang & Al-Shammari 2002), dividing them into a horizontal and a vertical defect component. Depending on their extent, vertical hard and soft tissue defects show a much better prognosis for augmentation than horizontal ones. In the latter, the attachment level at the teeth neighboring the defect limits the prognosis and therefore the prospective esthetic result.

Based on a personal evaluation, it seems that sound preoperative clinical measurements are often neglected. By publishing a clinical picture and the corresponding X-ray on social media, dentists were asked to choose one of the options out of five listed treatment modalities. It was surprising that just a minority of the more than one hundred respondents opted for "I don't know" while the majority took a treatment decision based on the very limited available information (Fig. 45-3).

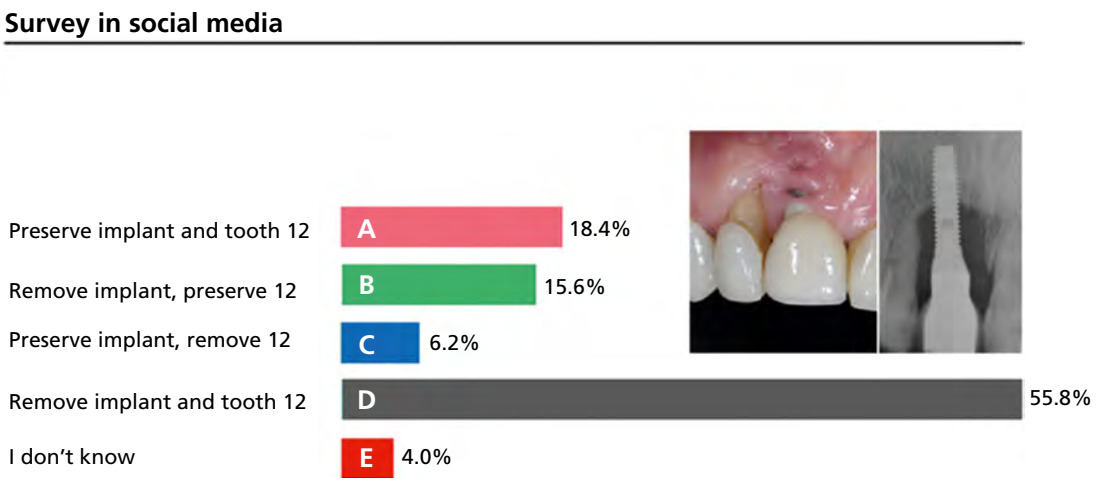


Fig. 45-3 A survey in social media confirmed the tendency that clinicians are ready to take a treatment decision without careful evaluation of important clinical parameters. Just based on a clinical picture and the corresponding X-ray, dentists were asked to choose one out of five treatment options. The graphic displays the distribution of the different answers and documents that just a minority of respondents was aware of the lack of information.

Image-guided diagnostics

To ensure proper planning of the implant position, which is a fundamental requirement in the zone of esthetic priority, the required information can be obtained from the aforementioned clinical examinations and additional appropriate image-guided diagnostics. To investigate an implant site in the anterior upper jaw, a clinician requires information on bone volume and quality, topography, and the relationship to important anatomic structures, such as the roots of neighboring teeth, nasal floor, vessels, and nerves. In the last decade, cone beam computed tomography (CBCT) has been rapidly adopted for implant planning. There is legitimate concern from experts in the clinical and radiology fields that these technical developments will lead to a significant increase in the radiation exposure of patients without a proper risk–benefit analysis. For this reason, guidelines for the use of diagnostic imaging in implant dentistry have been published, based on a consensus workshop of the European Association for Osseointegration (EAO) (Harris *et al*. 2012).

In the upper anterior maxilla, the recommended standard radiographic technique in sites with sufficient bone consists of an intraoral radiograph before replacing a missing single tooth, and an additional panoramic image in partially dentate and edentulous patients. The need for cross-sectional imaging has to be carefully evaluated for a sufficient net benefit, weighing the total potential diagnostic or therapeutic benefit against the detrimental effects the exposure might cause the individual.

In the zone of esthetic priority, a cross-sectional image (CBCT) can be indicated in clinical situations where clinical examinations or conventional radiography have failed to adequately identify the relevant anatomic boundaries or the absence of pathology. Specific challenges which justify a CBCT include (1) borderline cases with inadequate bone morphology and volume, (2) specific presurgical planning which helps to translate the information from radiographic evaluation into the clinical procedure (surgical guides) and (3) the virtual patient, a digital record that is used to plan the ideal implant position with respect to esthetic, prosthetic, and surgical requirements (Jacobs *et al*. 2018).

Visualization of prospective results for diagnostics and patient information

When treating the anterior zone of a patient's upper jaw, the wishes and expectations of each individual patient concerning the esthetic result have to be respected. Very often the patient's and the clinician's views of what constitutes an ideal esthetic outcome widely differ (Langlois *et al*. 2000). While the patient is influenced by his/her self-perception, the social environment, the media, his/her own dental history, and many other factors, the clinician bases his/her choice of a certain clinical strategy on the current dental knowledge, the empirical experience, and, possibly, on available medical checklists. The latter especially carries a risk of standardizing the prospective results and disregarding the individuality and personality of each patient. To address this, the contact and communication with the patient in the diagnostic phase, but also during the following treatment stages, requires special attention as patients are often unable to articulate their wishes and concerns (see Transparent risk communication and shared decision-making programs, previously).

By means of computer software, digital smile design programs offer new possibilities to capture facial, dentogingival, and dental esthetics and process the data into prospective esthetic treatment goals (for review see Omar & Duarte 2017). To close the gap between the true and the artificial environment, so called mixed reality digital applications (virtual reality, augmented reality) are available for different

simulations in implantology, showing huge potential and stimulating increased attention. Until now, these technologies are predominantly used for motor skills education, clinical analyses of maxillofacial surgical protocols, and investigating human anatomy (Joda *et al*. 2019).

New technologies, based on augmented reality principles, are currently under development for visualization of the esthetic results and improving the patient–doctor communication. Such software enables the patient to see within seconds the esthetic result of the dental reconstruction. A live video is taken of the patient's own teeth, on which a virtual model of the new set of teeth is superimposed. By just a mouse click, patients can try out several alternatives and adjust tooth length, width, shape, and color shade. Thanks to "virtual fitting", communication between the clinician, the patient, and the laboratory technician seems to be facilitated and expectations from all parties can be managed more easily.

Despite the many promises of innovations, we have to be aware that much of the policy rhetoric on new technologies rests not on what they have been shown to achieve in practice but on optimistic guesses about what they would, could, or may achieve if their ongoing development goes as planned, if the technologies are implemented as intended (Greenhalgh 2013). Additionally, a personal relationship cannot be replaced by digital technologies and the translation of a digital analysis with the help of computer imaging software may idealize the prospective results, which may not reflect the actual situation.

Especially in edentulous areas where a considerable amount of vertical tissue volume is missing, it can be difficult to reconstruct the tissue loss with surgical interventions alone, and clinicians must take care with what they promise patients regarding outcomes. Against this background, each treatment plan for a reconstruction in the zone of esthetic importance should be based on the interaction between all participating persons and must include the patient's opinions and desires.

All the rules that have been learned about tooth form, geometry, and harmony to recreate an esthetically pleasing smile can only be viewed as a general guide. Otherwise, all treatment goals would be the same for all patients and the facial physiognomy and uniqueness of each individual would be neglected.

Checklists can be helpful to clinicians in identifying problems, but they have a tendency to overlook patient individuality and usually follow a set pattern that ends with a standardization of the procedure.

Key factors for success when planning implant restorations in the zone of esthetic priority are taking the time to deal with the patient's esthetic problem, the communication within the treatment team, and the notes on each individual step in the development of the prospective esthetic outcome.

Preoperative risk assessment

Evaluation of alternative treatments and checklists

Prior to selecting an implant-based solution, one should carefully review all possible treatment alternatives that have the potential to solve a given problem. Additionally, the advantages and disadvantages of the solutions should be comprehensively pondered, not only in light of long-term survival but also with respect to the esthetic outcome and its stability over time. The therapeutic modalities that can be used to replace a tooth in the zone of esthetic priority, without placing implants, are listed in Table 45-1. In cases with unrestored neighboring teeth, adhesive, resin-bonded zirconia bridges have been shown to reliably replace single missing teeth in the anterior upper jaw with almost no preparations needed at the anchor teeth (Shahdad *et al*. 2018). In cases with minor incisal clearance, conventional porcelain-fused-to-metal-crowns will still render good service with promising long-term results, in some situations even without esthetic restrictions (Fig. 45-4) (Pjetursson *et al*. 2008).

In comprehensive esthetic treatment planning, attention should be directed not only to implant alternatives but also to strategies aimed at improving the implant sites prior to placing the implant or even at improving a tooth's prognosis such that implant reconstruction can be postponed or even avoided (Fig. 45-5). Based on our personal experience, orthodontic pretreatments especially can improve the clinical situation in many cases and provide a better esthetic prognosis for therapy. These pretreatments include forced eruptions (Giachetti *et al*. 2010) to increase the retention for placement of a conventional crown or to condition the site for later implant placement (Amato *et al*. 2012).

Another orthodontic treatment option consists of changing the distribution pattern of the edentulous spaces by turning a neighboring two-unit space into two one-unit spaces (Fig. 45-6). As previously mentioned, the latter situation has a much better predictability regarding the development of papillary-like structures, an important issue for a natural appearance. A palatally placed implant offers an absolute anchorage for orthodontic tooth movements without risk of negatively influencing the present occlusion. Additionally, the temporary implant may serve as an ideal anchor in many situations to firmly fix a provisional without

Table 45-1 Therapeutic modalities for tooth replacement in the zone of esthetic priority.

- Conventional fixed partial dentures, comprising cantilever units
- Adhesive, resin-bonded (cantilever) bridges
- Conventional removable partial dentures
- Tooth-supported overdentures
- Orthodontic therapy (closure of edentulous spaces)
- Implant-supported prostheses (fixed, retrievable, or removable suprastructures)
- Combinations of the above

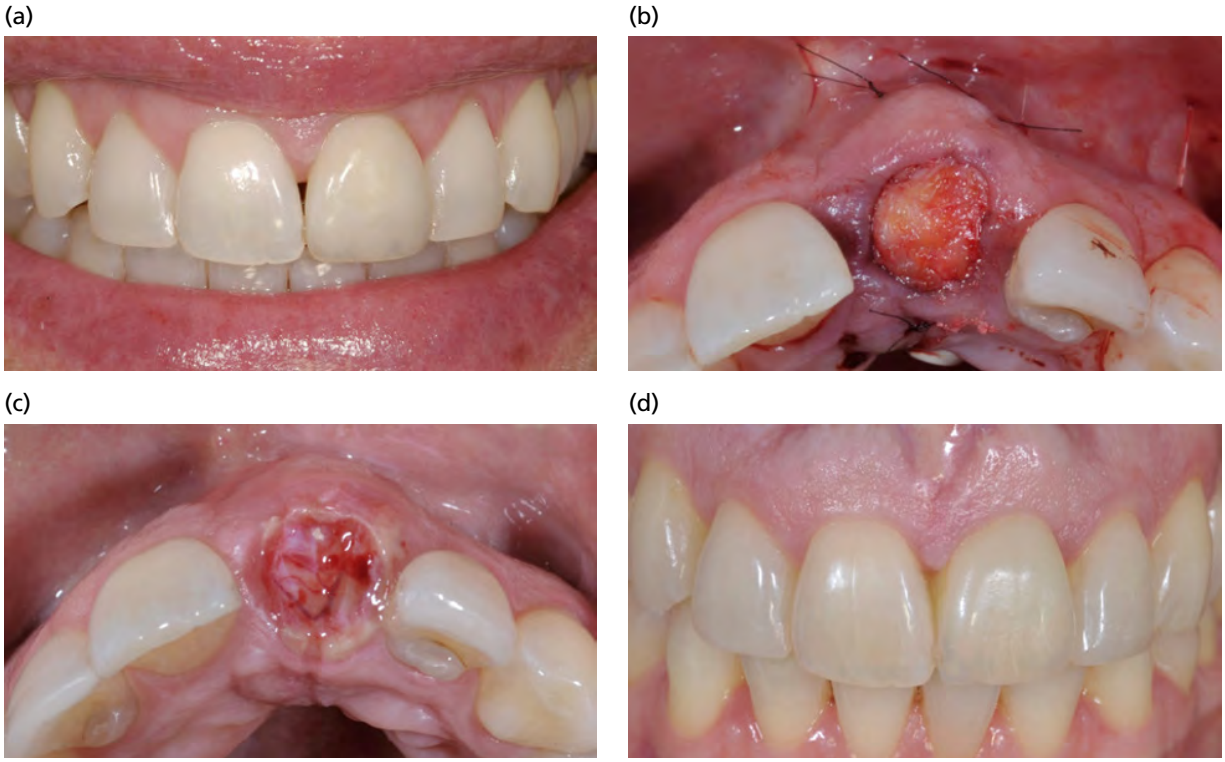


Fig. 45-4 (a) Preoperative view: left central incisor with root resorption has to be removed and replaced. (b) Situation after tooth extraction, alveolar ridge preservation procedure, and coverage with a connective tissue graft. (c) Uneventful healing of the site 8 days postsurgically, overcontouring of the lateral ridge to compensate for shrinkage of the buccal bone. (d) Final restoration with a resin-bonded adhesive bridge (metal framework), 8 months after tooth extraction.

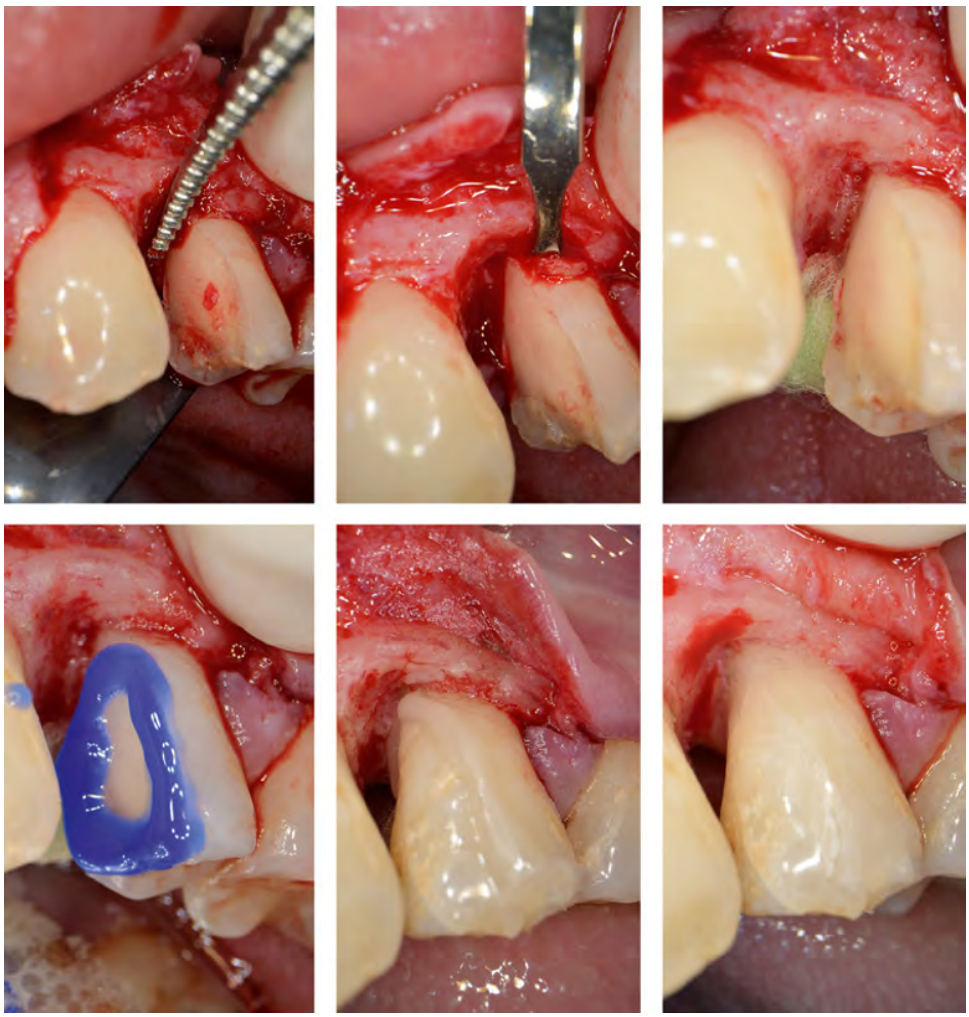


Fig. 45-5 Clinical situation after accident with infrabony fractured first premolar. Instead of extracting the tooth and replacing it with an implant, the tooth is saved using minimally invasive flap surgery and ostectomy. The broken piece can be fixed adhesively and tooth vitality is kept intact. Even if no scientific evidence exists for such treatment, for the individual patient it might perform well and preserves tissue.

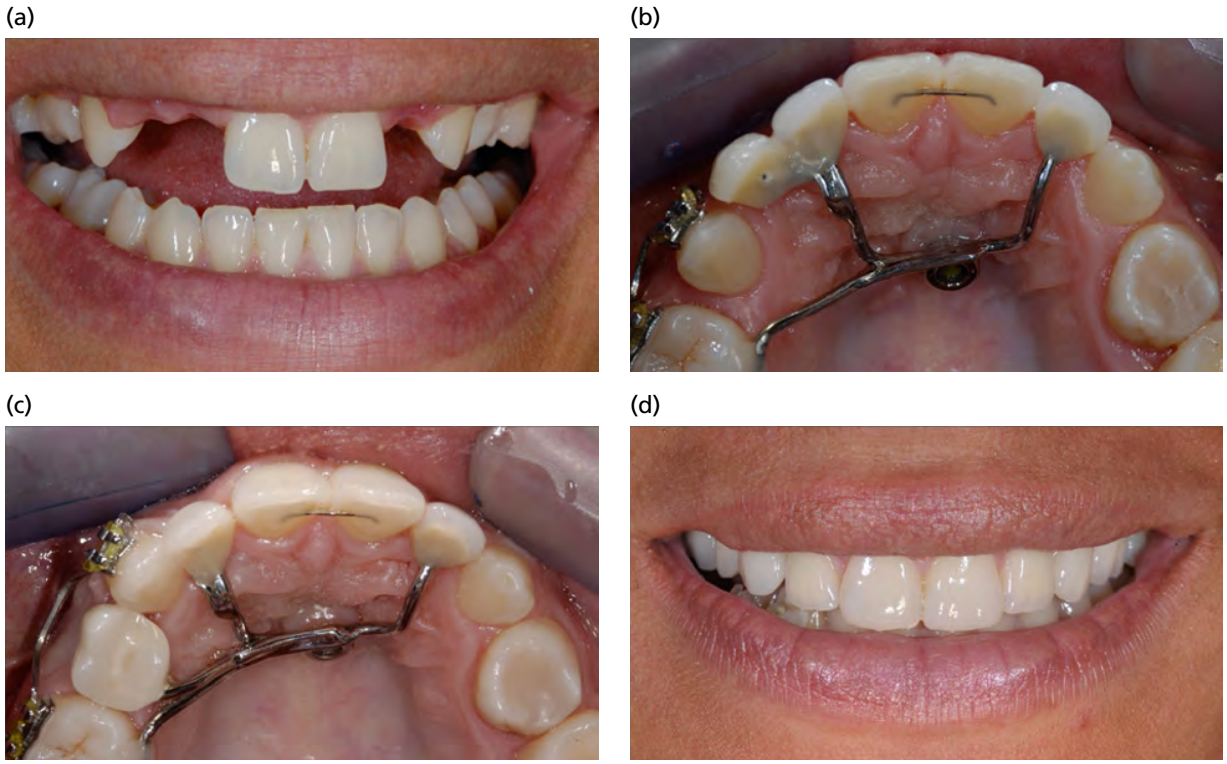


Fig. 45-6 (a) Patient with missing teeth in zone of esthetic priority. An edentulous single-unit gap is present in area 22 and a two-unit gap in area 12, 13. (b) Palatal implant for absolute anchorage and mesial movement of right upper canine. Additionally, the palatal implant serves as an ideal screw fixation for the provisional restoration which is shortened stepwise while moving the canine. (c) The orthodontic treatment is finished and the provisional has been adapted to the new situation. The palatal implant supports the provisional until the end of the implant treatment. As the patient is restored with a fixed provisional, the definitive restoration is not urgently required, which might be important in some cases to comply with the healing times. (d) Final prosthetic restoration with three single implants in the areas 14, 12, and 22.

any visible attachments on the anterior incisors and canines until the implants can be loaded with provisional crowns. Even if not documented by prospective studies, the long-term restoration supported by palatal implants seems to be a true alternative when esthetics are important and site-specific variables prevent the insertion of a conventional implant.

In patients with open interdental spaces and one or more missing teeth to be replaced, a conventional fixed approach will be critical as a single diastema cannot be closed for symmetry reasons and thus, an implant-supported reconstruction becomes the treatment of choice. Besides diastemata, other situations which favor the inclusion of implants in the treatment plan are: (1) unrestored, healthy neighboring teeth; (2) compromised, risky abutments; (3) extended edentulous areas; and (4) missing strategically important abutment teeth. The fulfilment of one or more of these criteria does not necessarily mean that the inclusion of implants in the treatment strategy is a given. Other risk factors related to the bone, soft tissue, and tooth (clinical crown) level have to be carefully evaluated and considered in the decision-making process (Table 45-2).

Surgeon-related risk factors

Because all implant interventions in the zone of esthetic priority are elective surgeries, there is enough time for detailed treatment planning, decision making, and communication of benefits and harms to the patient. As a result of this, coupled with available scientific evidence, adverse esthetic results in implantology should not routinely occur. Unfortunately, this is wishful thinking and corresponds well with elective surgeries in other fields. In the last decade, psychologists and behavioral scientists have addressed this problem and analyzed its origins (Ballard 2014). A dual-system framework has been introduced to explain human decision making and cognitive biases (Tversky & Kahneman 1974). System 1 refers to an unconscious, fast, and intuitive mechanism to take decisions, while system 2 is conscious, slow, and effortful to make deliberate decisions. It is suggested that cognitive biases are likely due to the overuse of system 1 or when system 1 overrides system 2. Despite the efforts in other fields, such as aviation or factory production (Dhillon 1989; Ballard 2014), to shed light on the influence of cognitive biases on the sequences of operations, little is known about the influence of such biases and personality traits on decision making in medicine and implantology. Evidence confirms that medical personnel are generally prone to show cognitive biases, but it is still unclear how these biases relate to the number of treatment errors (Blumenthal-Barby & Krieger 2015).

Table 45-2 Risk factors for implant placement in the zone of esthetic importance.

	Low risk	Medium risk	High risk
Patient factors			
General health	Systemically healthy		Reduced defense
Smoking conditions	Non smoker	Occasional smoker	Smoker, heavy smoker
Compliance	Good		Poor
Esthetic expectations	Within normal limits		Very high
Lip line	Low	Medium	High
Dental/facial symmetries	Symmetric		Visible asymmetries
Interarch relationship	Normal situation		Deep bite situation
Hard and soft tissue factors			
Attachment level of neighboring teeth	Intact		Reduced
Periodontal and endodontic health	Healthy		Compromised
Distance contact area –bone level at neighboring teeth	<5 mm	5 mm	>5 mm
Ridge deficiencies	Intact alveolus	Lateral defect	Vertical or combined defect
Mesio-distal gap distance	1 tooth (>7 mm)	1 tooth (<7 mm)	2 neighboring units
Mucosal phenotype	Low scalloped, thick	Medium	High scalloped thin
Soft tissue surfaces	Intact		Texture irregularities, scar formations
Mucosal scalloping	Regular		Irregular
Tooth factors			
Crown forms	Squared shape		Triangular shape
Structural integrity	Intact, healthy	Sufficiently restored	Decayed, insufficiently restored
Line of incisal edges	Following lower lip		Irregular

A recent systematic review (Saposnik *et al*. 2016) found that 50–100% of physicians were affected by at least one cognitive bias. The most commonly studied personality trait was tolerance to risk or ambiguity which might also have an impact when it comes to decide between implants in the zone of esthetic priority and the treatment alternatives. The most common cognitive biases were overconfidence and framing, the latter describing the fact that different wordings of a message, by expressing exactly the same content, affects the behavior and reaction of the recipient.

One may assume that a doctor's personality traits such as tolerance to uncertainty or cognitive biases do not equally influence patient outcomes in all disciplines. Time-urgency of the therapeutic decision may be a relevant characteristic. Even if implant placements in the zone of esthetic priority are elective interventions, it is hoped that future research will elucidate how the many described cognitive biases in medicine such as premature closure, ego bias, overconfidence, confirmation bias, and others (Croskerry 2005) affect decision making in implantology and how they are related to the reduction of errors and more realistic patient expectations.

Provisional restorations and timing of the treatment sequences

In the anterior zone, provisional restorations have a variety of important functions. Provisional restorations should be used to evaluate esthetic, phonetic, and occlusal function prior to delivery of the final implant restorations, while preserving and/or enhancing the condition of the peri-implant and mucosa tissues (Furze *et al*. 2019). An implant treatment approach in the edentulous anterior zone has three provisional phases: (1) the first phase, from tooth extraction to implant placement including immediate provisionalization after tooth extraction: (2) the second phase, after implant placement and prior to loading; and (3) the third phase, a loaded fixed implant-supported provisional and the ensuing emergence profile.

From tooth extraction to implant placement

After tooth extraction in the esthetic zone, several options are available to immediately replace the missing teeth with provisional restorations. These

provisional restorations can be in the form of removable or fixed prostheses. It is of great importance for the patient to discuss the options as well as the advantages and disadvantages prior to the therapy. When a patient is going to lose one or more teeth in the anterior area, an adequate provisional restoration will give the patient the confidence back after losing his/her own teeth.

Removable partial acrylic dentures have commonly been used after tooth extraction and maybe also throughout the entire implant therapy (Fig. 45-7). They are simple to construct, relatively inexpensive, and easy to adjust and fit. They can be easily modified in cases with additional extractions by adding provisional teeth to the existing removable dentures with minimal cost. Care must be taken with the mucosal portion supporting the provisional partial denture in order not to apply too much pressure to the healing site. Immediately after tooth extraction the provisional restoration can be placed with ovate pontics extending into the extraction sockets to partially preserve the pre-extraction soft tissue morphology. These removable partial acrylic dentures are not particularly comfortable because they have a certain resilience and cover part of the palate. Hence, there are alternatives to these tissue-borne provisional restorations. An Essix provisional (Fig. 45-8) may be used as a removable prosthesis in these cases, as well as in limited interocclusal space or deep anterior overbite (Santosa 2007; Siadat *et al*. 2017). This prosthesis is made from an acrylic tooth bonded to a clear vacuform material on a cast of the diagnostic wax up. The prosthesis provides protection to the underlying soft tissue and implant during the healing phase. Limitations of this provisional restoration include its inability to mold the surrounding soft tissue, and lack of patient compliance can cause rapid occlusal wear through the vacuform material (Santosa 2007). However, some patients may not like to wear, or are unable to tolerate, a removable provisional prosthesis; thus, fixed provisional prosthesis are sometimes necessary.

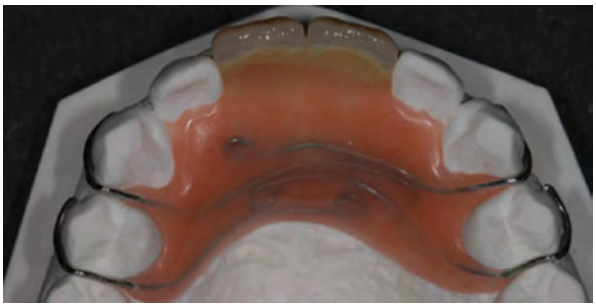
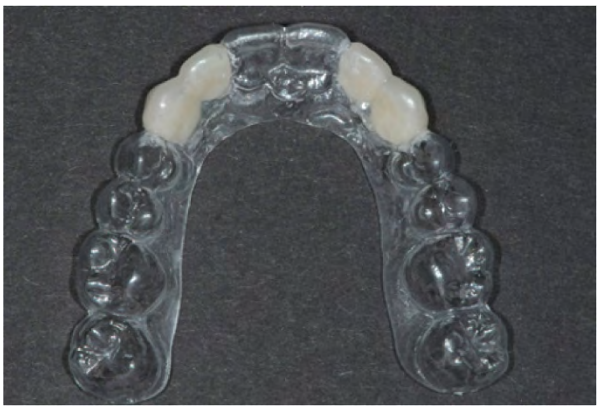
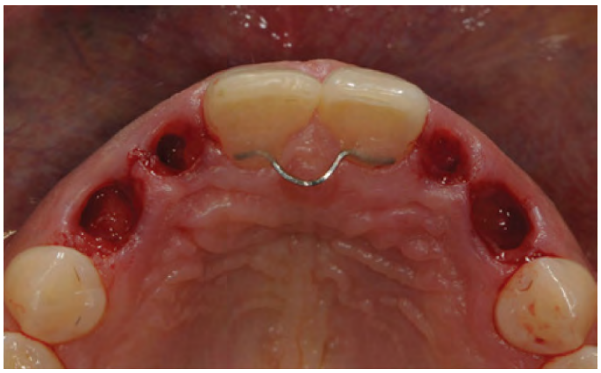


Fig. 45-7 Occlusal view of a removable partial acrylic denture on the cast with wires retained to the teeth 14, 13, 23, and 24.

(a)



(b)



(c)

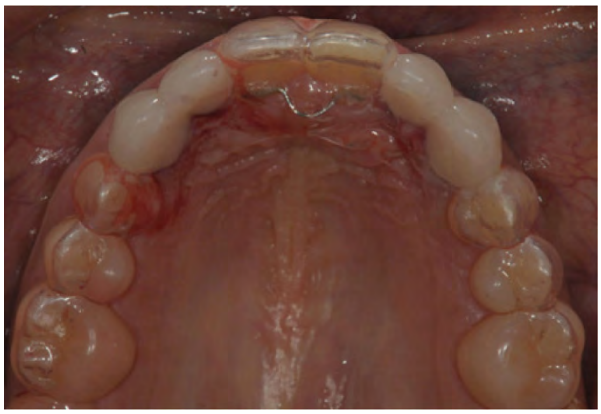


Fig. 45-8 (a) Occlusal view of an Essix provisional made from acrylic teeth bonded to a clear vacuform material. (b) Clinical occlusal view immediately after tooth extraction of the remaining deciduous teeth and before inserting the provisional restoration. (c) Clinical occlusal view of an Essix provisional after teeth extractions in the upper jaw.

Fixed tooth supported provisional restorations in the anterior region mainly include resin-bonded pontics or bridges (Siadat *et al*. 2017). The pontic can be in the form of an acrylic tooth, porcelain, or decoronated extracted tooth. The resin-bonded acrylic or natural tooth may be reinforced with composite resin and/or fiberglass. These types of provisional restorations are much more comfortable from a functional, phonic, and esthetic point of view. However, their removal and rebonding after the surgical intervention requires more time and work for the dentist. If a provisional restoration is needed for a longer time and more stability is required, a resin-bonded, cast metal framework prosthesis such as a Maryland Bridge is indicated (Grizas *et al*. 2018). These prostheses are cemented to the neighboring teeth by means of acid etching and the use of composites (Fig. 45-9). They can be detached by removing the composite within the palatal perforations and by using forceps interdentally and a hammer. This type of fixed provisional restoration also allows more than one missing tooth to be replaced. However, the relatively high laboratory costs of these resin-bonded, cast metal framework prostheses must be taken into consideration.

At implant placement with immediate provisionalization

Immediate provisionalization is a common procedure in daily practice that was initially developed for the esthetic regions in order to benefit patients during the implant treatment and prior to crown delivery (Donos *et al*. 2018). It is of outmost importance, however, that each case for immediate provisionalization undergoes a thorough risk assessment. The risk of soft tissue recession after insertion of the provisional reconstruction should be carefully considered. Upon the insertion of a provisional crown, the surrounding peri-implant soft tissue reacts and creates the so-called emergence profile. The aim of this structure is to allow a pleasing natural esthetic appearance through a smooth transition between the round and narrow shape of the implant connection and the oval and wider shape at the marginal area. This smooth transition is usually obtained after a few appointments by modifying the provisionals. Previous studies suggested, nevertheless, that the frequent exchange or dis/reconnections of abutments may disturb the surrounding tissues, resulting in marginal bone loss (Rodriguez *et al*. 2013; Bressan *et al*. 2017). The detrimental effect of this frequent manipulation has been documented preclinically (Rodriguez *et al*. 2013) as well as clinically (Bressan *et al*. 2017). In this context, a recent randomized controlled trial compared the radiographic, clinical, and esthetic outcomes of immediately provisionalized and conventionally restored implants for up to 24 months (Donos *et al*. 2018). The study revealed a significantly mean difference in bone loss in favor of conventionally restored implants but no differences in terms of clinical and esthetic outcomes (Donos *et al*. 2018).

Likewise, and based on a similar notion, the "one abutment–one time" protocol was introduced. This protocol proposes a definitive abutment instead of a provisional abutment at the time of implant placement in order to minimize the trauma to the surrounding tissues. A recent systematic review on this concept concluded that although definitive abutments minimized the changes in peri-implant marginal bone levels statistically, the clinical significance of this finding is still uncertain (Atieh *et al*. 2017). Moreover, the same review revealed no differences in terms of periodontal and esthetic outcomes (Atieh *et al*. 2017).

Digital technologies in implant dentistry are increasingly applied and are continuously replacing conventional provisional reconstructions. Intraoral scanning (IOS) and computer-aided design and manufacturing (CAD-CAM) have become common tools to fabricate these provisionals (Muhlemann *et al*. 2018). The fabrication process can either be executed via the dental laboratory (lab side) or directly by the dentist (chairside). The latter may simplify the fabrication of an implant-borne provisional reconstruction immediately after implant placement, resulting in fewer appointments and thereby improving patient comfort (Malo *et al*. 2007;

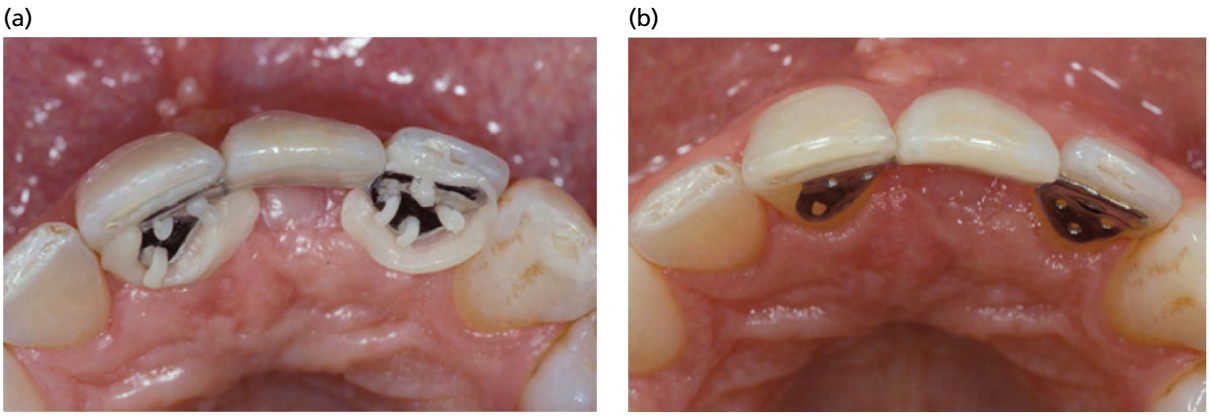


Fig. 45-9 (a) Placing of the provisional adhesive bridge with filling composite before removing the excess material. (b) Provisional adhesive bridge replacing the missing tooth 21 after cementing.

Arisan *et al*. 2010; Muhlemann *et al*. 2018). Consequently, digital workflows have been proposed as more efficient and less time-consuming compared with traditional approaches (Sailer *et al*. 2017; Muhlemann *et al*. 2019).

From implant placement to abutment connection

During the period from implant placement to abutment connection the same options of provisional restorations are available as after tooth extraction (Siadat *et al*. 2017). However, after implant placement, especially with the use of guided bone regeneration techniques, a significant swelling of the tissues must be anticipated during the first few postoperative days. Soft tissue-borne prostheses used during this healing period may cause uncontrolled soft tissue pressure defined as "transmucosal loading", leading to implant exposure, marginal bone loss, and/or failed integration (Santosa 2007). In order to avoid too much contact to the soft tissue and the healing implants the provisional dentures are adjusted to have a distance of approximately 2–3 mm to the tissue after surgical interventions. In this context, Essix provisionals have advantages because they are vertically stabilized through the neighboring teeth and, therefore, cause less pressure to the tissue in cases of swelling.

From abutment connection to final crown/bridge placement

According to the preoperative risk assessment, it has to be decided whether an implant will heal best with a submucosal or a transmucosal approach. In highly demanding situations with high lip line, thin phenotype, and tissue deficiency, a submucosal approach is generally chosen in order to create soft tissue extra volume. In less demanding situations with thick phenotypes, sufficient tissue, and possible soft tissue excess, a transmucosal approach with healing abutments or provisional reconstructions can be selected. Hence, the preoperative risk assessment and the intraoperative information (i.e. primary implant stability, bone defects, soft tissue quantity and quality) will determine the timing of the treatment sequences. In cases with lower risks and sufficient tissue, a more straightforward approach without abutment connection can be chosen (Fig. 45-10). In contrast, higher risk cases require another treatment sequence with a more complex approach, including abutment connections with or without soft tissue management (Fig. 45-11).

A recent randomized clinical trial compared the esthetic outcomes of implant-supported crowns with and without provisionals in the anterior region. The results after 3 years revealed better esthetic outcomes in the group with provisionals (Furze *et al*. 2019).

Hence, implant-retained provisional reconstructions are not only beneficial for the diagnostic phase but also for the treatment outcomes. Furthermore, they can serve as a communication tool between clinicians, laboratory technicians, and the patients. One of the most important functions of an implant-retained provisional restoration is to develop the desired soft tissue emergence profile. Dental implants differ from teeth in size and shape at the crestal bone level and at the mucosa level. After the healing period, the geometry of the tissue profile tends to be circular and

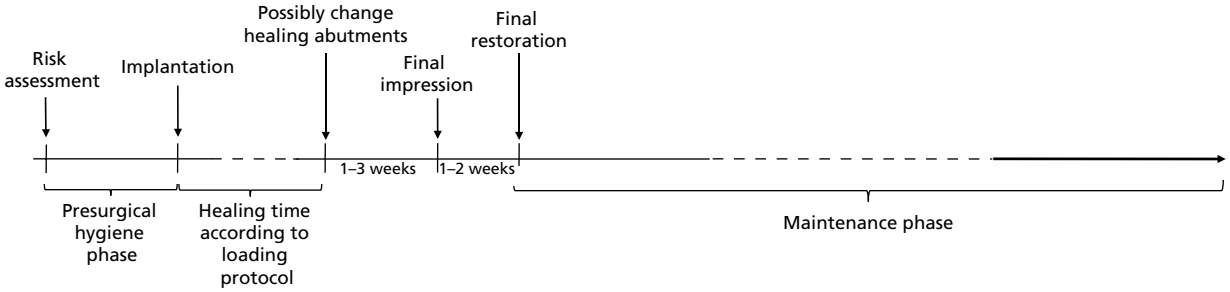


Fig. 45-10 Time sequence of a straightforward case without abutment connection and provisional implant retained restorations.

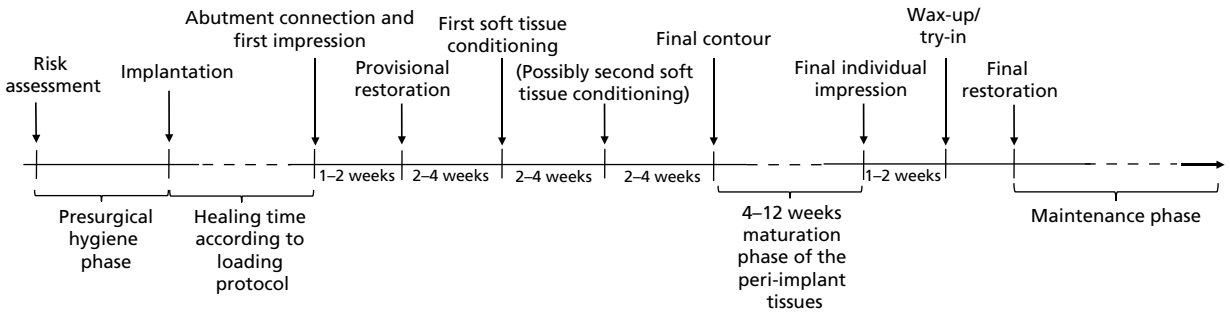


Fig. 45-11 Time sequence of an advanced/complex case with abutment connection and provisional implant retained restorations in order to condition the soft tissues.

does not match the corresponding one around teeth (Fig. 45-12). The tissue profile created by the emergence profile and form of the teeth has a more triangular shape, especially for incisors. Therefore, the peri-implant soft tissue profile has to be converted into a tissue profile that is in harmony with the neighboring dentition (Wittneben *et al*. 2013). This transition can either be performed through individualized healing abutments or implant-retained provisional restorations (Fig. 45-13). These implant-retained provisional restorations can either be fabricated in an ideal contour or with a reduced emergence profile (Fig. 45-14). For the provisional with an ideal profile, the clinician needs to work in a subtractive way by selectively reducing the diameter before being able to place the provisional restoration. In contrast, for the provisional with a reduced emergence profile the clinician is working in an additive way by selectively adding resin material before inserting the provisional (Fig. 45-14).

Provisional restorations can either be cemented or screw-retained. Chapter 44 provides a detailed discussion about the two types of reconstructions along with a decision tree (Fig. 44-23, Fig. 44-24). Overall, the decision whether to cement or screw retain a provisional or a final implant restoration depends on the clinical situation (i.e. angulation of the implant and implant position) and the clinician's preference regarding the method of fixation (Wittneben *et al*. 2017). For proper soft tissue conditioning, a screw-retained provisional is preferred due to the retrievability and the easy conditioning of the soft tissue in the desired direction. Fixed implant-supported provisionals can be fabricated either in the laboratory or chair-side. In order to improve the soft tissue contour, the provisional reconstruction is inserted thereby creating a slight pressure on the mucosa. The applied pressure generates an ischemic reaction, a so-called "blanching" of the peri-implant soft tissue, which should only be moderate and disappear within 15 minutes after placement of the provisional (Cooper 2008). By customizing the shape and the contour of the provisional restoration, the peri-implant contour is improved and the emergence profile formed. This soft tissue conditioning process is performed over a period of 8–12 weeks by selectively adding flowable composite material or light-cured acrylic resin to the provisional reconstruction (Wittneben *et al*. 2013). After achieving the final emergence profile it is important to transfer the created soft tissue profile (Fig. 45-15) to the final master cast. This can be attained by an individualized impression coping that has the same tissue profile as the clinically approved provisional restoration

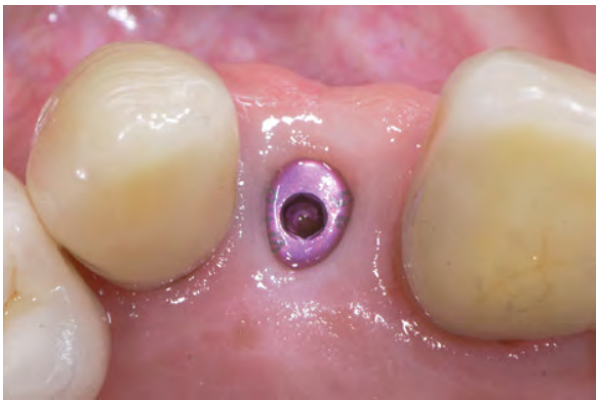


Fig. 45-12 Peri-implant soft tissue profile after a healing period of 3 months, revealing the lack of emergence profile.

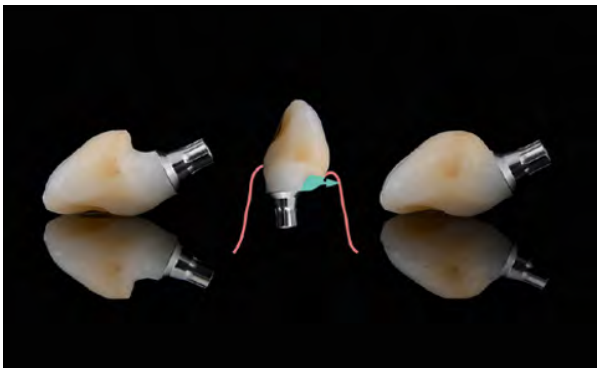


Fig. 45-14 Provisional screw-retained reconstruction with a reduced emergence profile which needs to be individually adjusted by adding resin material before insertion.

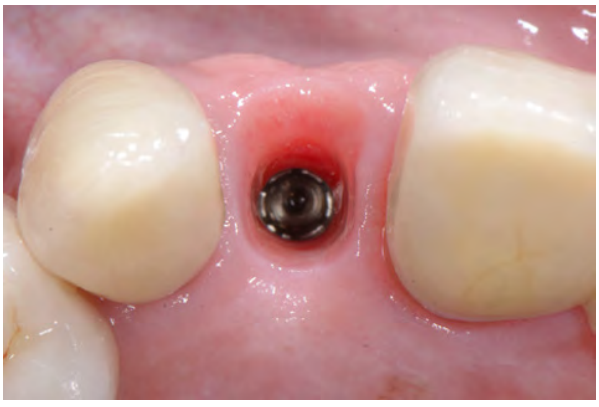


Fig. 45-13 Emergence profile after 2 months of soft tissue conditioning with a screw-retained provisional.

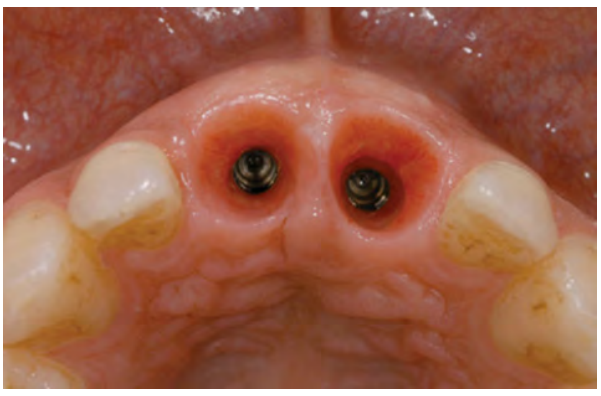


Fig. 45-15 Occlusal view after reaching the final emergence profile of the missing central incisors 11 and 21.

(Furze *et al*. 2019) (Fig. 45-16). As most of soft tissue recessions take place within the first 3–6 months (Oates *et al*. 2002), it has been assumed that the soft tissue margin after the conditioning process stays stable and therefore a final reconstruction can be fabricated. A recent long-term prospective study on immediately restored single tooth implants revealed that a provisionalization phase of 2 months was adequate to provide stability of the soft tissue margins at 8 years follow-up (Raes *et al*. 2018).

New manufacturing techniques (CAD-CAM and 3D printing)

With the advent of digital technologies in implant dentistry, conventional surgical and prosthetic approaches have been increasingly replaced by digital workflows (Schneider *et al*. 2018). Conventional approaches have demonstrated predictable long-term outcomes but they are not free of limitations. These limitations include a higher number of visits and an increased treatment time, which may result in higher costs for the patient. To overcome these limitations, digital workflows through IOS and computer-aided design (CAD) as well as computer-aided manufacturing (CAM) have been introduced (Muhlemann *et al*. 2018). Under a digital workflow, IOS replaces the impression taking and the traditional cast fabrication (Muhlemann *et al*. 2018). The digital impression obtained is then exported to a standard data file. Subsequently, the data file is digitally transferred to the dental laboratory, where the dental technician uses an associated system to design (CAD) and fabricate (CAM) the implant-supported prosthesis utilizing different materials (Pyo *et al*. 2020) (Fig. 45-17). The fabrication process of the different CAD-CAM materials relies on two methods: (1) subtractive or (2) additive manufacturing (Pyo *et al*. 2020). Subtractive manufacturing usually involves a milling process of a disc-shaped manufacturing material to obtain a provisional or a definitive prosthesis (Revilla-Leon *et al*. 2019). These protheses are mainly made out of ceramics including zirconia and lithium disilicate because excess material waste limits the use of metals. On the other hand, additive manufacturing, commonly referred to as 3D printing, is the joining of material layer by layer by means of a 3D printer (Jockusch & Ozcan 2020). This type of manufacturing is advantageous in material waste and reproducibility of complex structures (Galante *et al*. 2019). However, additive manufacturing is still under investigation and, therefore, has not yet been established in daily practice.

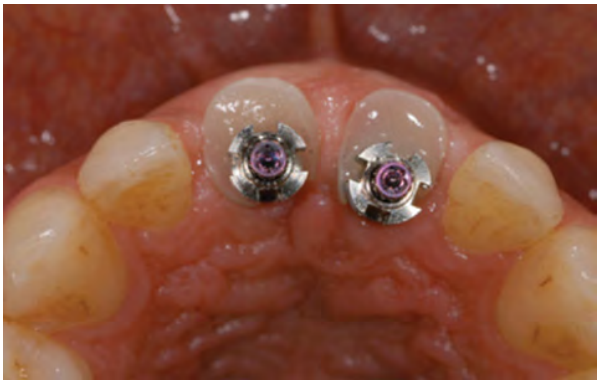


Fig. 45-16 Individualized impression copings in place before impression taking.

Surgical considerations when dealing with implants in the zone of esthetic priority

Surgical aspects for undisturbed wound healing

In general, denuded bone and exposed root surfaces as a result of the surgical intervention must be covered by the soft tissue flap if optimal outcomes are to be achieved. However, in implant surgery, inherent challenges may complicate the procedures. When

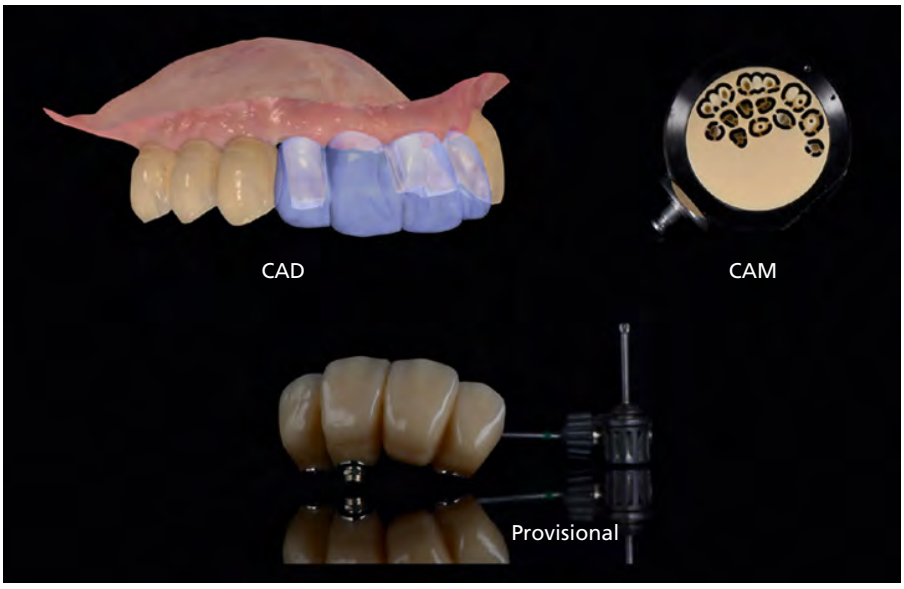


Fig. 45-17 Digital workflow. CAD, computer-aided design. CAM, computer-aided manufacturing.

dealing with implants in the zone of esthetic priority, clinicians are confronted with a variety of anatomic structures, such as hard and soft tissues adjacent to each other, resulting in wounds which are constituted of several interfaces of tissues that fundamentally differ in composition. Furthermore, flap stability and healing outcomes may be hampered during the postoperative phase as the oral cavity is an aqueous environment in which biofilm forms on non-shedding surfaces like teeth and implants and their prosthetic components. Consequently, bacterial colonization may jeopardize uneventful healing (Bartold *et al*. 1992). Also, the negative effect on wound stability and healing outcomes of mechanical influences of continuous masticatory and other functions of the dentition should not be underestimated.

Wound healing primarily depends on early formation and organization of the blood clot and the establishment of an attachment of the clot that is resistant to mechanical forces acting on the flap and opposing surfaces participating in the wound closure (Wikesjo *et al*. 1991). Impaired clot adhesion may weaken the tensile strength of the wound during early healing events and leave the implant–mucosal flap interface susceptible to tearing, compared with physiologic tensile forces on wound margins (Wikesjo & Nilveus 1990). Tensile forces vary depending on the stability of the blood clot and subsequently on the biochemical and mechanical properties of the wound bed (Burkhardt *et al*. 2016). The mechanical weakness of the interface between a debrided, non-shedding root surface, comparable to an implant surface, and the mucoperiosteal flap has been shown to be compensated by the interposition of a connective tissue graft or a collagen matrix, firmly affixed to the denuded root surface. Particularly, connective tissue grafts in thin layers substantially improved the wound healing strength and can be recommended to increase flap stability on non-shedding surfaces (Burkhardt *et al*. 2016), as healing of peri-implant defects following flap surgery involves conceptually more complex processes than wound healing in most other sites of the body.

Most models investigating the tensile forces on wound margins have considered the interfaces in recession coverages (Pini Prato *et al*. 2000). In only one study has the role of flap tension in primary wound closure been investigated in humans (Burkhardt & Lang 2010). In that study, 60 patients scheduled for single implant installation were recruited. Before suturing, the tensile forces on the flaps were recorded with an electronic device. After 1 week the wounds were inspected with regards to complete closure. While flaps with minimal tension of 0.01–0.1 N resulted in only a few (10%) wound dehiscences, flaps with higher closing forces (>0.1 N) yielded significantly increased percentages of wound dehiscences (>40%). This study also revealed that flaps with a thickness of >1 mm demonstrated significantly lower proportions of flap dehiscences at higher closing forces (>15 g) than thinner flaps (≤1 mm). The results of this study indicated a need to control the closing forces at the wound margins. In order to minimize tissue trauma, finer suture diameters may be helpful owing to the fact that thinner sutures (6-0, 7-0) lead to thread breakage rather than tissue tear and breakage (Burkhardt *et al*. 2008).

It is evident that flap design, flap advancement, and suturing should receive greater attention in situations where mucoperiosteal and/or mucosal flaps are positioned to cover large peri-implant defects. Owing to the fact that the peri-implant wound is constituted of the connective tissue surface of the flap and an avascular surface such as titanium, ceramics, or another alloplastic material, peri-implant defects require careful tissue management and stable flap adaptation, especially in the anterior zone of the upper jaw where the mucosal morphology and topography play an important role in the esthetic result.

Incisions and flap design

Flaps can be classified according to their form (e.g. semilunar, triangular), the direction of the intraoperative advancement (e.g. rotating, apically, or coronally advanced) or the composition of the contributing tissues (e.g. full thickness, split thickness). In contrast to connective tissue grafts, which receive their early nutrition by plasmatic diffusion, flaps are characterized by a still functioning network of vessels which provide the injured tissues with blood. Thus, it is evident that when planning the flap outline, attention should focus on the importance of maintaining a good blood supply from vessels entering at the base of a pedicle. To assure a good blood supply, it was recommended that two aspects are noted before starting with the first incision: (1) a broad flap base which allows many nutrient vessels to enter the flap and (2) a flap length-to-width ratio that should not exceed 2:1. These principles seemed to make sense because increasing the flap's width at its base increases the blood supply and supports a greater flap length. However, with a deeper insight into the biologic contexts and processes (Kleinheinz *et al*. 2005), these recommendations now appear rather too simplistic. It cannot be assumed that major vessels enter the base of mucosal flaps at regular intervals. Additionally, most conclusions from studies focusing on vascular impairment are based on histologic examination of specimens after vascular perfusion and suggest that blood vessels remain intact and patent following surgery. Alternative techniques like fluorescein angiography (Mörmann *et al*. 1975; Mörmann & Ciancio 1977) and laser-Doppler flowmetry (Retzepi *et al*. 2007a, b) are more reliable in qualitatively and quantitatively evaluating the vascularity and blood supply of an injured mucosal area.

An important difference between the blood supply of periodontal and peri-implant soft tissues

after wounding is the presence of the periodontal ligament around teeth. The dense capillary network has been shown to contribute to the early nutrition of the adjacent mucosa and to be a major source for sprouting capillaries in the angiogenetic process (Schröder 1986). Following horizontal incisions along the mucogingival junction, the blood supply of the gingiva was displayed with a fluorescent dye (Mörmann & Ciancio 1977). One day after the injury, the gingiva coronal to the incision line showed a severe anemia, which was more pronounced in the interdental and papillary area than in the tooth prominences. The authors explained the differences as the result of the influence of the collateral vessels coming from the ligament and contributing to the marginal tissue perfusion. It might have a minor influence on wound healing but the vascularity of the periodontal ligament around teeth increases gradually from the incisors to the molars, being least at lateral incisors of the upper jaw. In all single-rooted teeth, the mesial and distal surfaces are usually better perfused than oral and buccal ones (Schröder 1986).

These results have been confirmed in another angiographic dog study (McLean *et al*. 1995) which showed that the sole act of flap elevation initiates substantial and significant vascular trauma. Significant reduction in flap circulation in relation to the presurgical baseline lasts for at least 3 days in the mid-buccal sites, but persists for 7 days at the interproximal sites, independent of the applied suture techniques. This is an important finding and might have an impact on the decision regarding an ideal flap outline when dealing with implant placements or retreatments in the upper anterior zone where there is no collateral vascularity from the periodontal ligament.

Another critical factor influencing the vascularity of a flap is its length, especially when the flap is replaced on an avascular surface like a root or the alloplastic material of an implant or its components. Several studies confirm a decrease of the flap vascularity with increasing flap length (Mörmann & Ciancio 1977; McLean *et al*. 1995). Interestingly, in studies of the early healing stages, significantly greater portions of the flaps took up fluorescence from extravascular diffusion compared with from intracapillary circulation. While it is certainly prudent to avoid long pedicle flaps in implant surgery, other flap properties like thickness and alternate vascular sources deserve recognition.

Based on reliable knowledge of the distribution pattern and architecture of the arterial vascular system of the human oral mucosa, recommendations for ideal flap preparation and releasing incisions can be given (Kleinheinz *et al*. 2005): (1) avoid releasing incisions in the zone of esthetic priority; (2) place mid-crestal incisions in edentulous areas; (3) incise in the sulcular area around teeth and avoid marginal and paramarginal incisions; (4) if a releasing incision is required, cut the flap as short as possible and carry it out at the anterior border of the incision line. The releasing incisions should not be placed on the buccal root prominences as there the mucosa is thicker between two teeth (Müller *et al*. 2000). Incision lines in the concavity between two teeth facilitates a firm flap adaptation and provides a better vascular network within the pedicle flap.

Implant placement in the zone of esthetic priority is often combined with guided bone regeneration procedures and soft tissue augmentations to compensate for the lost tissue volumes and to restore the morphology of the implant housing in all three dimensions. To achieve a healing on primary intention, the soft tissue flaps must be mobilized to completely cover the augmented sites. Such flap advancement is limited and also has some adverse effects. The common method of flap lengthening consists of a periosteal incision at the base of the buccal flap to reduce its resistance. The extent of flap lengthening depends on the outline of the flap and has been evaluated in a cohort study on patients (Park *et al*. 2012). Simply by placing one vertical releasing incision and pulling with a tension of 5 g, the flap could be mobilized by 1.1 ± 0.6 mm, which corresponds to 113.4% of its original length. These values increased to 1.9 ± 1.0 mm (124.2%) when a second vertical incision was made at the opposite end of the horizontal incision and became statistically highly significant after combining the two vertical releasing incisions with a periosteal releasing incision, yielding a flap advancement of 5.5 ± 1.5 mm (171.3%).

The abovementioned surgical technique facilitates primary wound closure but shows distinct disadvantages as the coronal mobilization of the masticatory mucosa might decrease the amount of masticatory mucosa lateral to the implant-supported crown. Additionally, the irregularity of the mucogingival junction can cause an esthetic problem in high lip line cases when a broad zone of soft tissues is displayed apical of the mucosal margin. A variety of advanced flap techniques have been described to achieve primary wound closure and overcome the abovementioned drawbacks (Tinti & Parma-Benfenati 1995; Nemcovsky *et al*. 1999; Triaca *et al*. 2001; Penarrocha *et al*. 2005; Stimmelmayr *et al*. 2010). Even if a certain approach shows promising clinical results, some of them should be applied with caution as they are technically highly sensitive and hold pronounced risks for adverse outcomes. Successful implant treatments in the zone of esthetic priority include many variables of flap management that are interconnected and which have to be carefully evaluated and assessed in relation to the patient's expectation and the expertise and psychomotor skills of the individual clinician.

In order to maintain the original tissue morphology for esthetic reasons and to shorten the treatment duration, an increasing number of publications favor the placement of the implants immediately after tooth extraction (Slagter *et al*. 2014; Cosyn *et al*. 2016; Buser *et al*. 2017; Noelken *et al*. 2018). Most of them are in combination with free connective tissue grafts,

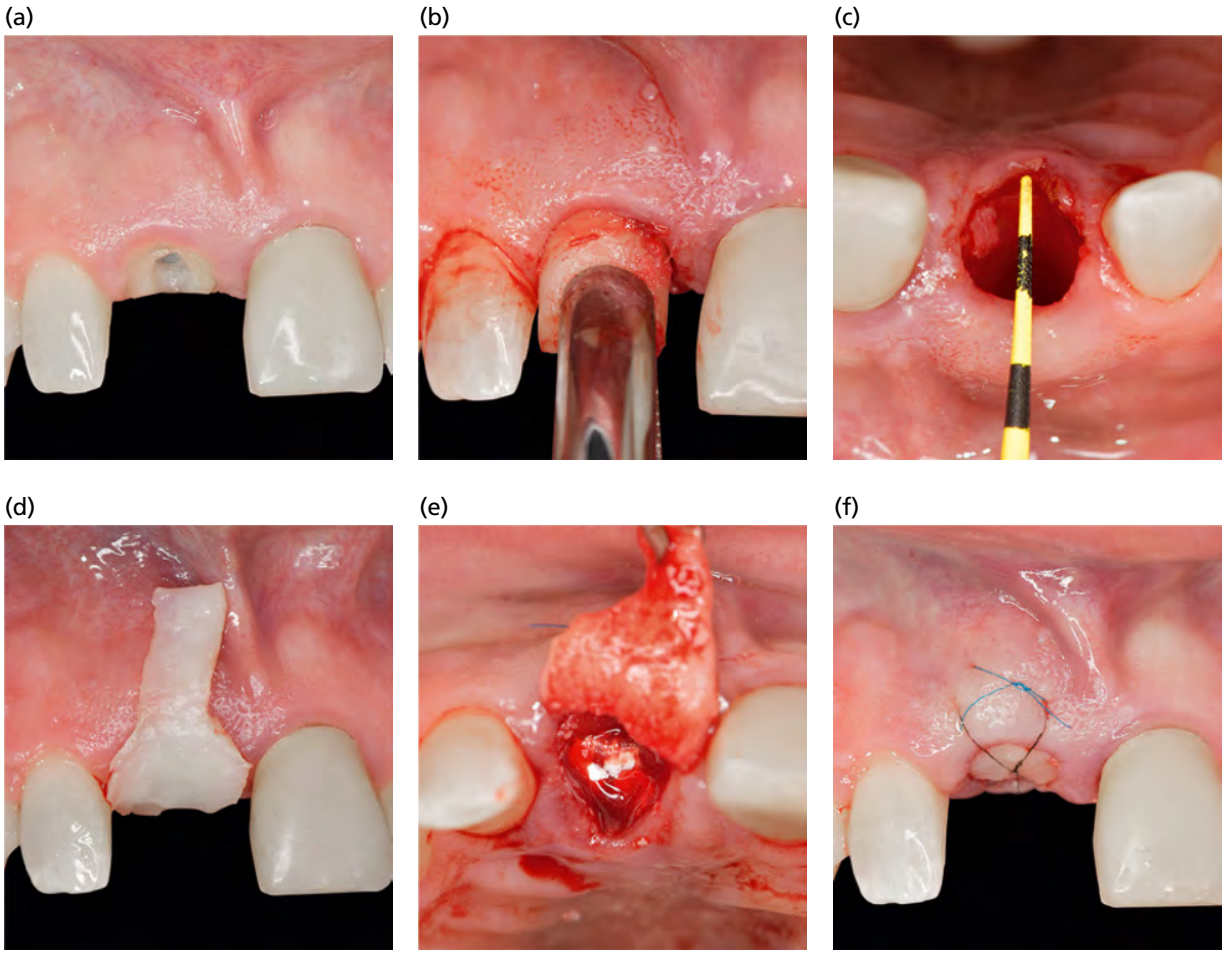


Fig. 45-18 (a) Preoperative view from above: central incisor with root resorptions that have to be removed and replaced. (b) Tooth extraction after careful circumferential dissection of the supracrestal connective tissue fibers. This treatment step can only be performed under visual control when the clinical crown has been removed presurgically. (c) The dimension of the tooth cross-section at the level of the gingival border defines the size of the connective tissue graft ensuring sufficient coverage buccal and orally and by the adjacent mucosa of the col areas. (d) Connective tissue graft harvested from the palatal lamina propria and trimmed to the appropriate dimension. (e) Graft fixation after implant placement and covering the socket with a resorbable membrane. (f) Lateral view of postsurgical site. The socket is primarily closed by the connective tissue graft, secured by only three fine sutures.

either to compensate for postoperative buccal tissue shrinkage or to achieve primary wound closure (Fig. 45-18). Overall, short- and long-term results seem to be comparable to the ones with immediate-delayed and delayed implant insertions (Chen & Buser 2014), but factors such as mucosal phenotype, thickness of the facial bone, and vertical level of the facial bone crest need more careful attention to avoid the increased risks of adverse esthetic outcomes compared with implants placed using a delayed approach. Additionally, other aspects should be noted in the decision-making process for immediate implant placement in the anterior zone of the upper jaw. Firstly, several of the described implant insertion and flap procedures are highly technically sensitive (Baumer *et al*. 2017; Mosea 2018; Zuhr *et al*. 2018) and there are no commonly accepted meaningful measures to assess technical expertise of implant surgeons. A recent study confirmed the findings from other surgical specialties (Eva & Regehr 2005; Saposnik *et al*. 2016) that the self-assessed expertise of clinicians does not correspond with objectively collected data and surgeons tend to be overly self-confident (Burkhardt *et al*. 2019). Secondly, it should be noted that in a majority of studies reporting about the positive esthetic results with immediate implants, no detailed information is available about the reasons for tooth loss and about the periodontal, endodontic, and prosthetic aspects that led to the decision for tooth extraction and which might have an impact on the final esthetic result.

Clinical concepts for replacement of a single missing tooth

Before any implant placement in the anterior region, a comprehensive presurgical risk analysis of the single-tooth gap is of utmost importance. An increasing body of evidence indicates that the most determinant parameter for achieving esthetic results in the anterior region is the interproximal bone height at the neighboring teeth confining the edentulous gap

(Jung *et al*. 2018; Roccuzzo *et al*. 2018). The related bone should be within a physiologic distance (i.e. approximately 2 mm) of the cementoenamel junction (CEJ), thereby providing the essential support for the overlaying soft tissue compartments. Consequently, the preoperative diagnosis will include interproximal radiographic bone height assessment and periodontal probing of the soft tissue attachment level. If a case presents missing interproximal bone, alternative conventional prosthetic solutions need to be taken into consideration. In this particular case of a 38-year-old woman, a zirconia adhesive bridge was inserted after alveolar ridge augmentation procedures (Fig. 45-19).

Sites with no or minor tissue deficiencies

If the risk analysis confirms a favorable vertical level of both soft tissue and underlying alveolar bone at the interproximal aspect of the two adjacent teeth on the one hand, and no major vestibular bone deficiencies on the other hand along with a normal to thick phenotype, the site can be considered compatible with a straightforward implant surgical protocol including immediate implant placement. In order to ensure the best probability of a successful and long-lasting esthetic treatment outcome, the actual implant placement has to be carried out meticulously, including key parameters such as low-trauma surgical principles in general and precise three-dimensional ("restoration-driven") implant positioning in particular.

A 51-year-old man was referred to the dental clinic due to a tooth fracture at tooth 11 (Fig. 45-20). The patient formerly smoked and had no underlying health conditions. Apart from a thick gingival phenotype, the patient had a low smile line and according to the CBCT, tooth 11 exhibited a thick facial bone (>1 mm). Based on these findings and the latest Consensus Report of the European Workshop in Periodontology (Tonetti *et al*. 2019) where the current evidence regarding the implant placement protocols were appraised, this patient was a suitable candidate for an immediate implant placement protocol (type 1) (Gallucci *et al*. 2018; Cosyn *et al*. 2019). It should be emphasized that the patient was thoroughly informed about the slightly higher risk of early implant loss that immediate implant carries compared with delayed implant placement (4% excess implant loss). This protocol, however, tends to be preferred by the patients because it may involve tangible shorter treatment time and cost-efficiency (Tonetti *et al*. 2019).

Sites with extended tissue deficiencies

The risk analysis of a 23-year-old female patient revealed a demanding clinical situation with missing buccal bone and a buccal probing pocket depth of 11 mm at the left central incisor (Fig. 45-21). The radiographic analysis demonstrated intact mesial and distal crestal bone levels (Fig. 45-22). This is an important prerequisite in order to be able to maintain the interdental soft tissue level. Based on the clinical and radiographic findings the diagnosis was a vertical root fracture of tooth 21. After patient information and discussion of the therapeutic options it was decided to extract the tooth and to replace it by an implant supported single crown. Due to the extended buccal bone defect it was decided to perform a socket preservation technique to improve the soft tissue quality and quantity before implant placement and bone augmentation procedure. In this case of extended horizontal alveolar bone crest deficiencies, a simultaneous implant placement and lateral bone augmentation procedure becomes technically more difficult and less predictable, as the ultimate goal remains an optimal "restoration-driven" implant positioning. Therefore, the feasibility of combining implant placement with simultaneous bone regeneration procedure was evaluated by performing preoperative diagnostics and a CBCT scan. The CBCT scan revealed an extended buccal bone defect with a minimal amount of apical bone to stabilize the implant (Fig. 45-23). After three-dimensional computer-assisted implant planning a computer-guided template was fabricated within the dental laboratory. After a healing period of 6 weeks following tooth extraction a mucoperiostal flap was elevated. This was advocated by a palatal crestal

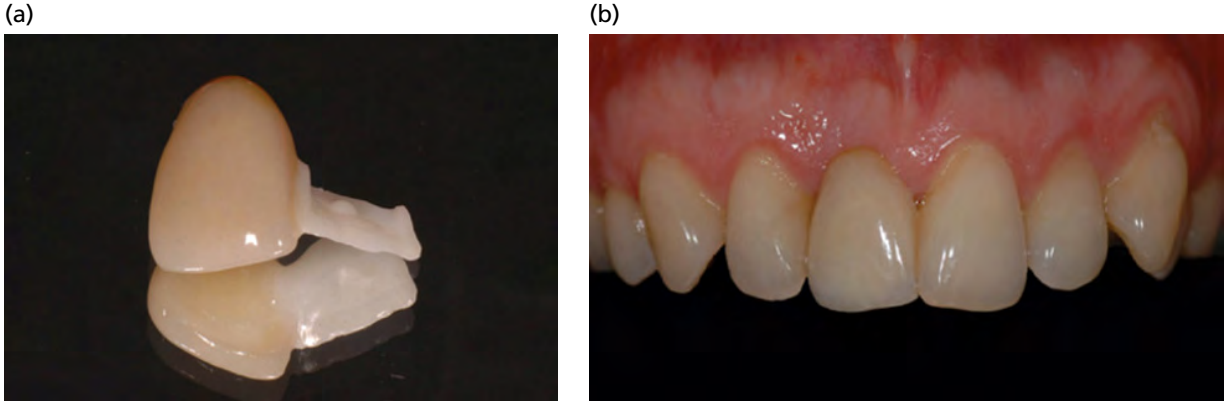


Fig. 45-19 (a) Extraoral view of a zirconia-based adhesive bridge with backing to tooth 21. (b) Final zirconia adhesive bridge in place 1 year after cementation.

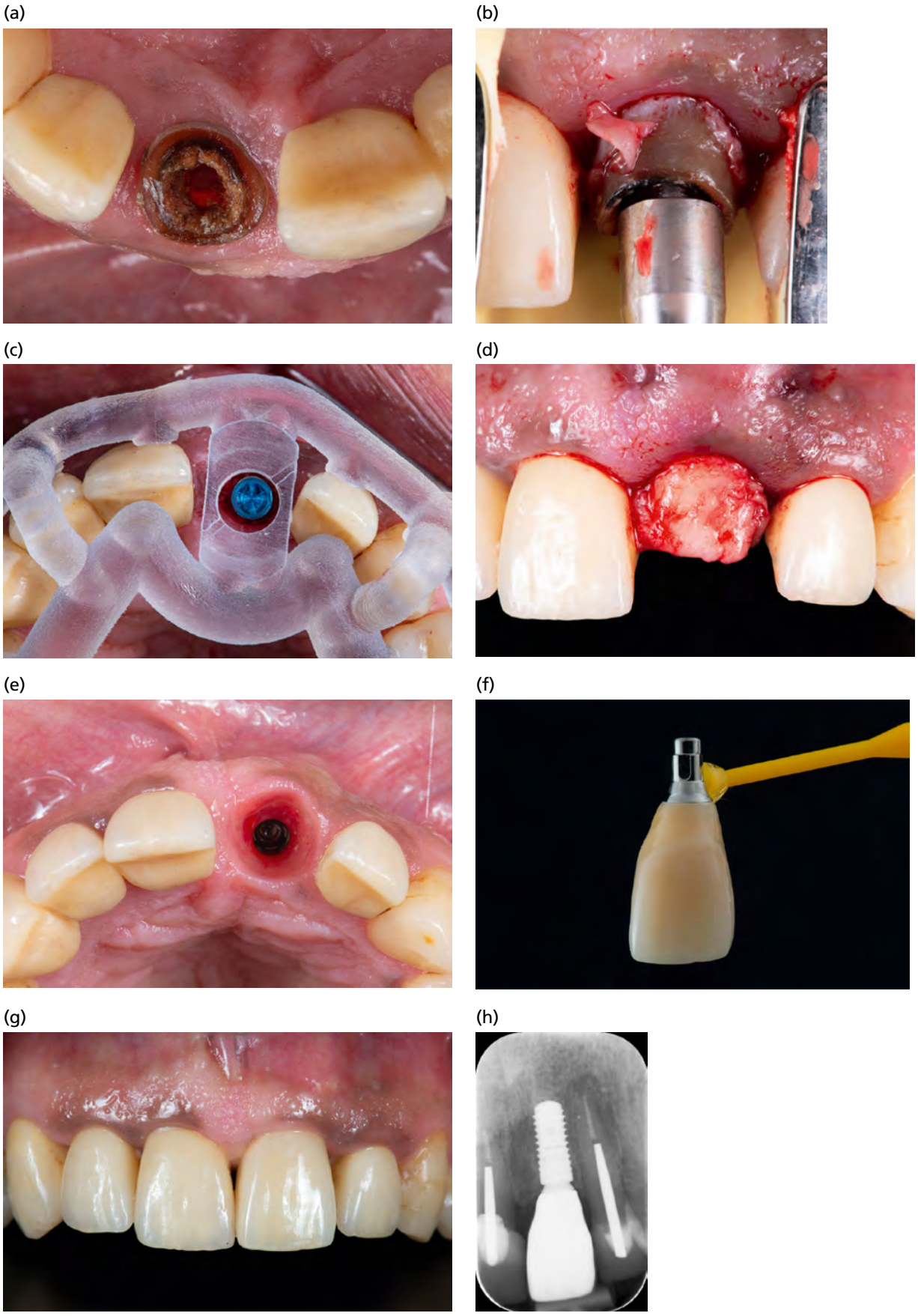


Fig. 45-20 (a) Initial clinical situation of tooth 21 after the removal of the crown. (b) In order to avoid additional bone resorption a flapless tooth extraction was performed using a tooth extraction device. (c) Immediate implant placement using a 3D-printed stent to achieve a prosthetically driven insertion. (d) Placement of a connective tissue graft following implant placement. (e) Final emergence profile after an immediate provisionalization period of 4 months. (f) All-ceramic crown made from zirconia cemented extraorally to a stock hybrid abutment with a titanium base. (g) All-ceramic reconstruction delivery at region 21 showing healthy peri-implant tissues along with sufficient keratinized mucosa. (h) Periapical radiograph revealing optimal osseointegration at 6 months follow-up.

incision followed by sulcular incisions and a vertical releasing incision distal 22. With the help of the computer-guided stent it was possible to ideally place the implant in the proper prosthetic position (Fig. 45-24). Because of the complete loss of the buccal bone a volume stable non-resorbable membrane was chosen. After grafting the site with autogenous bone particles and demineralized bovine bone mineral (DBBM)

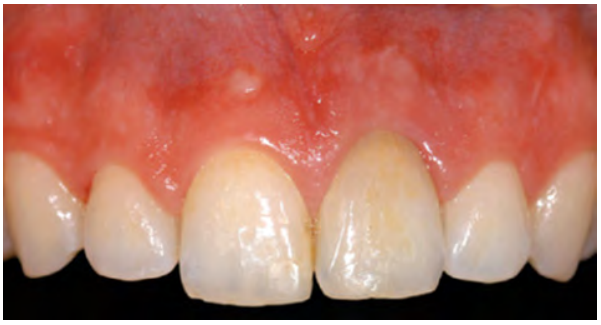


Fig. 45-21 Preoperative view of a 23-year-old woman. Left central incisor shows slight discoloration and apical migration of the gingival margin.

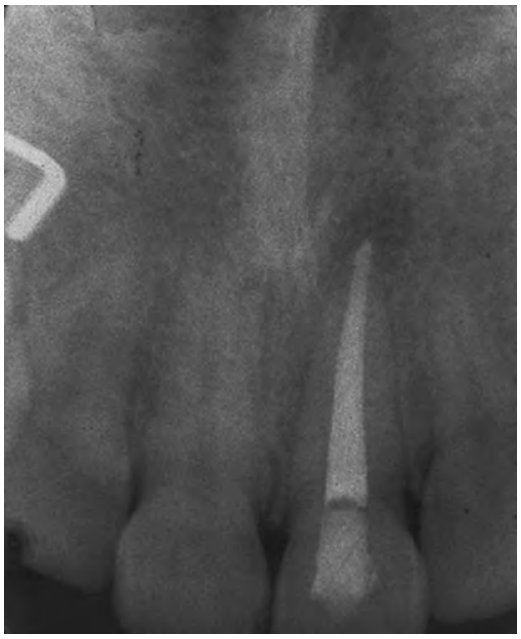


Fig. 45-22 Radiographic analysis revealed an endodontically treated incisor and an apical radiolucency. Mesial and distal bone levels were intact.

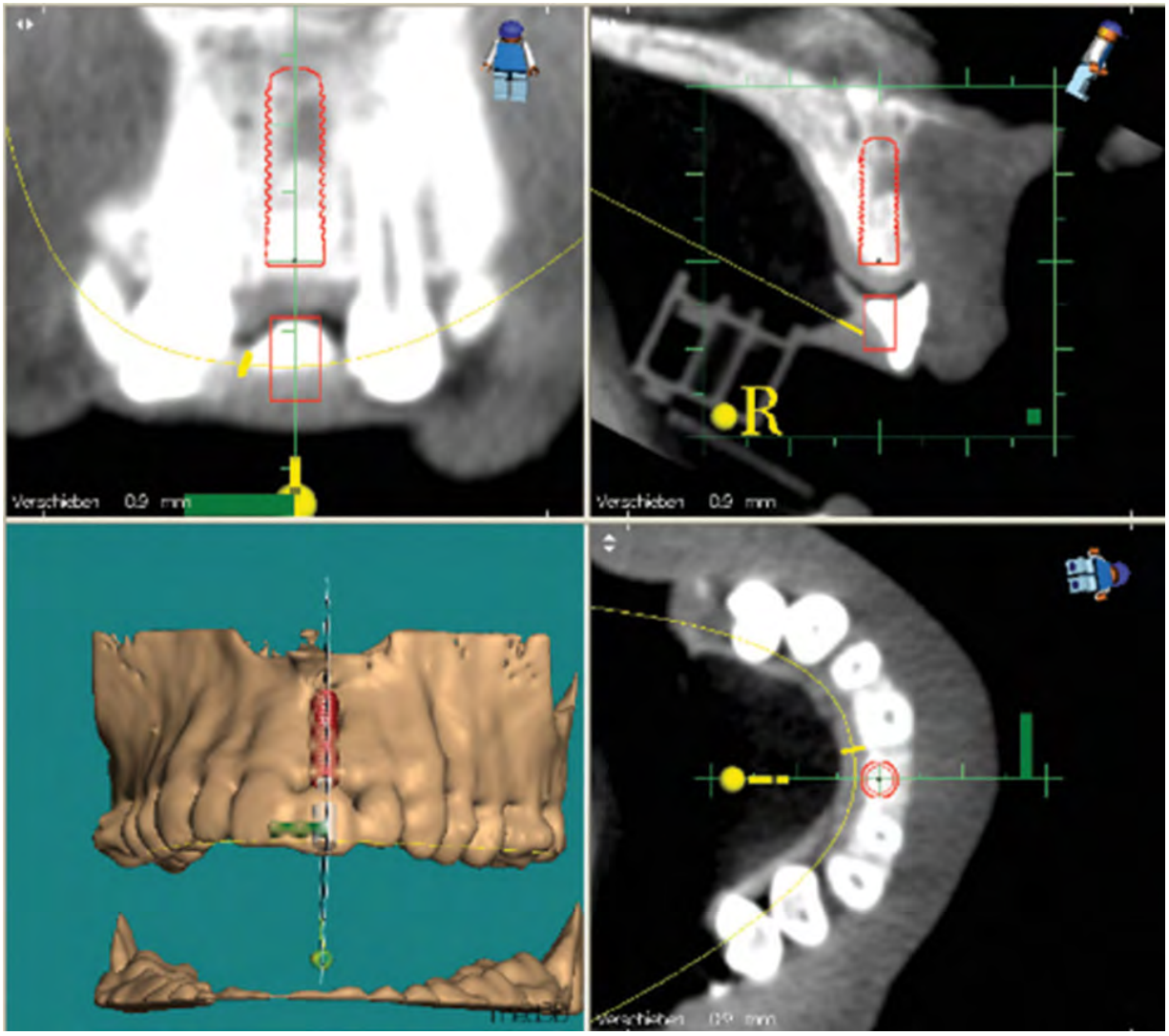


Fig. 45-23 CBCT was obtained using a scanning template with barium sulfate (BaSO4) teeth according to the previously performed wax-up. The ideal implant position was established using 3D planning software and a surgical guide was fabricated.

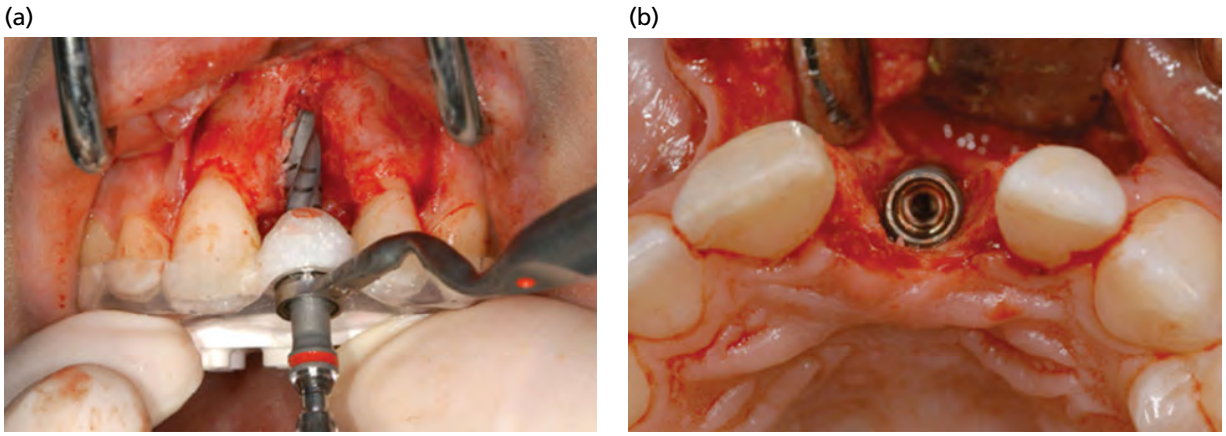


Fig. 45-24 (a) Guided implant drilling was performed based on the CBCT and implant planning software helped to stabilize the drills during the preparation process. (b) Occlusal view of the implant in place. Note the non-self-containing buccal osseous defect, which limits the guided bone regeneration options.

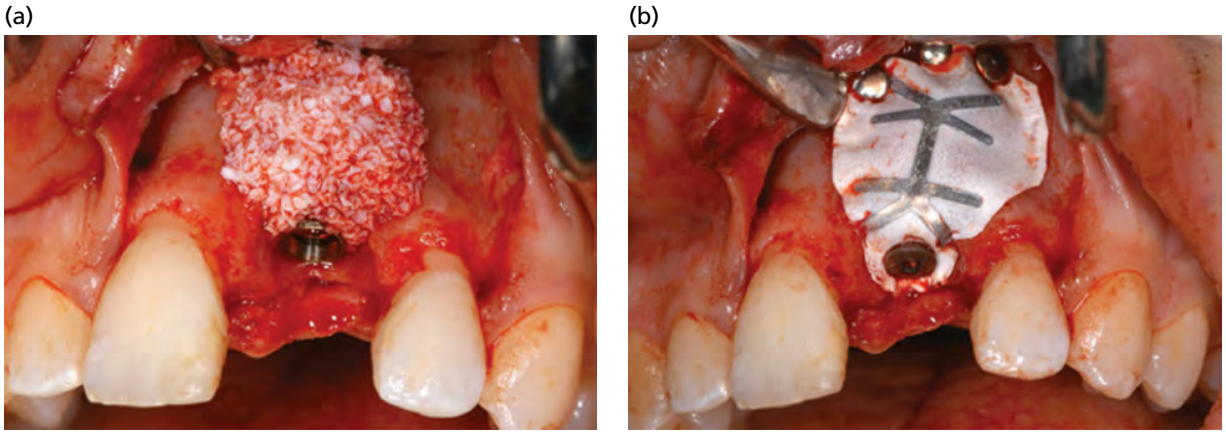


Fig. 45-25 (a) After placement of autogenous bone particles, harvested from the neighboring area, an additional layer of deproteinized bovine bone mineral (DBBM) was added on top of the implant in order to recreate the missing contour. (b) Due to the non-self-containing osseous defect, a volume of stable non-bioresorbable titanium-reinforced e-PTFE membrane was used in combination with titanium fixation pins. Additionally, the implant cover screw was used to stabilize the membrane.

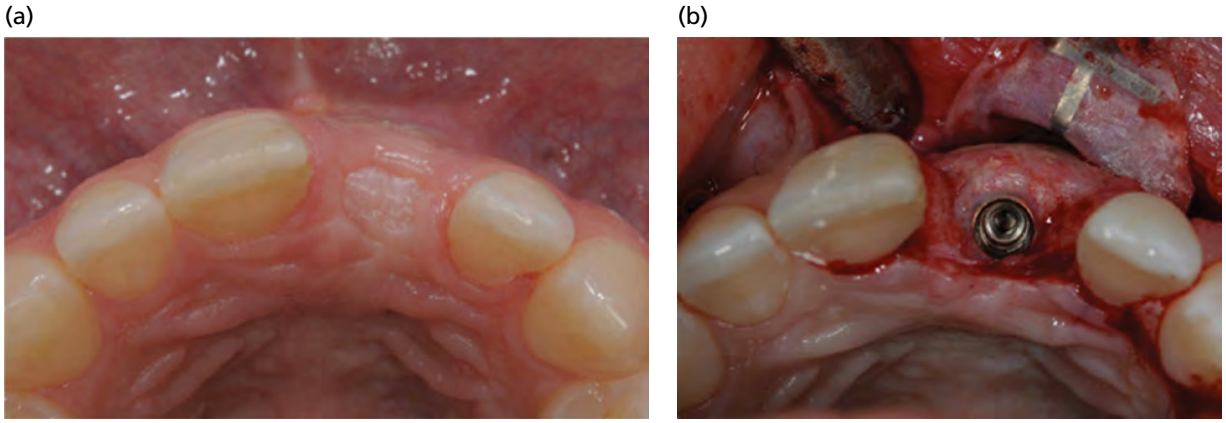


Fig. 45-26 (a) Occlusal and buccal views after a healing period of 6 months. Note the maintained buccal ridge contour. (b) Full thickness flap was raised in order to remove the volume of stable e-PTFE non-bioresorbable membrane. The implant was completely covered by bone and the buccal contour was recreated.

a titanium reinforced ePTFE membrane was applied to the defect morphology and adapted with titanium pins (Fig. 45-25). Subsequently, the periosteum was released in order to facilitate a completely flapless soft tissue closure. After a healing period of 6 months a full thickness flap was elevated again in order to remove the non-resorbable membrane and the titanium pins (Fig. 45-26). In addition, a connective tissue graft harvested from the palate was placed underneath the flap in order to increase the soft

tissue volume (Fig. 45-27). Six weeks later, a minimally invasive abutment connection was performed by using a u-form incision and rotation of this flap to the buccal. Simultaneously to the abutment connection an impression was taken on the level of the implant shoulder. The screw-retained implant-borne provisional crown was used for diagnostic purposes and to form the emergence profile. After reaching the final soft tissue contour (Fig. 45-28) a definitive individual impression was taken in order to capture the information from the temporary restoration. In this way, the clinical situation is transferred to the master model, which contains a replica (analogue) of the implant. This master model was subsequently scanned in order to produce an individual zirconia abutment by means of a CAD-CAM procedure. By directly veneering this zirconia abutment it was possible to provide the patient with a very natural-looking screw-retained all ceramic crown (Fig. 45-29).

Clinical concepts for replacement of multiple missing teeth

The normal consequence following the loss of two or more adjacent upper anterior teeth comprises a flattening of the edentulous segment (Tan *et al*. 2012). In particular, the disappearance, in an apical direction, of the crestal bone originally located between the incisor teeth can be observed (Tan *et al*. 2012). This phenomenon is not, or only minimally, present at the interproximal aspect of the remaining anterior teeth and thus explains the fundamental difference between a maxillary anterior single-tooth gap and a multiunit edentulous segment.

If two standard screw-type titanium implants are inserted to replace two missing maxillary central incisors (Fig. 45-30), an additional peri-implant bone remodeling process will take place. In the frontal plane, two different characteristic processes, one between the tooth and the implant and the other between the two implants, can be distinguished. At the site between tooth and implant, the tooth-sided interproximal bone height should theoretically remain at its original location, i.e. within 2 mm from the CEJ, from where the implant-sided interproximal bone height drops in an oblique manner towards the first implant-to-bone contact, normally located approximately 2 mm apically of the junction ("microgap") between the implant shoulder and the abutment or suprastructure. This phenomenon has been referred to in the literature as the establishment

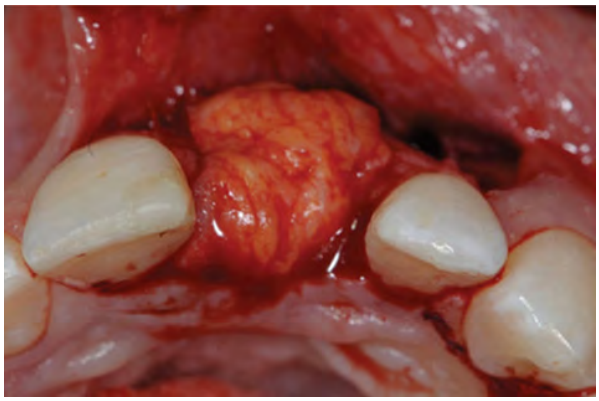


Fig. 45-27 Additionally, a connective tissue graft, harvested from the palate, was placed to augment both the occlusal and buccal aspects of the ridge. It was first sutured to the palate and then mobilized to the buccal site.

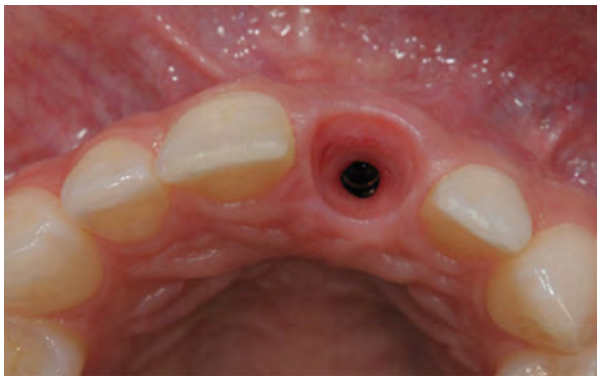


Fig. 45-28 Simultaneously, an impression was taken at the level of the implant shoulder and sent to the laboratory to fabricate a screw-retained acrylic provisional.

(a) (b)

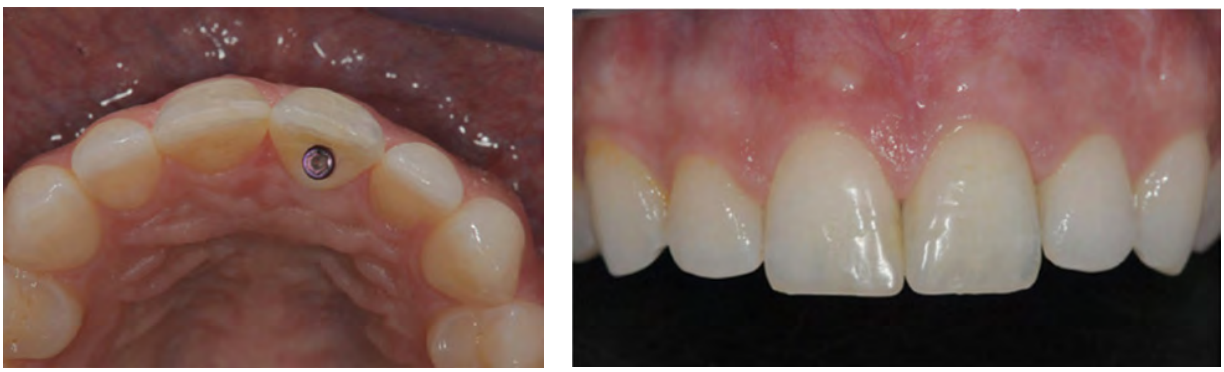


Fig. 45-29 (a) Occlusal view of the final screw-retained restoration. Note the ideal position of the access hole for the prosthetic screw. (b) Final restoration was fabricated by direct ceramic veneering of the zirconia abutment. Note the symmetry between the soft tissue margin and contour compared with the right central incisor.

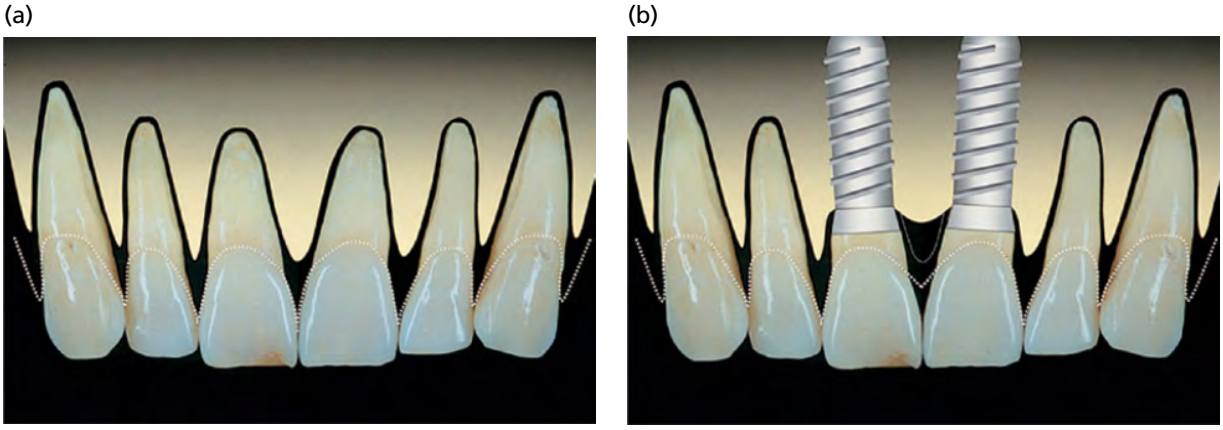


Fig. 45-30 (a) The six maxillary anterior teeth, including their bony support and the course of the marginal soft tissue, corresponding ideally approximately to the cementoenamel junction (dotted line). (b) Loss of the two central incisors and their subsequent replacement by implant restorations normally leads to well-defined bone loss ("micro-gap", establishment of a "biologic width") around the implant sites. The main consequence from an esthetic point of view is vertical soft tissue deficiencies, namely between the adjacent implants (dotted lines).

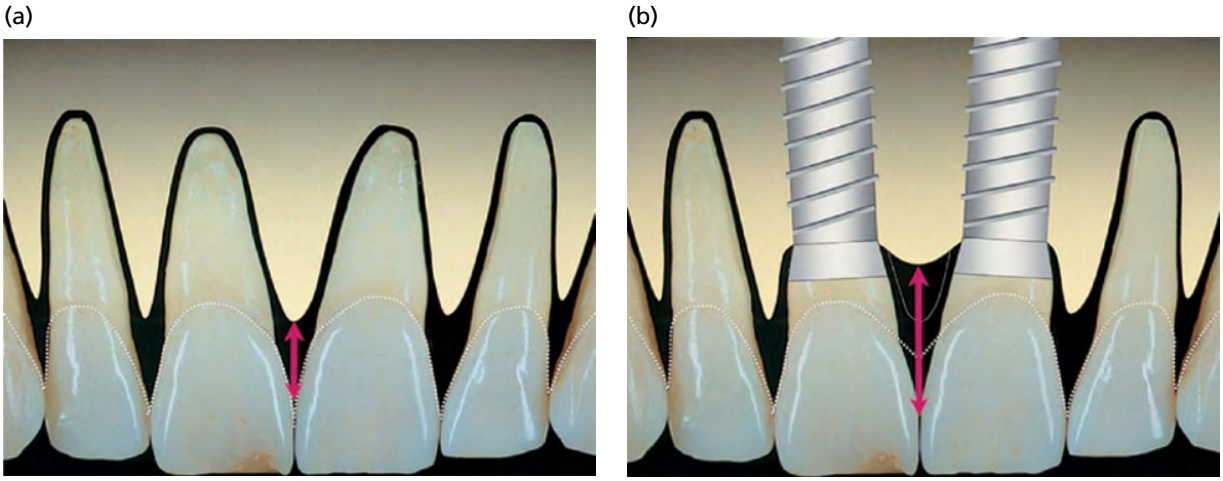


Fig. 45-31 (a) Close-up view of the relationship between the cementoenamel junction, alveolar bone, and gingiva in the maxillary incisor area. (b) Same area after implant therapy. The arrow represents the distance between the interimplant bone crest and the interdental contact point. The lack of bony support for the interdental soft tissue often causes the appearance of black triangles, compromising the esthetic treatment outcome.

of a "biologic width" (Sculean *et al*. 2014; Araujo & Lindhe 2018). In contrast, the interimplant bone height normally decreases further in an apical direction, once the respective abutments or suprastructures are connected to the implant shoulder (Caricasulo *et al*. 2018). This process is mostly accompanied by a loss of interimplant soft tissue height and hence may lead to unsightly, so-called "black interdental triangles". The schematic close-up views comparing the original dentate situation with the status after integration of two adjacent implant restorations, clearly demonstrate the negative consequences on the course of the marginal soft tissue line in a case of multiple adjacent maxillary anterior implants (Fig. 45-31).

For all the abovementioned reasons the implant position and distribution in cases with multiple missing teeth in the esthetic area are of great importance. With two missing central incisors, two implants are placed with sufficient distance between them (Fig. 45-32). In cases of a missing central and a missing lateral incisor, it is preferable that only one implant at the position of the central incisor is placed, with a cantilever replacing the lateral incisor (Fig. 45-33). Because of the small diameter of a lateral incisor the mesiodistal dimension often does not allow two implants to be placed with sufficient interimplant distances. In a clinical situation with three missing incisors including teeth 11, 21 and 22, it is recommended that two implants are placed. One option is to place two implants at positions 11 and 22 in order to have sufficient space between the implants (Fig 45-34). The drawback of this option is the difficulty with creating a similar appearance of the emergence profile of an implant restoration (implant 11) and a pontic at postion 21 with a prosthesis. Alternatively, if there is a sufficient mesiodistal dimension in the area of the two missing central incisors, one implant can be placed at position 11 and the other at position 21, with a cantilever to replace 22 (Fig 45-35). With this second option, two identical emergence profiles

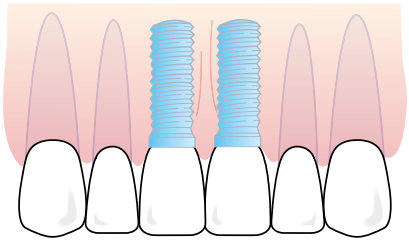


Fig. 45-32 Replacement of both central incisors with non-splinted implant-supported crowns.

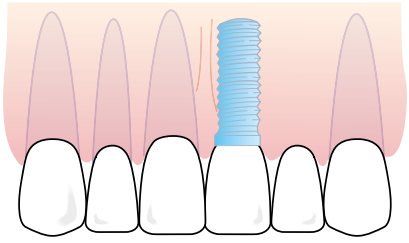


Fig. 45-33 Replacement of a central incisor with an implant and the lateral incisor with a distal cantilever.

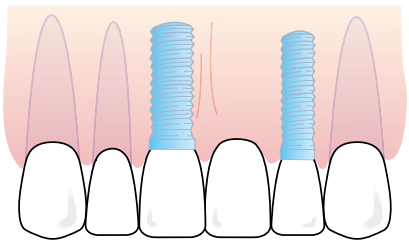


Fig. 45-34 Replacement of 3 missing incisors with an implant supported bridge with the pontic at position 21.

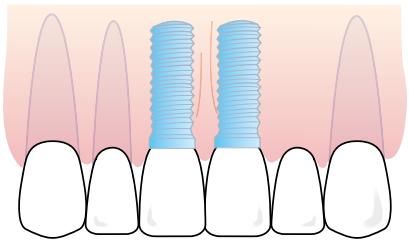


Fig. 45-35 Replacement of 3 missing incisors with 2 implants at position 11 and 21, and 21 with a distal cantilever.

can be created, but has the drawback of having two implants next to each other. When all four incisors are lost, generally two implants are placed at the position of the two lateral incisors (Fig 45-36). This concept has also been proven with the use of reduced diameter implants at positions 12 and 22 over an observation period of 5 years (Moraguez *et al*. 2017).

Sites with minor tissue deficiencies

In cases with minor tissue deficiencies, the previously described shortcomings are also inherent in multiple adjacent implant restorations. Therefore, some restorative "tricks", including peri-implant soft tissue conditioning and a

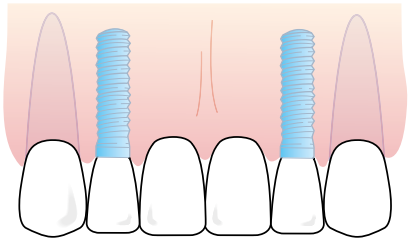


Fig. 45-36 Replacement of all four incisors with two implants and two pontics in between.

particular interproximal crown design, need to be implemented to predictably achieve an acceptable esthetic compromise. The initial prosthetic planning, the implant surgery, and the prosthetic reconstruction for a 54-year-old man who in an accident had lost three incisors and one pontic at the position of 21 are shown in Fig. 45-37.

Sites with severe tissue deficiencies

A 24-year-old patient, because of a riding accident, lost teeth 11, 12, 13, 14, and 15, resulting in severe soft and hard tissue deficiencies. Apart from the severe tissue deficiencies, the clinical examination revealed a high smile line along with a thin phenotype. In this context, a complex surgical reconstruction of the region was unavoidable. The risk analysis and treatment plan were presented to and discussed with the patient. Key factors in favor of the procedure were the good general conditions, young age, and willingness to undergo orthodontic treatment. The clinical steps are shown in Fig. 45-38.

Prosthetic reconstruction in the zone of esthetic priority

As high implant survival and success rates have been reported, the esthetic outcome of the reconstruction has become the main focus of interest in these sensitive areas. The prosthetic reconstruction should imitate the appearance of the healthy teeth as closely as possible. When deciding the final prosthetic reconstruction, the dentist and the dental laboratory technician should assess and consider the following aspects.

Decision-making process: standardized versus customized abutments

Each clinical situation should be individually analyzed in order to decide whether to use a standardized prefabricated abutment or a customized abutment in the esthetic area. In order to facilitate the decision-making process, a decision tree has been provided in Chapter 44. A thorough assessment should include the following factors so that the right choice can be made: (1) soft tissue morphology including soft tissue scalloping and vertical implant position,

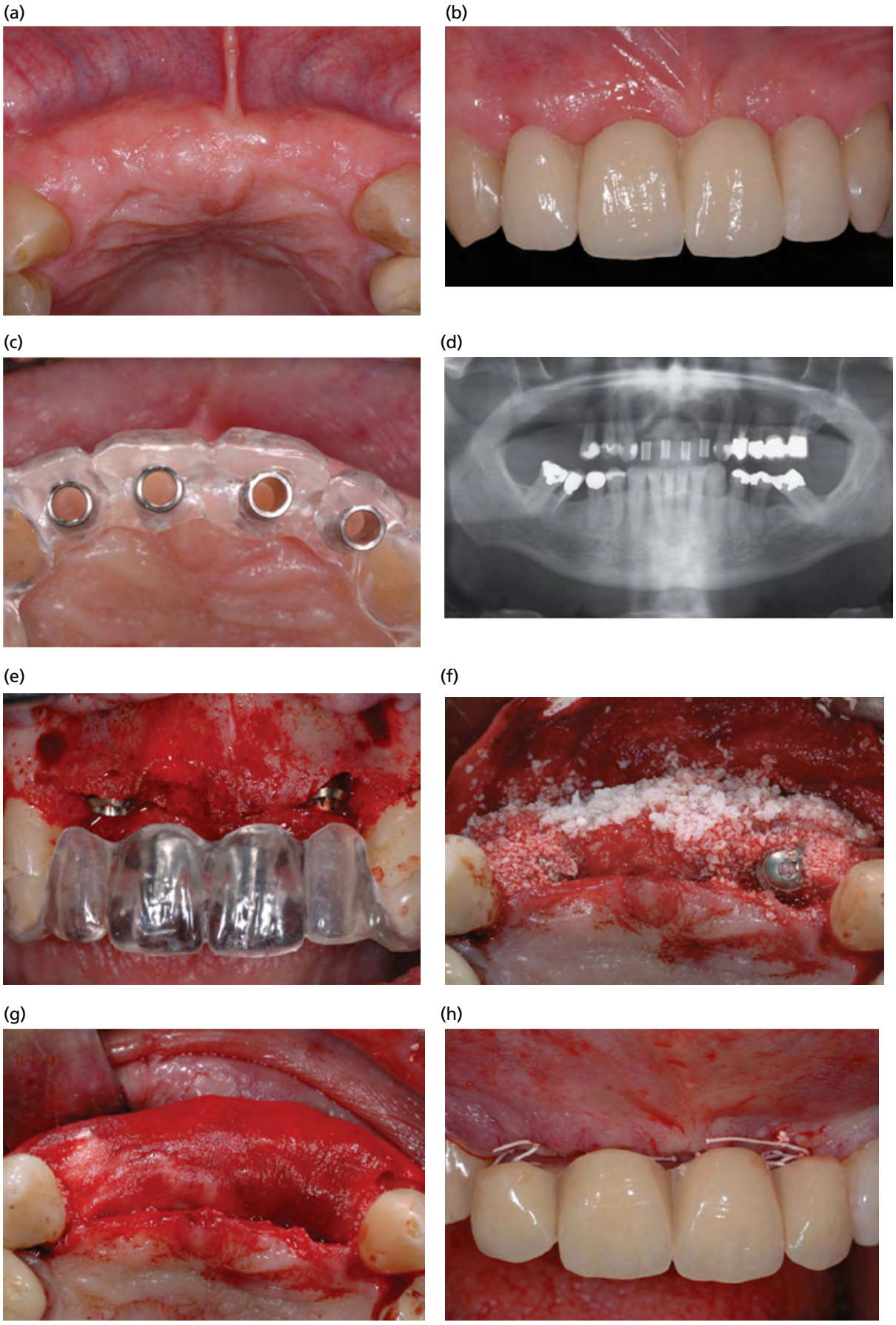


Fig. 45-37 (a) Initial occlusal view of four missing incisors revealing minor contour deficiencies. The 54-year-old male patient was referred after an accident, to restore these four missing teeth with a fixed dental prosthesis. (b) After placing the set-up within the patient's mouth, the functional, phonetic, and esthetic outcomes were assessed. Note the long contact areas in between the teeth that compensate for the lack of scalloping. (c) Occlusal view of the radiographic and surgical template with four titanium cylinders indicating the four possible implant positions. (d) Initial panoramic X-ray with the radiographic template in place. According to the available bone and the ideal implant distribution, two implants at positions 12 and 22 were planned. (e) The surgical template indicated the proper vertical implant position to be approximately 2 mm apical to the future implant crown margin with this type of soft tissue level implant. (f) A slowly resorbing bovine graft material was chosen to fill the gap between the implant and the buccal bone plate and to further augment the buccal bone contour. (g) A collagen membrane was used to cover the grafted area before soft tissue closure. (h) The removable temporary reconstruction was released to give a distance of 2–3 mm to the mucosa in order to compensate for the postsurgical swelling.

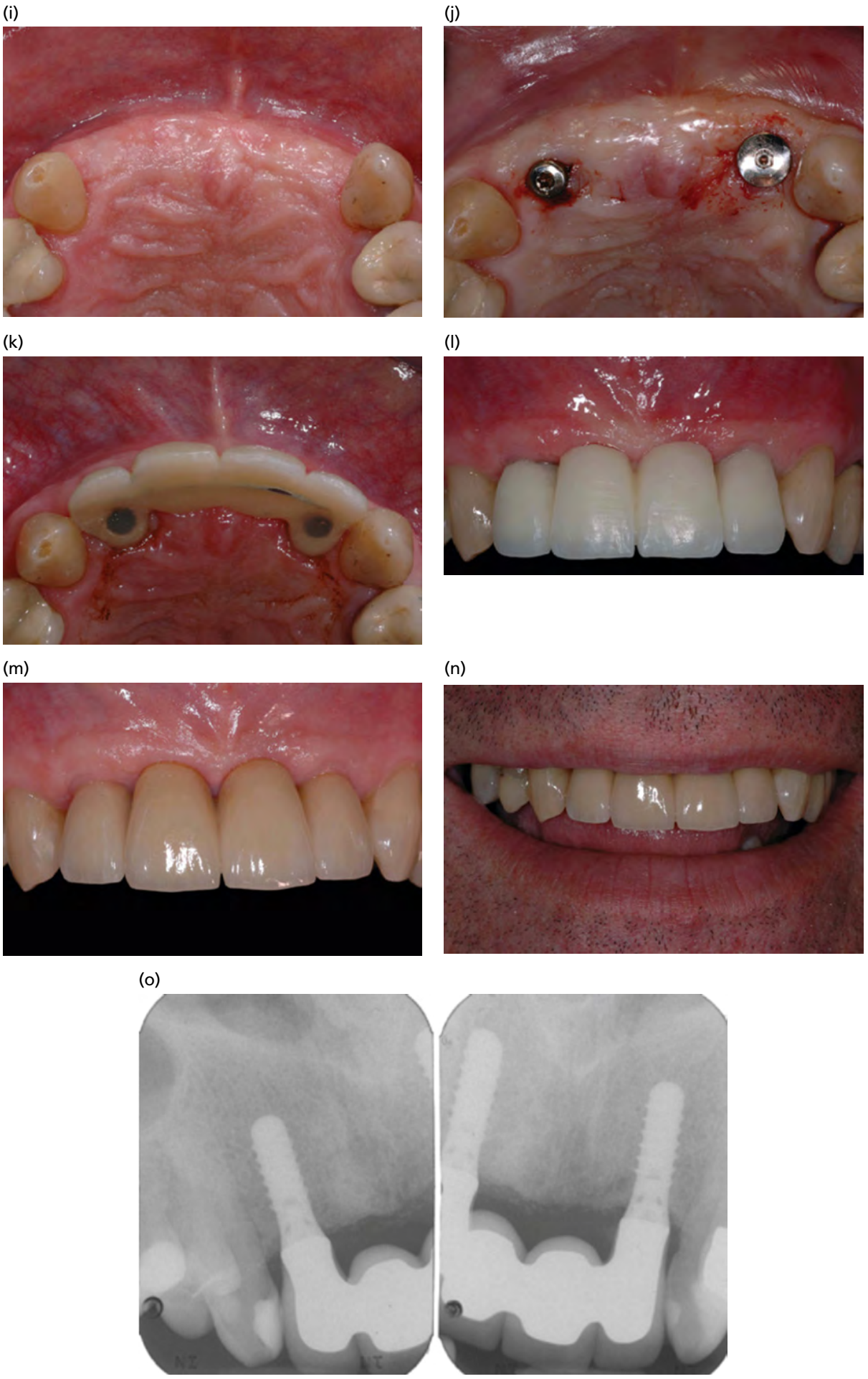


Fig. 45-37 *(Continued).* (i) After soft tissue grafting, an ideal bucco-oral contour was achieved. (j) Titanium healing abutments were chosen and placed in such a way as to avoid overlap with the level of the neighboring soft tissue. (k) Occlusal view of the screw-retained temporary reconstruction. (l) Wax-up within the patient's mouth, checking again for function, phonetics, and esthetics. (m) Buccal view of the final reconstruction in place. Note the slight papilla in between the two central incisors, but almost no papilla between the implant sites and the central incisors. (n) Final lip line of the patient without visible mucosal aspects apical to the implant-supported crowns and pontics. (o) Periapical X-rays 2 years after insertion of the final reconstruction, showing stable bone levels.

(2) discrepancy of the cross-sections of implant and tooth, (3) clinical and dental technical handling, and (4) costs.

Anterior implant sites are often characterized by a high scalloped mucosa margin (Fig 45-39). Implant shoulders, which are positioned 2–3 mm apical to the buccal mucosal margin have proximal depths of up to 7–8 mm depending on the individual scalloping of the soft tissue. Using a standardized abutment not following the soft tissue margin would lead to a difficult removal of the excess cement especially in the mesial and distal areas (Linkevicius *et al*. 2011). Outcomes from a recent systematic review identified cement remnants as possible risk indicators for peri-implant diseases (Staubli *et al*. 2017). Therefore, the emergence profile may play a pivotal role in terms of cement remnants. A recent *in vitro* study tested whether a concave or a convex emergence profile design was superior in terms of remaining cement following the cementation of reconstructions on customized abutments. The results revealed that a concave emergence profile, along with a deep

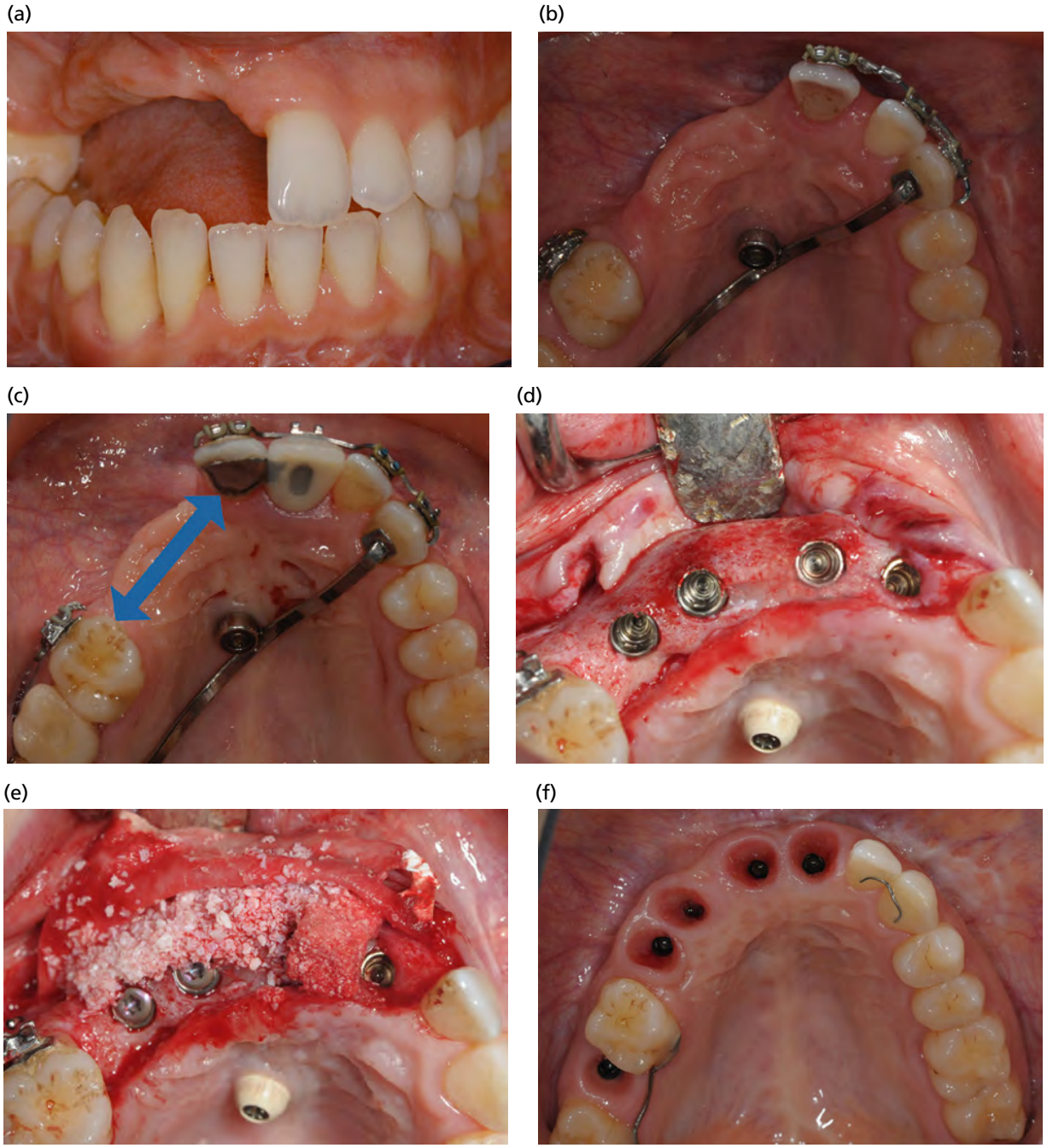


Fig. 45-38 (a) Initial clinical situation, revealing the absence of multiple teeth, a severe deficiency of soft and hard tissues, as well as a thin phenotype. (b) Occlusal view showing a palatal implant as anchorage for the orthodontic therapy. (c) Clinical situation after orthodontic therapy showing the reduction of the edentulous gap. (d) Intraoperative situation following flap elevation and implant placement in region 15-11. (e) Guided bone regeneration using a xenogeneic graft and a resorbable membrane made from collagen. (f) Final emergence profile after 3 months of soft tissue conditioning.

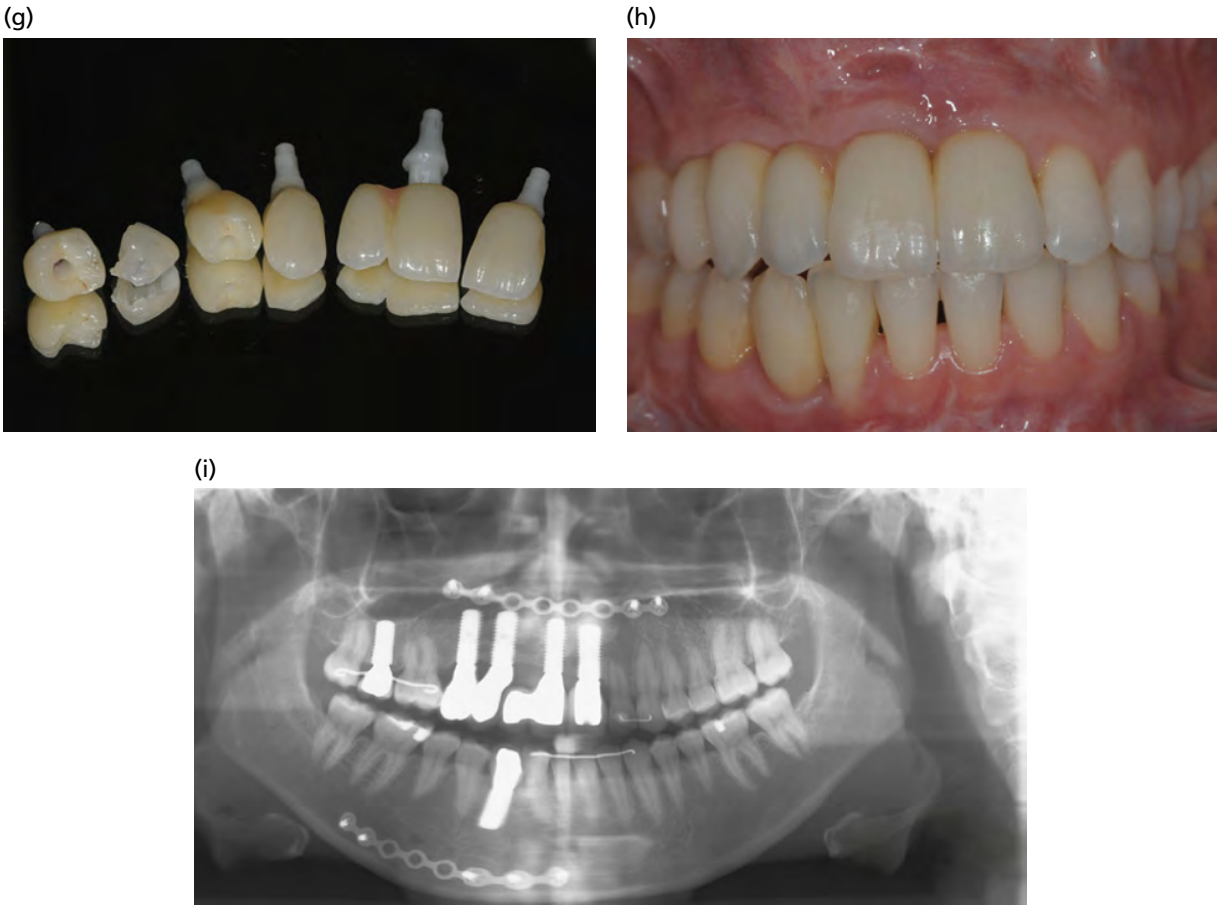


Fig. 45-38 *(Continued).* (g) All-ceramic reconstructions made out of zirconia cemented to a customized CAD-CAM zirconia abutment. (h) Final prosthetic reconstructions revealing an optimal result. (i) Panoramic radiograph at 6 months follow-up.

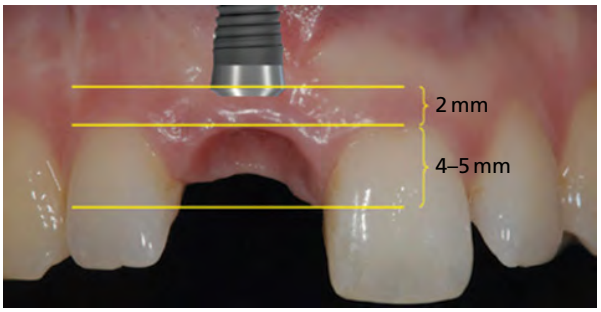


Fig. 45-39 Depth of an implant shoulder in a normally scalloped anterior site.

crown–abutment margin position, increases the risk of cement excess (Sancho-Puchades *et al*. 2017). Nevertheless, the clinical evidence linking the presence of submucosal cement and peri-implantitis is still limited (Berglundh *et al*. 2018).

In clinical situations with high scalloped soft tissue morphologies and deep vertical implant positions, customized abutments have been recommended (Fig. 45-40). Hence, the crown margin can be located not more than 1.5 mm below the soft tissue margin and following the scalloping of the mucosa (Fig. 45-41). However, a 3-year randomized multicenter trial comparing prefabricated and CAD-CAM customized abutments for implant-supported crowns in the esthetic region, showed no significant differences in terms of clinical and esthetic outcomes (Wittneben *et al*. 2020). These findings, nevertheless, should be interpreted cautiously since studies comparing stock and CAD-CAM customized abutments are scarce (Schepke *et al*. 2017).

Customized abutments can be fabricated either by copy-milling techniques or by means of computer-aided (CAD-CAM) systems. For CAM, these abutments can be scanned, digitized, and the data is thereafter sent to a central production facility via the internet (Joda *et al*. 2017; Pyo *et al*. 2020). In the future, more and more customized CAD-CAM abutments will be virtually designed without the need of prefabricated abutments. This procedure allows multiple options in terms of individualizing the abutment to the clinical situations. However, from a clinical and technical handling perspective, it is more time consuming and slightly more expensive compared with standardized prefabricated abutments. Therefore, in clinical situations with flat gingival morphologies, shallow-placed implants, and minor discrepancy between the cross-sections of implant and tooth, standardized prefabricated abutments can still be used. Once the decision has been made to use either prefabricated or customized abutments, it is important to choose the material for the abutment and the reconstruction.

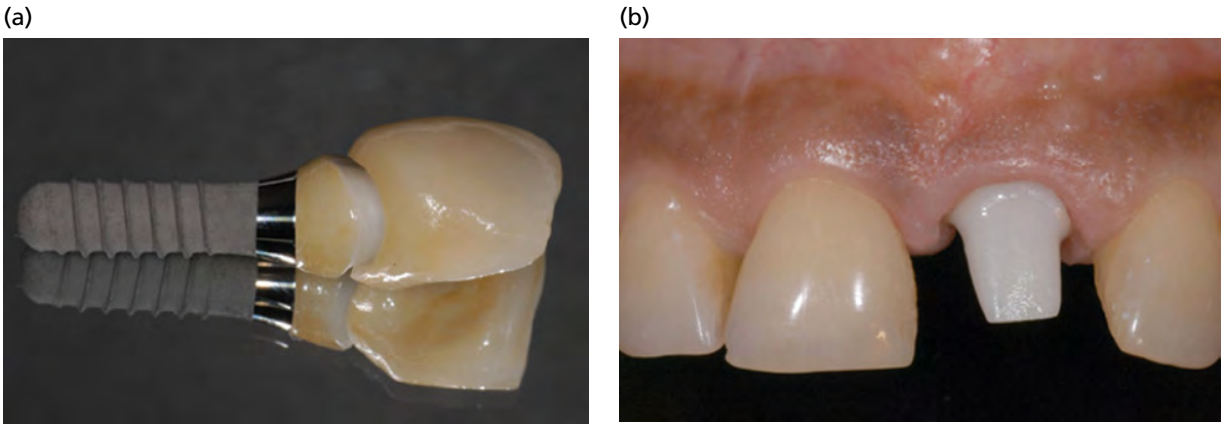


Fig. 45-40 (a) Individualizing the CAD-CAM abutment in order to better match the color of the all-ceramic crown. (b) Customized zirconia abutment following the gingival morphology before cementing the all-ceramic crown.

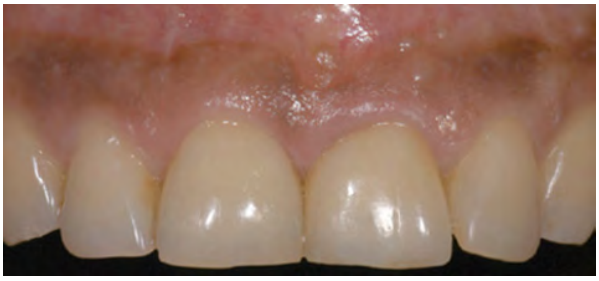


Fig. 45-41 Final clinical result after cementing the all-ceramic crown 21.

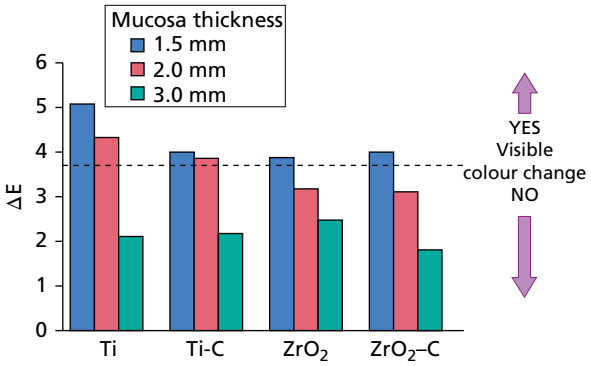


Fig. 45-42 Bar chart illustrating the ΔE values for the different materials evaluated under different mucosal thicknesses. The line at ΔE = 3.7 represents the critical ΔE threshold for intraoral color distinction as perceived by the naked eye. Ti, titanium; Ti-C, veneered titanium; ZrO2, zirconia; ZrO2-C, veneered zirconia.

Decision-making process: all-ceramic versus porcelain-fused-to-metal reconstructions

In the esthetic zone, the choice of the reconstructive material is mainly influenced by the soft tissue architecture, the esthetic expectations of the patient, and the esthetic goal to be achieved with the reconstruction (i.e. the value and color of the neighboring teeth). The gray color of titanium abutments needs to be masked by means of metal–ceramic reconstructions. Because of refinements in veneering ceramics for metallic frameworks, excellent esthetic results can be achieved with this kind of reconstruction. However, many studies, including systematic reviews (Linkevicius & Vaitelis 2015), indicate that the grayish color of the abutments can impair the esthetic result due to a discoloration of the peri-implant soft tissues. In this context, several studies have suggested that ceramic abutments may be more advantageous and esthetically pleasing because of their tooth-resembling color (Linkevicius & Vaitelis 2015). In order to prove these claims, different clinical and preclinical studies evaluated the color change effect of all-ceramic versus porcelain-fused-to-metal (PFM) restorations on the marginal peri-implant soft tissue. For example, it was demonstrated that all-ceramic restorations exhibit a significantly better color match to the unrestored neighboring teeth compared with PFM restorations (Jung *et al*. 2008). Furthermore, the same study revealed that the increase of soft tissue thickness by connective tissue grafts, reduces the risk for soft tissue discoloration regardless of the reconstruction material (Jung *et al*. 2008). These observations were further validated by another study in pig jaws demonstrating that the soft tissue discoloration is reduced by the increase of soft tissue thickness (Jung *et al*. 2007) (Fig. 45-42). The same study showed that titanium induced the most pronounced color change of all tested materials. Zirconia, however, did not induce a visible color change at mucosa thicknesses of 2 and 3 mm, irrespective of whether it was veneered or not. According to these findings, the authors concluded that 2 mm was the critical mucosa thickness and came up with the following clinical recommendations: (1) with a mucosa thickness of more than 2–3 mm PFM or all-ceramic reconstructions can be recommended and (2) with a thin gingiva of 2 mm or less either a soft tissue graft should be performed or an all-ceramic reconstruction is indicated (Jung *et al*. 2007).

In addition to the esthetic evaluation, the decision whether or not to use an all-ceramic or a metal–ceramic reconstruction should also be based on the clinical performance and the mechanical properties. Metal–ceramic reconstructions were considered to be

the "gold standard" (Jung *et al*. 2008), but since the introduction of high strength ceramics, these new materials are competing with the well-documented metal–ceramic materials. So far, mid-term clinical data are encouraging in the esthetic zone (Wittneben *et al*. 2017; Heierle *et al*. 2019). A recent systematic review evaluated the survival and complication rates of zirconia–ceramic and metal–ceramic single implant-supported crowns (Pjetursson *et al*. 2018). Based on 36 studies, the review revealed similar survival rates between zirconia–ceramic (97.6%) and metal–ceramic (98.3%) implant-supported single crowns at 5 years follow-up. Furthermore, the biological and technical complication rates were similar between both reconstructions. Although zirconia showed fewer esthetic complications, it also exhibited more catastrophic core fractures (Morton *et al*. 2018; Pjetursson *et al*. 2018). In this sense, and in order to overcome the mechanical issues of one-piece zirconia abutments, the so-called hybrid abutments have been introduced. Hybrid abutments consist of a standardized titanium base extraorally cemented to a CAD-CAM all-ceramic reconstruction (Kurbad & Kurbad 2013). These reconstructions have been increasingly used in clinical practice mainly because of the possibility to be cemented to various all-ceramic materials, along with the low costs. *In vitro*, these abutments have shown a comparable strength to metal abutments while still providing esthetic benefits of all-ceramic reconstructions (Sailer *et al*. 2018). However, it needs to be emphasized that there is a lack of long-term clinical data, which limits to some extent this type of reconstruction (Joda *et al*. 2017; Asgeirsson *et al*. 2019). In addition, the biological impact of the cement gap close to the marginal bone needs to be further investigated.

Adverse esthetic outcomes

Origin, causes, and prevalence of adverse esthetic outcomes

All treatment modalities in any dentoalveolar segment that are visible upon full smile and which include the placement of one or more implants, must be classified as advanced or even complex procedure. For that reason, esthetic failures do occur, most often due to the lack of proper preoperative diagnostics and planning or the previously described cognitive biases such as overconfidence, or personality traits such as tolerance to risk.

In general, implant-supported clinical crowns have been evaluated to be longer than the non-restored contralateral teeth, and factors such as topography of the surrounding soft tissues, form of the crown, and contact point position were found to have a statistically significant influence on the clinician's determination of the overall satisfaction with appearance (Chang *et al*. 1999). Data on the prevalence of adverse esthetic outcomes at implants are scarce and difficult to estimate, but peri-implant mucosal dehiscences seem to be the most frequent reason for esthetic complaints (Sculean *et al*. 2017). Taking into account the many influencing variables and, correspondingly, the paucity of data, it is estimated that at least 25% of the implants immediately placed in the zone of esthetic priority exhibit mucosal dehiscences (Cosyn *et al*. 2012) and that, generally, mucosal dehiscences at implant sites can be judged as a common finding (Mazzotti *et al*. 2018). Follow-up studies document that most of the soft tissue changes happen within the first 6 months after prosthetic loading (Bengazi *et al*. 1996; Schropp *et al*. 2003; Cosyn *et al*. 2012; Pieri *et al*. 2013).

The site-specific etiological factors for peri-implant dehiscences may be related to various elements such as the mucosal phenotype (thick versus thin bordering mucosa), the presence of an insufficient width of keratinized and/or attached mucosa, the height and thickness of the facial bone wall, an orofacial malposition of the implant, the inclination of the implant body, the implant–abutment connection, and the contour of the prosthetic crown (Evans & Chen 2008; Chen & Buser 2014).

Another frequently observed esthetic impairment is the lack of papillary-like structures between tooth and implant or between two implants (Schropp *et al*. 2005; Chow & Wang 2010; Perez *et al*. 2012; Chang & Wennström 2013). Regarding this aspect, the esthetic appearance seems to improve over time, mainly dependent on the attachment level of the adjacent teeth (Finne *et al*. 2012). The lack of papillae may not only influence the patient's satisfaction with the esthetic appearance, but also his/her phonetic speech, especially when multiple teeth are replaced by implants (Suphanantachat *et al*. 2012).

Clinical findings and classification of esthetic adverse outcomes

The new classification system of gingival recessions has shown to reliably fulfil the requirements of a classification, namely to allow a distinct assignment of each particular lesion into its own class and to enable clinicians to make a reliable prognosis regarding treatment outcome of each single recession type (Cairo *et al*. 2011). As there are no naturally grown reference points around implants such as the CEJ around teeth, the definition of peri-implant mucosal dehiscences seems to be more vague and therefore difficult to verbalize in unequivocal terms. Peri-implant mucosal dehiscences can best be defined as an apical shift of the soft-tissue margin of the implant-supported crown with respect to the homologous natural tooth, with or without exposure of the metallic part of the implant (Burkhardt *et al*. 2008; Mazzotti *et al*. 2018). By trying to classify peri-implant dehiscences and opt for a surgical treatment with the best possible prognosis we should always keep in mind that each treatment of such lesions should be guided by patients' esthetic

demands and that the final outcome is not only a complete dehiscence coverage but a satisfactory esthetic result based on patient-related outcome measures.

To date, there is no reliable classification system that guides clinicians to make a treatment decision for peri-implant mucosal dehiscences based on scientific evidence. Only a few authors have proposed classification systems for peri-implant mucosal lesions but most of them did not provide reliable clinical recommendations for surgical treatment of the mucosal problems or the options were mainly based on the clinical experience of the authors (Decker *et al*. 2017; Mesquita De Carvalho *et al*. 2019).

A recently published classification system for peri-implant mucosal dehiscences at single implants, based on the amount and specificity of the labial bordering soft tissues, the bucco-oral position of the implant, and the interproximal papillae dimension, relates each individual type of mucosal lesion with a treatment recommendation (Zucchelli *et al*. 2019). Four different classes reflect the bucco-oral position of the implant and the quality and location of the buccal soft tissues while the three subgroups in classes II to IV refer to the interproximal soft tissue level (Fig. 45-43). The management of the cases is divided into two categories, namely surgical and combined surgical–prosthetic approaches, including crown removal. The combined approaches are the preferred treatment modality when implants are located buccal to the tangent of the neighboring teeth and the interproximal tissues receded compared to the unrestored contralateral teeth. In severe cases with far too buccal implant positioning and substantial interproximal tissue loss, the soft tissue augmentation with submerged healing or the removal of the implant following new prosthetic rehabilitation are the only options to improve the esthetic appearance (for detailed information regarding the classification system and treatment recommendations, see Zucchelli *et al*. 2019).

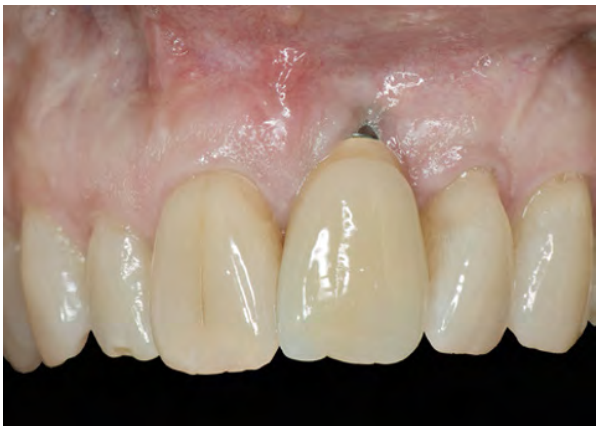


Fig. 45-43 Buccal peri-implant mucosal dehiscence in area 21 (class IIIb) with thin bordering tissues. The implant is buccally positioned and mucosal margin is apical to the gingival margin of the contralateral tooth. As the interproximal tissues distally of the implant are receded, a combined surgical–prosthetic approach has to be considered.

Strategies for retreatment of esthetic adverse outcomes and clinical results

Given the variety of influencing factors (e.g. site-, patient- and surgeon-related), and the biocomplexity of the problem, it becomes obvious that reliable prognoses of surgical retreatments of peri-implant mucosal dehiscences might be difficult to achieve and the importance of proper diagnosis and decision making prior to the surgical intervention must be emphasized.

A literature research revealed that a variety of surgical and restorative techniques have been proposed, most of them in case reports (Hidaka & Ueno 2012; Cosyn *et al*. 2013; Happe *et al*. 2013; Fickl 2015), three prospective studies (Burkhardt *et al*. 2008; Zucchelli *et al*. 2013; Roccuzzo *et al*. 2014), and only one randomized controlled trial (Zucchelli *et al*. 2018). The results of the prospective cohort studies varied from 66% to 75% mean and no complete coverages (Burkhardt *et al*. 2008) to 89.6% mean, and complete implant soft tissue coverage in 56.3% of cases (Roccuzzo *et al*. 2014). As the outcome variables in the two studies are incongruent, the former taking the mucosal margin of the unrestored contralateral tooth as a reference, the latter just aiming at covering the denuded metal part of the implant abutment, the results of the two cohort studies cannot be compared. The best results in absolute numbers, with a mean coverage of 96.3% and complete coverage of 75% after 1 year, was achieved with a combined surgical–prosthetic–surgical approach (Zucchelli *et al*. 2013). The difference in the treatment modalities, again, did not allow comparison of the results of the different studies and conclusions could not be drawn regarding the preferred approach.

Almost all of the published studies reported positive results but long-term data regarding the maintenance of the 1-year results after surgical peri-implant dehiscence coverage are scarce. Zucchelli *et al*. (2018) published data on 5 years follow-up after peri-implant mucosal dehiscence coverage which confirmed stable successful esthetic results, with 99.2% mean and 79% complete dehiscence coverages.

Despite the abovementioned articles differing regarding the chosen clinical approach for peri-implant mucosal dehiscence coverage and the invasiveness of the execution, most used a combined approach which created a tunnel or flap and interpositioned a connective tissue graft. This observation might confirm previous findings that (1) connective tissue grafts, well sutured to the immobile neighboring tissues, have the capacity to increase wound stability in the early healing phases (Burkhardt *et al*. 2016) and (2) that the thickness of the labial mucosa might be a key factor in preventing future dehiscences after successful coverage.

Beyond the cases with severely malpositioned implants, which have to be removed and restored by a completely new prosthetic rehabilitation, the surgical approaches to cover peri-implant mucosal dehiscences can be classified as (1) coronally-advanced

flaps with or without releasing incisions and with or without connective tissue grafts or its replacements, (2) laterally-positioned flaps with connective tissue grafts (Fig. 45-44), (3) envelope flap/pouch/tunnel techniques with connective tissue grafts, and (4) submerged techniques with connective tissue grafts (for overview see Zucchelli *et al*. 2019) (Fig. 45-45).

The treatment guidelines given in the literature are mainly based on expert opinions and must be considered in the light of the little available scientific evidence. As previously mentioned, most of the approaches to improve peri-implant esthetics belong to a high complexity level in periodontal and peri-implant mucosal surgery and success does not only depend on the required advanced psychomotor skills but even more on diagnostic and prognostic skills and the expertise of the clinician.

As the ultimate goal of those surgical interventions is to alter the self-perception of the patients regarding their esthetic appearance and to improve their satisfaction with the dental restoration, and as many of these patients already have been exposed to a treatment error, a shared decision making approach, with communication of all the inherent risks, is fundamental.

Concluding remarks and perspectives

Since the last edition, much has been published that has substantially contributed to the content of this revised chapter. We thank the many authors for their contribution and for their help in increasing patient safety in this specialty.

There is no doubt that esthetics affect the self-perception of patients, impacting their psycho-social well-being and their oral health. However, restoration in the zone of esthetic priority means more than satisfying patient demands regarding the esthetic appearance of the prosthetic restoration. There is also a responsibility to deliver treatment that provides each individual patient with the best possible benefit, which requires empathy and social skills to capture the needs of the patient and health literacy to amalgamate them with the available scientific evidence. Healthy, critical self-reflection by the clinician guarantees a treatment plan that is within his or her circle of competence, and consequently a reliable prognosis. Keeping in mind that implant placements are non-reversible and most adverse esthetic outcomes are treatment errors rather than esthetic complications, the time dedicated to key issues such as diagnostics and treatment planning and the effort to openly communicate benefits and harms of implant therapy with alternatives options, is vital.

This, in turn, means that beyond the available scientific evidence in the specialty of implantology, clinicians must develop an awareness of cognitive biases and become familiar with the many non-technical skills such a decision making, debiasing, and communication of risks and uncertainties to patients.

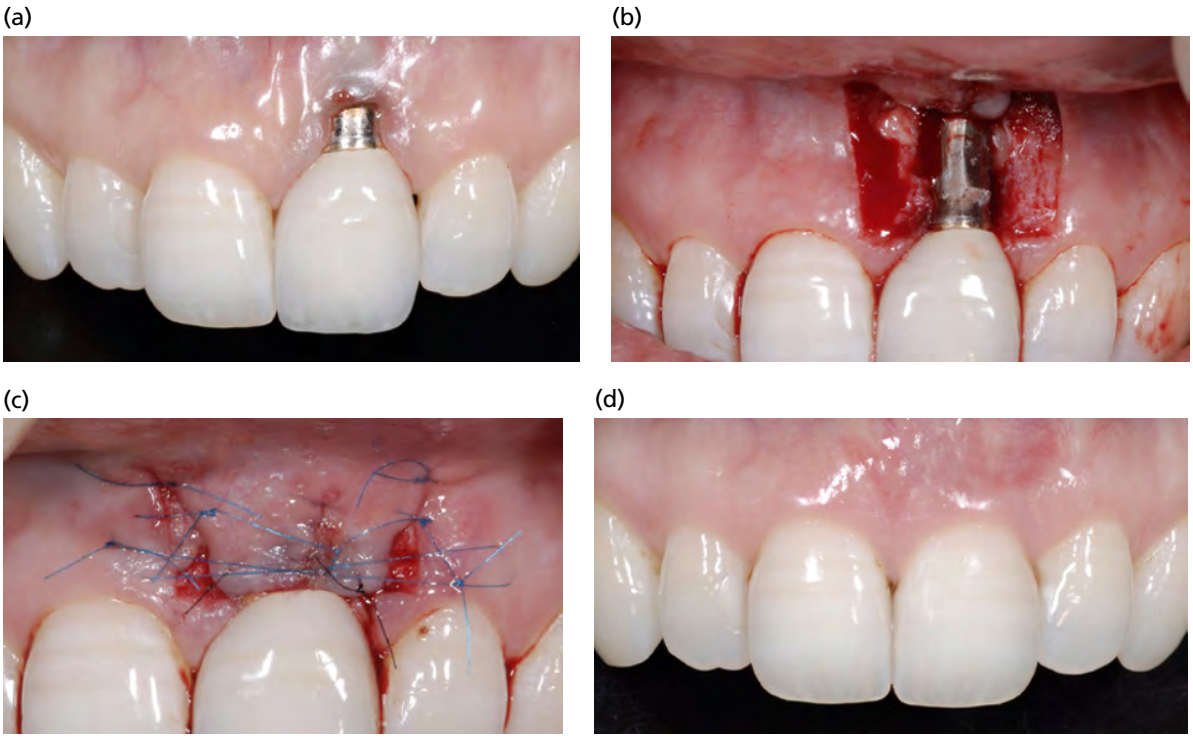


Fig. 45-44 (a) Buccal peri-implant dehiscence in area 21 (dehiscence class IIa). (b) Frontal view after flap elevation (double pedicled and laterally positioned flaps) and site preparation. (c) Postsurgical situation after flap closure and interposition of a connective tissue graft, firmly sutured to the underlying periosteum. (d) Healed situation 6 months postsurgically. Even if the primary outcome in this particular case was the increase of the buccal masticatory mucosa and thickening of the soft tissues, a complete coverage of the mucosal dehiscence could be achieved.

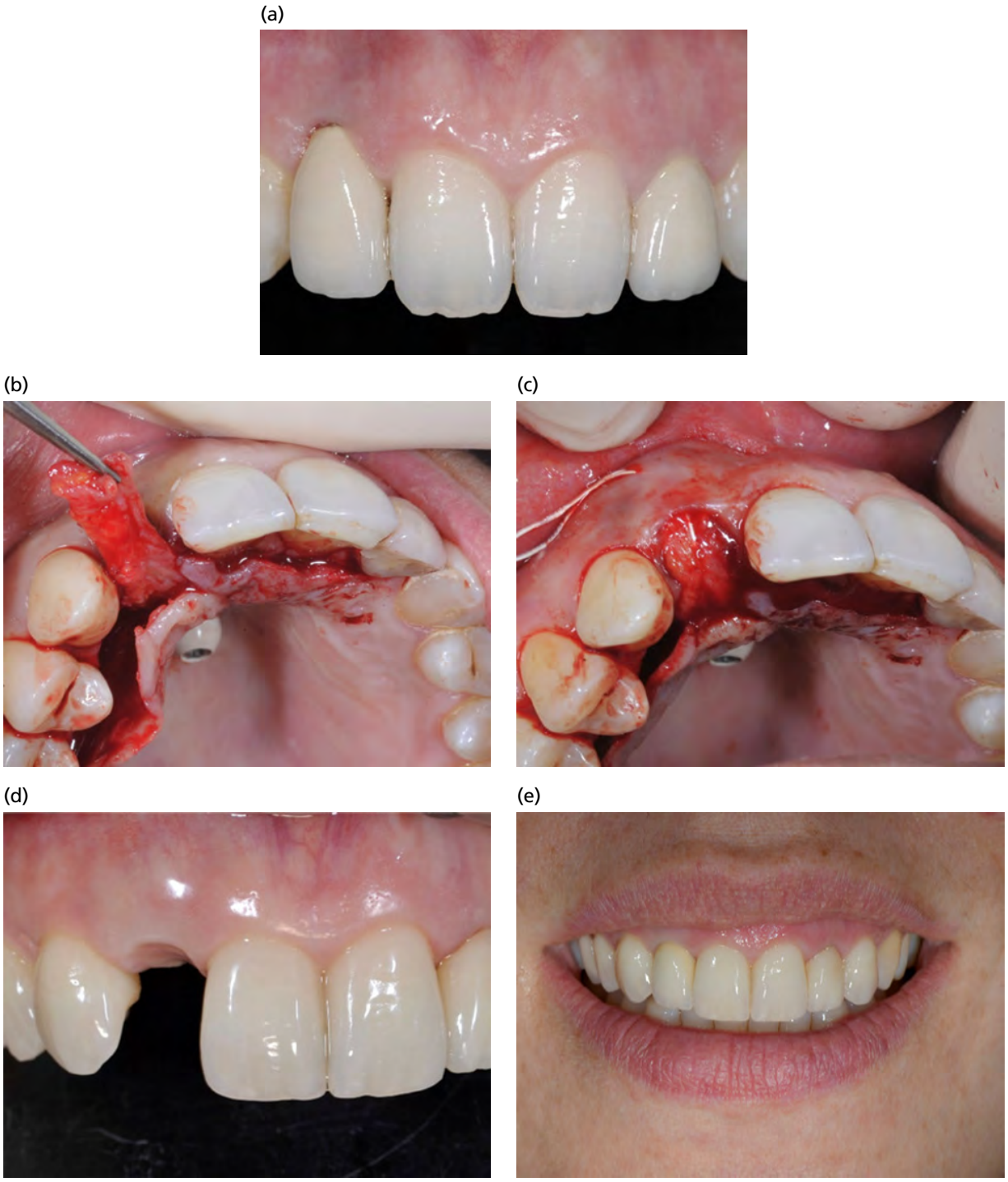


Fig. 45-45 (a) Frontal view of peri-implant mucosal dehiscence in area 12 (class IVb). (b) Intrasurgical situation after palatal flap preparation in the gingival area (connective tissue from the lamina propria). (c) Flap positioning in the buccal pouch for vertical and horizontal site augmentation. (d) Healed interdental area, 6 months postsurgically. (e) Final restoration with newly fixed implant-supported crown.

Acknowledgments

The authors gratefully acknowledge the help of the Drs. Alfonso Gil and Thomas J.W. Gasser as well as the Dental Technician Thomas Barandun (Clinic of Reconstructive Dentistry, University of Zurich, Switzerland) for their clinical contribution and their help in preparing the clinical cases for this chapter.

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Chapter 46

Technical Complications in Implant Dentistry

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Introduction

Technical complications are a part of dental implant therapy. Complications and expected wear (maintenance) should be differentiated, although both can be considered "technical" complications. Complications are unexpected technical issues such as fracture, misfit, unusual wear and abrasion, or compromised hygiene access due to prosthetic contours created to satisfy esthetic demands. Maintenance is a measure of the expected service life of the prosthetic restoration and is an anticipated part of informed consent. The goal with maximal service life is a restoration providing a functional, phonetic, and esthetic prosthesis fulfilling patient desires and matches the functional capacities of the patient to manage the daily preventive needs to reduce the risk factors associated with biological complications. Systematic reviews indicate incidence(s) of technical complications exceed biologic complications (Zembic *et al*. 2014). Thus, understanding the potential technical complications affecting implant prosthesis is an essential part of the lifelong management of the implant patient. The components and restorative materials used to provide implant prostheses are all subject to loading and wear in an environment challenged by various antagonists including changes in lubrication, abrasives, forces (their magnitude, direction and velocity) and pH or chemistry of the environment (e.g. plaque fluid or saliva). While long-term success is certainly feasible, the reality of continuous implant supported dental prosthesis use is that wear, fatigue, and potential mechanical failure is inevitable (Dhima *et al*. 2014). The impact of technical complications though will shorten the expected service life of the prosthesis.

Dental implant treatment is growing worldwide. For example, a recent study of the prevalence of implant use in the USA indicates there is currently a 5% prevalence of dental implant use that will expand to 17% in the next decade (Elani *et al*. 2018). It can be extrapolated that, without significant advances in materials and techniques, there will be a parallel increase in the numbers of technical complications associated with implant prostheses. With increasing duration of use, the absolute number of technical complications presenting for resolution may increase. Importantly, given that technical complications of implants increase with time, we may see a non-linear increase in implant-related complications in the coming decade. Are we prepared?

Technical complications in implant therapy can have significant impacts. Technical complications encouraging plaque accumulation can influence peri-implant mucositis and peri-implantitis. Technical complications can cause pain, social discomfort, and psychological distress. Complications typically are accompanied by time and direct and indirect financial impacts influencing patient-reported outcome measures, and when left

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

unattended, these complications do create functional and esthetic limitations. Technical complications have a significant impact on the patient's perception of implant therapy (Adler *et al*. 2016).

The aim of this chapter is to identify the technical complications affecting dental implant therapy and to implicate potential risk factors influencing these complications as well as to suggest possible solutions. We focus on and summarize the current knowledge regarding technical complications relating to implants, implant components, and implant prostheses.

Implant fractures

Postloading implant fractures occur infrequently and account for less than 1% of all complications (Gealh *et al*. 2011). Both horizontal and vertical fractures present and require implant removal/replacement (Fig. 46-1). The fracture of an implant may, however, result in the loss of an entire prosthesis. Five factors were identified to be significantly associated with implant fracture. They included (1) the grade of titanium, (2) bruxism, (3) implants adjacent to cantilevers, (4) increased implant length, and (5) decreased implant diameter (Chrcanovic *et al*. 2018). A recent systematic review of implant fractures that included 12 studies reporting on 594 subjects (868 implants) demonstrated a 2% incidence of implant fracture. In this study, narrow implants demonstrated a higher incidence of fracture. Fractures occurred more frequently in the maxilla than the mandible. Fractures were reported to occur from before loading to 17 years follow-up (Goiato *et al*. 2019). This implies that fatigue and overload are not the only factors influencing implant fracture. One must question the significance of high insertion torque in contributing to implant fracture (Fig. 46-1).

There exist several potential factors predisposing an implant to fracture (Box 46-1). Among the most often discussed factors is the role of implant design. In an *in vitro* study, narrow diameter implants with three implant-abutment connection designs were loaded at 75 N and 200 N: external hexagon, internal hexagon, and internal conical connected to a titanium abutment. The results indicated narrow implants with external or internal hexagon connections presented the lowest reliability at high loads compared with internal conical connections (Bordin *et al*. 2018). Although this report suggests implant design can influence fracture of narrow implant, other clinical factors must be considered more widely. The vast majority of factors influencing implant fracture are within the clinician's control.

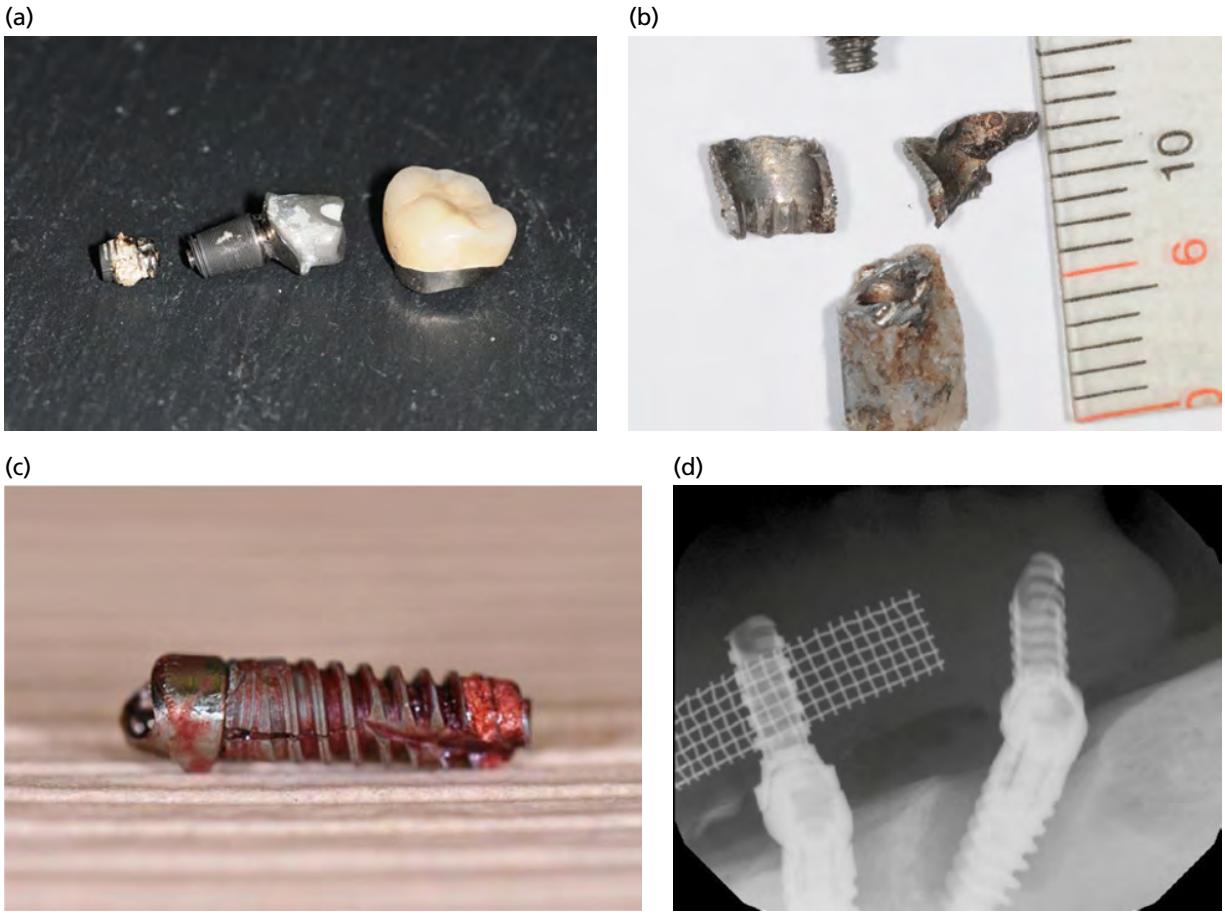

Fig. 46-1 Implant fractures are an uncommon but irreversible technical complication. (a) Horizontal fracture of implant that resulted in removal of the molar implant abutment and crown. (b) Vertical fracture of implant that is observed for internal implant/abutment connections. (c) Remarkable vertical implant fracture that may be caused by stress incurred because of high insertion torque. (d) Radiographic image of bone loss associated with vertical implant fracture (not observed radiographically)

Box 46-1 Factors predisposing implants to fracture.

1. Low grade titanium implant
2. Inappropriate diameter for the functional loads expected at the site
3. Bruxism (and/or loss of anterior guidance creating shear fractures on posterior restorations)
4. Large bending moment (cantilever or excessive crown/implant ratio) affecting adjacent implants
5. High insertion torque resulting in implant damage and/or stress

(Source: Adapted from Chrcanovic *et al*. 2018. With permission from John Wiley & Sons.)

There are several clinical signs of potential vertical implant fractures affecting internal conical or internal parallel connection implants. First, repeated and frequent abutment loosening is one sign that the implant is fractured or the internal aspect of the implant has been deformed. Vertical fractures are also associated with vertical bone loss adjacent to the implant fracture. This bone loss will appear circumferentially around the implant (e.g. Figure 46-1d).

Unfortunately, there are few solutions for vertical or horizontal implant fractures. The implant may be buried or removed. The implant may be maintained by altering the prosthesis to connect with the residual portion of the implant. In many multi-implant scenarios, the prosthesis may be modified or an alternative prosthesis provided (e.g. an overdenture) to account for implant fracture without additional implant replacement.

Implant complications

Iatrogenic damage to an implant occurs and has not been well documented. However, attempts to remove overtightened cover screws or abutments or to remove broken abutment screws may lead to inadvertent damage to the internal aspects of the implant. Damage to the threads or the internal interface can result in inability to replace the fractured abutment screw or abutment. Iatrogenic damage to an implant is the result of using rotary instrumentation to loosen fractured components within the implant; attempts to remove broken abutment screws should apply hand instrumentation, careful isolation, and high-power magnification where the fractured component may be visualized.

Iatrogenic damage to the implant may occur upon implant insertion. Improper engagement of implant drivers can lead to deformation of external or internal abutment interfaces. Application of non-axial forces to internal connection implants may result in fracture of the thinner wall of the implant. High torque upon insertion can also deform the implant/implant driver interface. For example, in an experimental model of implant insertion, three different implant/implant drivers were shown to be deformed by insertion in simulated dense bone (high torque) versus insertion in simulated lower density bone (low insertion torque) (Romanos *et al*. 2019). This suggests that high torque protocols may increase the risk of implant damage upon insertion.

Implant complications include situations where an intact, osseointegrated implant is non-restorable. Three situations are typically encountered (Fig. 46-2). The first is where the implant is placed too shallowly (or deeply) to permit three-dimensional space

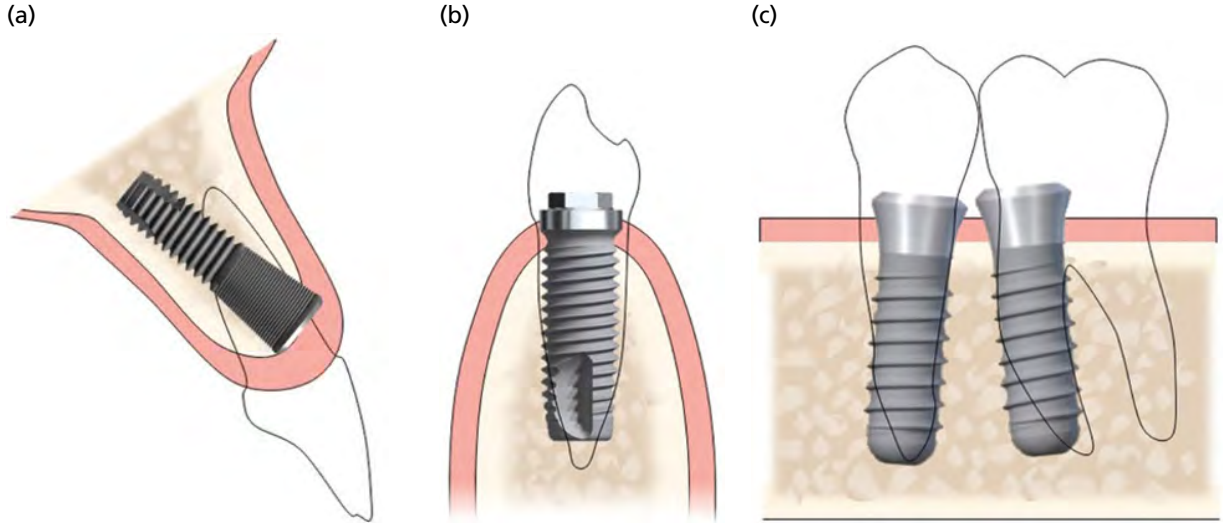

Fig. 46-2 Iatrogenic implant placement causing technical challenges. The installation of implants in non-restorable positions lead to unesthetic, unhygienic, or mechanically inferior abutments and restorations. (a) Excessive rotation of the implant axis in the sagittal plane creates conditions where an abutment cannot resolve the position, leading to an unesthetic and unhygienic restoration. (b) Shallow implant placement creates a situation where a ridgelap restoration is required to resolve the esthetic limitation. (c) Implants erroneously placed in non-parallel and proximal positions can preclude fixture-level impression making, restoration, and hygiene.

to create an abutment transition zone compromising hygiene contours and esthetic restoration. The second is when the implant is placed too facially or lingually to permit restoration. The third situation is that the implant is oriented too close to an adjacent tooth for restoration, proximal tilting or rotation has occurred, or two implants are too closely approximated to permit restoration (or eventual hygiene). These iatrogenic complications require careful consideration of potential implant removal and the management of what may be a compromised restoration.

Abutment and abutment screw complications

Abutment fracture is not common. However, when abutments do fracture, the prosthesis is at risk of complete replacement. The connection of teeth to implants is often mediated by an intermediary component or abutment. The abutment is typically attached to the implant by means of a central screw. The connecting interfaces of abutments vary appreciably and have evolved dramatically since the introduction of the external hex implant. They are generally represented by close sliding interfaces and conus interfaces. Relative to external hex systems, a conus interface may offer mechanical advantages by reducing or eliminating micromotion and more favorable distribution of forces along the implant and to bone (Gracis *et al*. 2012; Yamanishi *et al*. 2012). One interesting potential complication observed for conus interfaces is the 'settling' of the abutment and related screw loosening (Lee & Lee 2012). It has been speculated that the implant itself is deformed, permitting conus interfaces to seat deeper within the implant and resulting in loss of preload. Alternatively, novice clinicians may not realize the abutment is not completely seated; the device becomes wedged into the internal indexing slots or grooves and the abutment screw torques into place. Within a short period of time the abutment comes loose (because the lateral conical walls are not engaged between the abutment and the intaglio of the implant, or the apical portion of the abutment fractures). This is a suspected cause of screw loosening and infraocclusion. Although not universally observed and perhaps related to material selection (Jo *et al*. 2014), it suggests that internal conical implants and abutments must be sufficiently robust to support the conical abutment-derived forces.

In a recent review by Pjetursson *et al*. (2018), at 5 years, the estimated incidence of technical complications with fixed prostheses was approximately 5%. Regarding implant abutment material effects on the incidence of complications, the 5-year failure rates were 2.4% for ceramic versus 1.5% for metal abutments. There were no significant differences among the reported low 1.4–1.9% incidence of abutment failures for cement- versus screw-retained restorations. Regarding implant position effects on abutment complications, the 5-year abutment failure rate was significantly higher in the anterior than the posterior regions (2.5% versus 0.5%). Suggested reasons for improved performance of internal connection versus external hex connection abutment and abutment screws was that the load on the screw is reduced in internal implant-abutment connections. The authors concluded that "the implant-abutment connection appears to have an influence on the incidence of biological and technical complications". Yet, this complication is observed and may be related to abutment material (Fig. 46-3). Externally connected abutments encountered more technical problems such as abutment or screw loosening, whereas internally connected abutments were more associated with biologic problems" (Pjetursson *et al*. 2018). This recent review indicated that abutment failure rates at single crowns were low and were reported to be 2.3% and 1.3% at internal and external connection rates, respectively.

In a 2009 systematic review, abutment screw loosening was the most frequently reported technical complication. While not statistically significant,

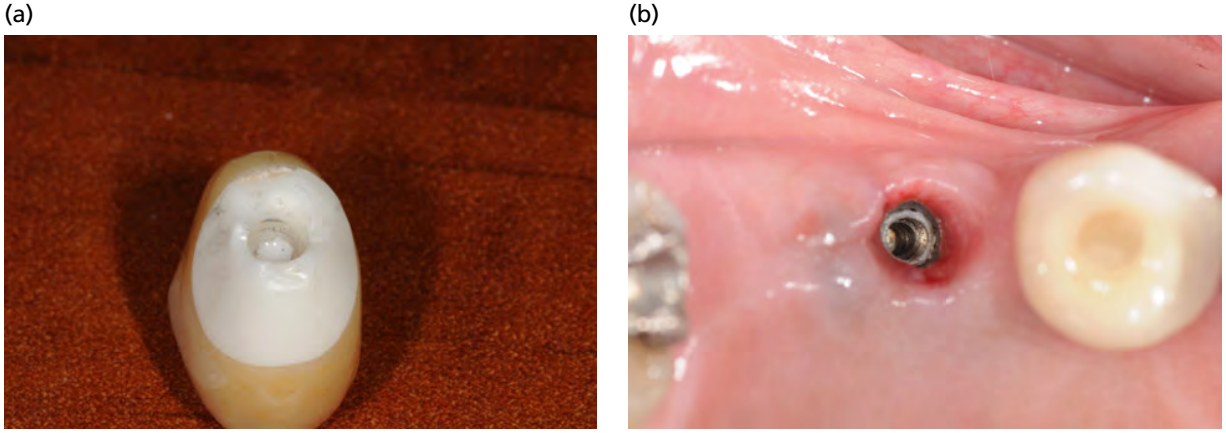

Fig. 46-3 Abutment fracture. (a) Catastrophic fracture of a zirconia abutment. This typically occurs along the conical portion at the junction of the internal or external hex of abutments. (b) The residual fractured fragment of a zirconia abutment is retained within the internal aspect of the implant. This is a challenging clinical scenario that requires removal of the fragment without marring or damaging the internal aspect of the implant.

Box 46-2 Factors influencing abutment screw loosening.

1. The lack or inappropriate use of a torque control device
2. Abutment binding to cortical bone at initial seating
3. Internal versus external connections
4. Cast abutment vs. CAD-CAM abutment
5. Anterior/posterior location of restoration
6. Single versus multiunit reconstruction
7. Excess inciso-gingivial crown dimension or cantilever

there was a trend for a lower incidence of problems at internal connection abutments (Sailer *et al*. 2009). There was significantly more screw loosening at external implant-abutment connections. Higher complication rates were experienced for fixed dental prostheses; there were 9.4% and 12.2% total technical complications recorded for internal versus external connection abutments. The incidence of abutment screw or occlusal screw fracture was significant (P = 0.01). This may reflect the clinical challenge of obtaining a passive fit of complex prostheses at multi-implant prostheses. There are numerous factors that contribute to abutment screw loosening (Box 46-2) and several of these factors were the subject of a recent review (Huang & Yang 2019). Abutment screw loosening can be the result of clinician error. A torque wrench is required for proper tightening of abutment screws (Goheen *et al*. 1994). Because abutment diameters are often greater than the implant osteotomy or mucosal contours, abutments may be bound by bone or dense collagenous mucosa that precludes complete seating of the abutment, even when sufficient torque has been achieved. Additionally, clinicians may place the abutment with incorrect timing in the implant. Such binding of an abutment with an implant may preclude its seating as further torqueing can damage the implant interface. These human errors can be avoided by use of a seating guide and evaluation using a periapical radiograph.

Abutment screws can loosen from a preloaded state. This is due to inelastic deformation of the screw itself reducing the initial clamping force of the screw. Subsequent micromotion leads to greater loosening and greater movement (and ultimately fatigue of the metal screw and fracture). One potential cause is excessive torque that can permanently deform the screw. It is also possible that upon torqueing to establish preload, there is minor deformation of the screw/implant thread interfaces that causes reduction in preload or settling. Retorqueing of the abutment screw following a 10 minute period is suggested by some clinicians. However, laboratory studies suggest that retightening does not enhance the clamping preload (Cardoso *et al*. 2012).

The nature of the implant abutment interface may influence abutment screw behavior. Several studies have shown that internal connection (particularly internal conus/morse taper interfaces) demonstrate less abutment screw loosening than external hex implants (Gracis *et al*. 2012; Bidra & Rungruanganunt 2013). In a more recent review, Pjetursson *et al*. (2018) identified superior abutment survival for metal versus ceramic abutments. Abutment or occlusal screw loosening was more prevalent at external versus internal connections. Importantly, the abutment complication rates for fixed dental prostheses were greater than for single crowns. The authors also noted greater abutment failure rates for anterior versus posterior implants, albeit at low levels (2.5% vs 0.5%). The review affirms laboratory studies that demonstrate higher strength and resistance to bending of internal abutment constructions. It was concluded that abutments exhibit high survival rates but the implant abutment connection and abutment materials influence the incidence of technical complications. Despite these conclusions, several prospective clinical studies have demonstrated that zirconia abutments provide for high success when used for single tooth, anterior implant restorations (Cooper *et al*. 2016; Meijndert *et al*. 2020).

The reason for using a zirconia abutment is largely one of esthetics. Dental implant esthetics is influenced by both abutment-related discoloration of the crown and the abutment. In a comparative study involving 98 implants, both implant crowns and surrounding mucosa was compared with that of natural teeth. The comparison of zirconia, titanium, gold hue titanium, and zirconia abutments revealed that the gold or gold hue abutment with a zirconia coping was the best for the esthetic crown and the zirconia abutment was best for peri-implant soft tissue coloration (Peng *et al*. 2017). In a study using the mini pig maxillae, spectrophotometric measurements were used to examine the impact of mucosal thickness and various zirconia, gold, gold anodized titanium, pink anodized titanium, and titanium abutment materials. When the color differences (ΔE) were measured, the use of fluorescent zirconia or a gold alloy resulted in the least discoloration. Importantly, discoloration was reduced with increasing mucosal thickness (1–3 mm) (Ioannidis *et al*. 2017). When compared with titanium, zirconia has minimal effect on mucosal color difference when placed beneath 1.5 mm of mucosa in the pig maxillae model (Happe *et al*. 2013). This technical complication is one that requires consideration of the biologic foundation for implant therapy; management by enhancing the soft tissue thickness on the facial aspect of the abutment is a valid alternative to managing this discoloration.

Prosthetic (bridge) screw loosening increases with the complexity of the prostheses. The reported incidence of screw loosening has been reported to be higher for full arch and multi-implant prostheses than for single tooth implant restorations.

A suggested cause for this is the role that passive fit of the prostheses has on preload behavior of the abutment screws. Recurrent screw loosening of a multi-implant prosthesis requires evaluation of the prosthesis fit as a root cause affecting recurrent screw loosening. Another factor that has been suggested to influence abutment screw loosening, particularly for single tooth implants, is the crown to implant ratio. However, a recent systematic review concluded that crown-to-implant ratios of 1–2 did not demonstrate significant technical complications (Meijer *et al*. 2018).

Attempts to restore implants at the fixture level have included use of milled or cast prosthesis frameworks with direct to implant interfaces. When these frameworks are designed to engage tilted implants, the internal connections of the abutment are removed to enable insertion (path of draw). This leaves the bridge screw as the sole mechanical agent to resist lateral loading (Fig. 46-4). Imposed loads can then exceed established abutment screw preload, which ultimately results in loosening and possible fracture. Subsequent prosthesis retrieval at the implant level versus the abutment levels creates relatively greater effort and challenges to replace or tighten a screw. At least two prospective comparative clinical studies have recently demonstrated that fixture level restorations are associated with greater inflammation and marginal bone loss than abutment level restorations (Gothberg *et al*. 2018; Tola *et al*. 2019). The authors concluded that restoration at the abutment level may be a safer procedure than at the implant level with regard to peri-implant tissue health. Abutment-level restorations should be selected and treatment planning must include consideration of the necessary restorative dimension required to accommodate the approximately 2-3 mm of additional transmucosal dimension needed for successful abutment level restoration.

Residual cement as a technical problem

The relative advantages and risks of cement versus screw-retained implant restorations were revealed by a systematic review (Sailer *et al*. 2012). For example, ceramic chipping is greater for screw-retained versus cement-retained restorations. There are fewer reported biologic complications for screw-retained versus cement-retained implant restorations. There are advantages and risks associated with both forms of implant restoration retention. Pragmatically, esthetic considerations often drive the selection of a cement retained implant restoration. The use of angled screw access channels to position screw access to the lingual of anterior implant restorations offers a direct alternative to esthetic anterior implant restorations (Fig. 46-5). Posterior restorations can be placed using screw retention to achieve a positive esthetic outcome when steps are taken to fill the access channel (e.g. opaque resins or ceramic plugs).

Although it is not the intent of this chapter on technical complications to discuss the long-known association of residual cement and peri-implant inflammation (Pauletto *et al*. 1999; Wilson 2009), the control of residual cement is a restorative matter of consequence. There is a reported high incidence of undetected residual cement on abutments (up to75%) (Wasiluk *et al*. 2017). Despite concerns for residual cement and peri-implantitis, cement-retained restorations can be used with appropriate caution. Three points can be made with regard to proper cementation:

1. Patient-specific abutments (CAD-CAM) should be designed with shallow crown margin locations circumferentially (<1.0 mm). Laboratory studies have shown that cement is not accessible for removal from abutments when the crown margin is located further than 1 mm from the mucosal margin (Linkevicius *et al*. 2013).

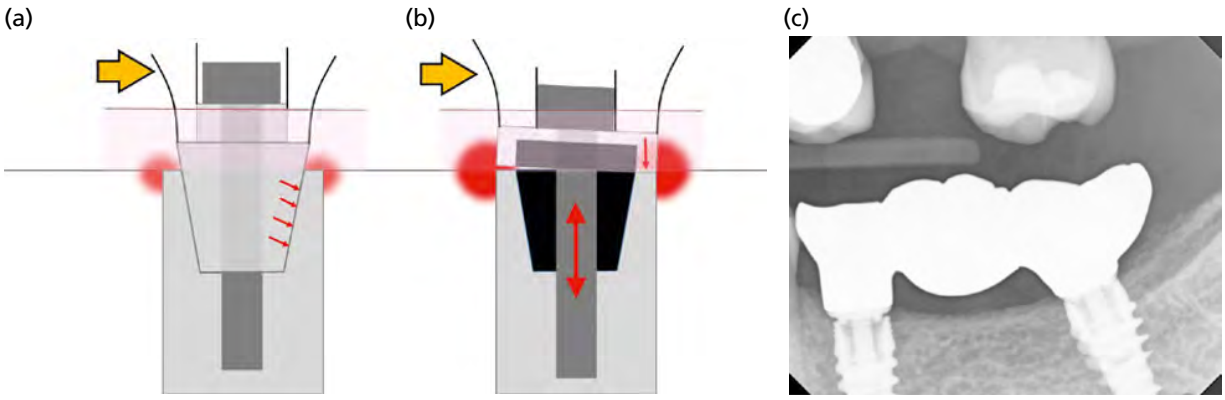

Fig. 46-4 Construction of implant prostheses at the implant level is contraindicated. (a) Construction of the prosthesis at the abutment level results in (1) force transmission from the prosthesis to the implant abutment interface, thereby reducing effects on the abutment screw, and (2) places the restorative margin at a distance from the implant/bone interface. It is suggested that this reduces inflammation at the implant/abutment interface. (b) Construction at the implant level often results in the absence of internal engagement with the implant. Upon loading, the forces are directed to the abutment screw. If these forces exceed the elastic limit of the screw, the screw is permanently deformed and loosening or fracture occurs. The micromotion and bacterial leakage contribute to greater inflammation at this implant/prosthesis interface. (c) Example of an implant prosthesis constructed at the implant level without engagement of the internal aspects of the prosthesis. The mesial abutment screw has fractured.

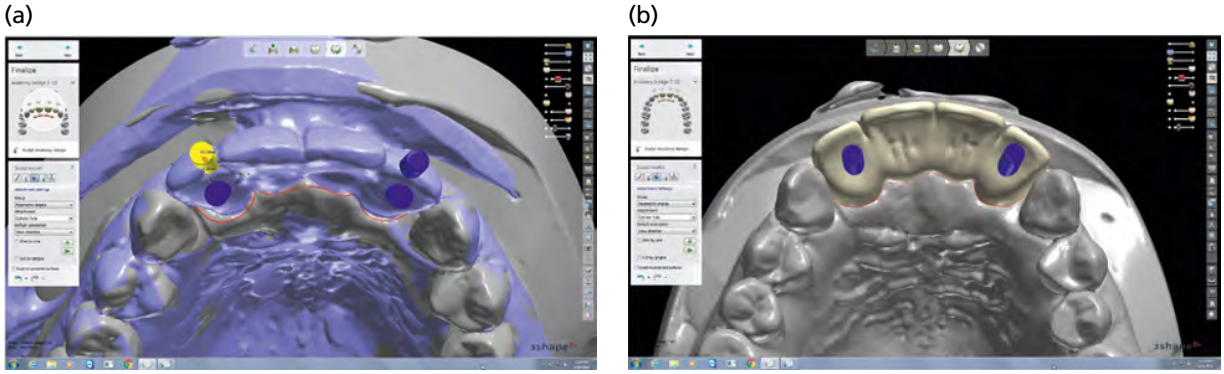

Fig. 46-5 Advantages of angled screw access. (a) Digital design of implant prosthesis demonstrating interference of screw channels with esthetics. (b) The use of angled screw access permits screw access to be in an esthetically acceptable position, in a position that favors robust prosthesis design, and one that is readily accessible.

2. Cementation techniques to reduce residual cement have been broadly advocated and include precementation on abutment replicas, venting of crowns, and applying cement as a monolayer using a brush (Wadhwani & Piñeyro 2009).
3. Where peri-implant mucositis is observed, the primary suggestion for the cause must be the presence of residual cement.

Recent studies have suggested additional risk factors influencing increased residual cement and include the shape of the abutment, the degree of undercut, and implant position in the arch (Vindasiute *et al*. 2015). The type of cement may influence the occurrence of peri-implantitis. In a series of studies, the relative absence of purulence and bleeding on probing was noted around implant crowns cemented with zinc oxide eugenol cements versus resin-based cements (Korsch & Walther 2015). When resin-based cements were replaced with a zinc oxide eugenol cement, peri-implant inflammatory signs were significantly reduced (Korsch *et al*. 2017). These findings that suggest cement type for implant prostheses influences peri-implantitis merits further investigation.

Prosthesis attrition and fracture

Full arch implant restorations, originally restored according to the Branëmark protocol, involved the use of metal frameworks with acrylic denture teeth or "hybrid" prostheses attached by bridge screws to abutments. These prostheses demonstrated high implant and bridge survival (Adell *et al*. 1981). Over the past 20 years, published data has demonstrated time-dependent increasing complications with implant supported or retained full arch prostheses. In a detailed review, Bozini *et al*. (2011) demonstrated an accumulating and increasing number of complications involving wear, tooth, veneer fracture, and to a lesser degree, framework and screw fracture, and the frequency of prosthesis complications increasing over time (Fig. 46-6). Since then, other retrospective cohort studies have affirmed that complications are commonplace and part of the patient experience, requiring management during the maintenance phase of therapy. A cohort study with a mean follow up of 35 months suggest that complications occur in over 15% of cases within the first few years of use. In a 29-year study of implant-retained metal acrylic prostheses, the majority (89%) of prostheses demonstrated complications by 20 years (Dhima *et al*. 2014). Another cohort study also demonstrated a time-dependent reduction in prosthesis survival, thus demonstrating that these prostheses require maintenance, repair, and likely replacement over time (McGlumphy *et al*. 2019). Given the high level of occlusal function, lack of proprioception, and use of a low strength denture tooth, wear often occurs on the posterior aspect leading to anterior tooth fracture. In extreme cases, this can result in multiple acrylic tooth fractures and the need to (re)establish the vertical dimension of occlusion and stabilize the posterior occlusal stability (Fig. 46-7).

When considering risk factors, framework design was predominant and other prosthesis factors such as acrylic thickness, occlusal contacts, or bruxism were not statistically associated with the reported complications (Coltro *et al*. 2018). Regarding the evidence that there is increasing risk of technical complications associated with implant prostheses over time, a more recent review indicated a reduction in the prevalence of minor technical implant prosthesis complications (Pjetursson *et al*. 2014).

A comprehensive assessment of the performance of full arch metal acrylic implant prosthesis has focused on the cantilever length and its relationship to anterioposterior spread of the implants (Drago 2018). When evaluating 193 full arch prostheses over a 48-month period, a very low acrylic fracture rate was recorded (<1%). The average cantilever length was approximately 15 mm and the average anterioposterior spread was approximately 18 mm. The calculated cantilever length/anterioposterior ratios were not associated with the frequency or type of prosthetic repairs. However, in a related report of this same cohort the author

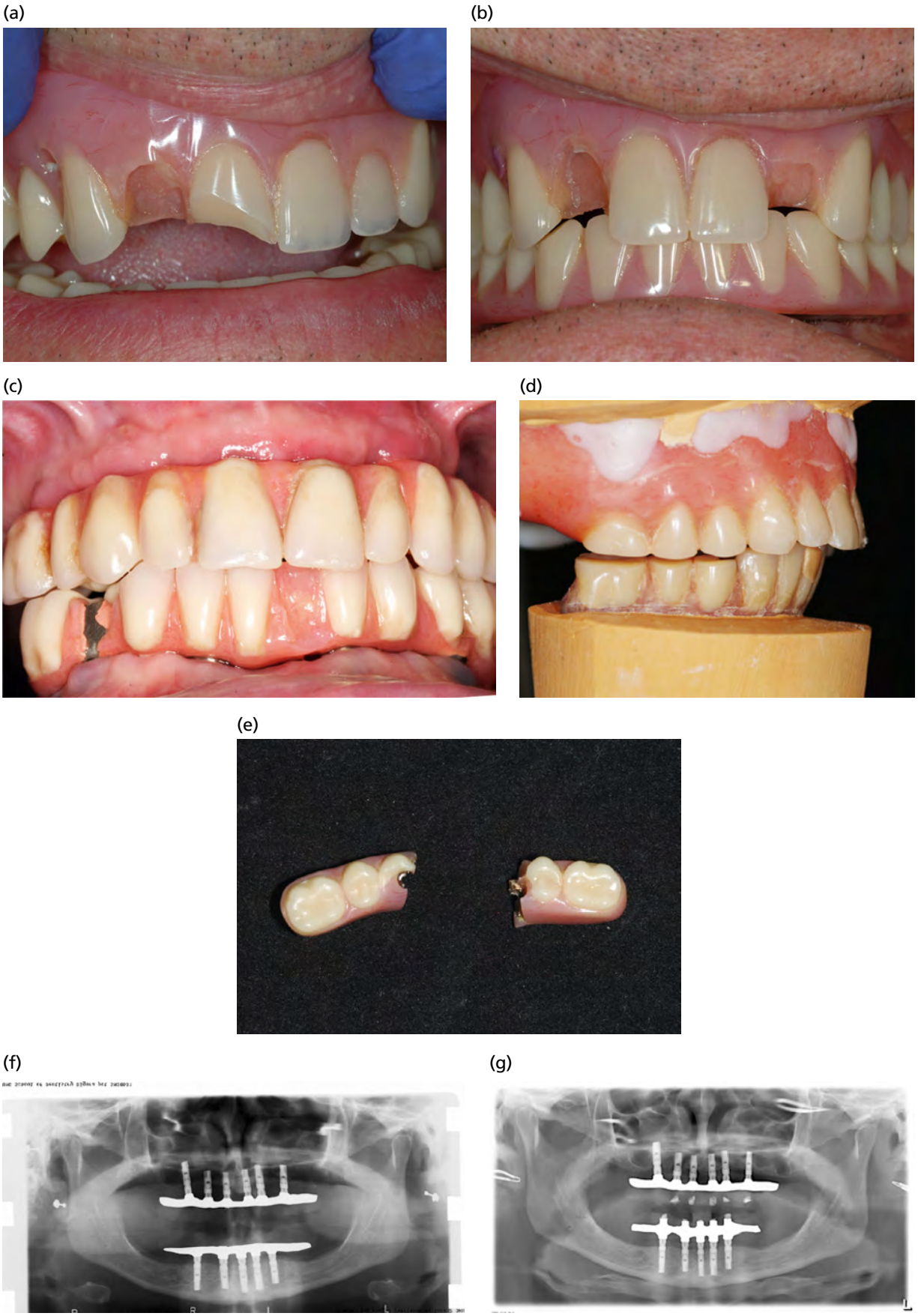

Fig. 46-6 Veneer fracture is a common complication with metal acrylic hybrid prostheses. (a) Fracture of teeth, (b) tooth loss, (c) acrylic fracture/debonding, (d) wear, and (e) framework fracture. It is essential to provide sufficient restorative dimension to enable the construction of a framework that will resist fracture. (f) Panoramic radiograph demonstrating framework design and cast in gold alloy to support hybrid prosthesis prior to fracture illustrated in (e). (g) Panoramic radiograph demonstrating new framework with greater restorative dimension (enabled by increased vertical dimension of occlusion) and cast in cobalt/chrome alloy.

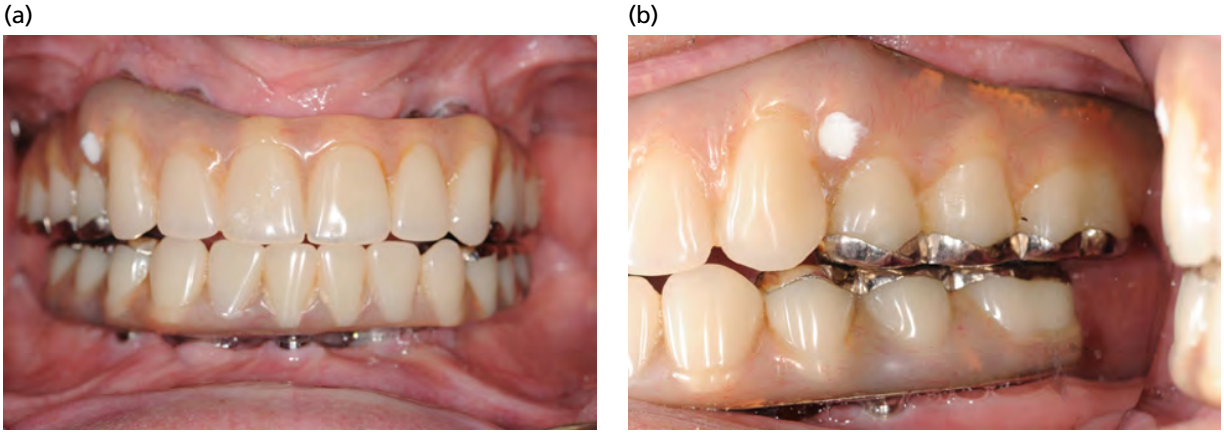

Fig. 46-7 Restorative solutions to wear include use of gold occlusal tooth surfaces. (a) Intraoral facial view demonstrating the absence of anterior tooth wear after years of metal acrylic hybrid prosthesis with gold occlusal surfaces. (b) Intraoral lateral view illustrating the cast gold occlusing surfaces of the maxillary and mandibular prostheses. Today this can be accomplished using milled ceramic materials or selective laser sintered materials in lieu of cast gold materials.

demonstrated interim acrylic prostheses were associated with significant technical complications including fracture of the prostheses (Drago 2017). These reports indicate that planning may significantly reduce the near term technical complications for metal acrylic full arch implant prostheses, yet the interim prostheses used (often via conversion of dentures) present technical complications (17% of patients treated) that challenge the clinical management of these patients.

Alternatives to the metal acrylic (hybrid) prosthesis include porcelain-fused-to-metal, unit constructions, and monolithic zirconia prostheses. There exists less data regarding the outcomes of such restorations. However, porcelain-fused-to-metal restorations have been reported to possess a relatively high porcelain chipping complication rate of 20% (Kinsel & Lin 2009). In 11 studies with at least a 5-year follow-up, there was a relatively low incidence of technical complications when compared with metal acrylic prosthesis. However, veneer fractures were common. The 5- and 10-year complication rates for metal ceramic restorations were 22.1% and 39.3% (Wong *et al*. 2019). A retrospective cohort evaluation of 55 metal ceramic full arch prostheses also reported high technical complications including porcelain wear and chipping; at 5 and 10 years there were 56.4% and 9.8% prostheses free of technical complications (Papaspyridakos *et al*. 2019). In a similar retrospective analyses involving both metal ceramic and acrylic metal full arch prostheses, with a mean observation period of 5.2 years, increased risk of chipping was greater for (× 4.6) for ceramic versus metal acrylic type prostheses. Bruxism and the absence of nightguard use were associated with increased ceramic chipping (Papaspyridakos *et al*. 2020). The use of metal ceramic prostheses is also not without significant, time-dependent technical complications that often require repair.

In a systematic review by Millen *et al*. (2015), comparing outcomes for screw- versus cement-retained full arch prostheses, the authors concluded that there were no differences in the reported incidence of complications, but higher rates of mechanical (and biologic) complications were observed for cement-retained prostheses. In a recent retrospective study including 71 prostheses in 53 subjects with an observation period of 1–12 years (mean = 5.2 years), the most common minor and major complications included wear of the veneering material and fracture of the prosthetic material. Similar to the study of Dhima *et al*. (2014), largely considering metal acrylic prostheses, they demonstrated a time-dependent increase in the incidence of prosthesis complications (85.5% versus 30.1% complication-free restorations at 5 and 10 years respectively) (Papaspyridakos *et al*. 2020). These studies infer that porcelain-fused-to-metal restorations do not represent a universal solution for technical complications associated with full arch implant restorations (Millen *et al*. 2015).

The development of monolithic zirconia restorations for full arch restorations have met with early success. Initial studies and systematic reviews imply few complications (Abdulmajeed *et al*. 2016; Bidra *et al*. 2018; Tischler *et al*. 2018). Veneered zirconia frameworks are not immune from chipping complications (Spies *et al*. 2018) and have been largely replaced in the market by monolithic zirconia prostheses. A recent comparative clinical study demonstrated veneered zirconia prostheses were associated with a higher incidence of technical complications when compared with the monolithic zirconia prostheses (Caramês *et al*. 2019). In a limited study involving bruxing patients, comparison of veneered and monolithic zirconia prostheses demonstrated the absence of minor chipping complications compared to high rates of chipping in the veneered zirconia prostheses (Levartovsky *et al*. 2019). These various reports suggest that monolithic zirconia prostheses may reduce technical complications that plague full arch implant restoration.

Fig. 46-8 Zirconia bridge fracture. While recent studies indicate no or only rare fracture of monolithic zirconia implant supported prostheses, fractures are non-repairable and require replacement of the entire prosthesis. Fortunately, if the digital files have been retained, a duplicate can be constructed with minimal clinical effort.

When monolithic zirconia prostheses fail, failure may be catastrophic in nature (Fig. 46-8). This phenomenon has not been widely reported in the literature and may reflect a low rate of major technical failures. The possible causes of catastrophic monolithic zirconia failures may include: ceramic flaws caused by improper handling following sintering, use of higher cubic ZrO content in more translucent ceramic systems, improper sintering, post sintering adjustments, hydrolytic aging and inadequate three-dimensional framework designs. High translucency zirconia materials possess lower biaxial flexural strength and are differentially influenced by mechanical cycling or aging *in vitro* (Muñoz *et al*. 2017). Regarding dimensional requirements for full arch zirconia implant prostheses, prosthesis height should permit 10 mm of vertical dimension and connectors should be as large (and especially tall) as feasible (> 25 mm^2). The thickness of zirconia surrounding the titanium cylinders should be greater than 3 mm circumferentially (Rojas Vizcaya 2018). Thus, screw access must be directed through the body of crowns and their location interproximally should be avoided. Additional detailed attention should be paid to the connector and embrasure design of these prostheses as laboratory studies indicate that blunt embrasures and large interproximal separations decrease the measured load to fracture (Bakitian *et al*. 2019). Meeting the expectations for reduced technical complications with monolithic zirconia implant prostheses requires careful attention to details of design and manufacture.

Prevention of technical complications

The current data suggests that technical complications will be frequently encountered in implant dental practice. The more common problems appear to include abutment screw loosening and prosthesis veneer fracture. More rarely, catastrophic technical complications requiring prosthesis replacement are encountered. When considering early complications, they may represent inadequate implant placement planning and/or prosthesis design.

To assure robust prosthesis function over time, two important features must be considered at the time of implant planning. One is the assurance of an adequate restorative dimension that is determined by both proper management of the vertical dimension of occlusion and recognition that the depth of implant placement may require alveolectomy. Related is the biomechanical approach to reduce the bending moments by reduction of cantilever length through tilted implant positioning. Together, these features of planning can ensure that a prosthesis of sufficient bulk is provided and will avoid being loading by excessive forces.

A third aspect of planning to reduce potential technical complications is to utilize components of "optimal" dimension. This includes avoiding the use of narrow implants for posterior implants or use of narrow abutment platforms for posterior implants. Related is the use of implant components with precise interface connections; today's dental technology largely avoids casting of components due to the precision of CAD-CAM manufacture. The selection of abutment dimension for strength is dependent on implant selection. Thus, surgical planning is the phase in treatment when many decisions must be made to reduce potential technical limitations (Box 46-3).

Technical complications may also be associated with procedural errors in implant restoration. These errors accumulate in two areas. One is in the management of the implant abutment interface. As reviewed, it is strongly recommended that all multiple implant restorations be restored at the abutment level and not the implant level. Abutment connection to the

Box 46-3 Implant planning steps to reduce technical complications.

1. Plan implant number to account for imposed loading
2. Select implant dimensions (and materials) to oppose these loads
3. Plan implant location vertically to allow sufficient restorative dimension
4. Reduce cantilevers to minimize anticipated bending moments
5. Design 'shallow' occlusion to reduce lateral loading

implant must be performed with fidelity; the components must be correctly assembled, be free of tissue interferences, and be tightened appropriately using torque control to achieve the manufacturer's recommended torque level. The prosthesis to abutment interface must also be connected with high fidelity and there must be absolute passivity to reduce potential high stresses in bridge screws or – in extreme cases – the prosthesis. Careful attention must be paid to each step in the prosthetic process, including abutment selection, abutment insertion, impression, verification of master cast accuracy and/or digital image recording, framework design, framework assessment, and esthetic veneer designation and assessment. Stepwise assurances help to limit potential risks leading to technical complications or failure.

Conclusion

Currently available data indicates technical complications are commonly encountered in implant dental therapy and shorten the service life of the restoration. These complications span the range of implant, abutment, and prostheses complications. Minor complications typically do not require replacement of abutments or prostheses. However, they impact practice and patient perceptions of implant treatment. Major complications require major modification or replacement of the prosthesis and have a significant impact on the practice of implant dentistry. The root causes of complications must be identified when possible and these causes should be addressed to prevent recurrent complications. Understanding the factors that lead to technical complications enable clinicians to improve the planning of implant surgery and prosthesis fabrication to anticipate risk and limit complications that lead to therapeutic dissatisfaction.

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Part 17: Orthodontics and Periodontics

Chapter 47

Tooth Movement in the Periodontally Compromised Patient

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Introduction: biologic principles of orthodontic tooth movement

The objective of orthodontic therapy is to correct altered tooth positions and the resulting malocclusions by the application of orthodontic appliances and techniques that once applied to the tooth surface exert the appropriate pressure and tension forces (Dolce *et al*. 2002; Meikle 2006; Wise & King 2008). This therapy presents distinctive characteristics when it is applied to dentitions when the bone is still growing, such as in children and adolescents, in comparison with adult dentitions where the bone has finished its growth. In the first case, orthodontic therapy aims both to elicit tooth movements within the alveolar bone housing and to guide the growth of the jaws to attain adequate intermaxillary relationships. In adults, orthodontic therapy is limited to dentoalveolar tooth movements and in many instances these movements need to be applied in teeth with a healthy but reduced periodontal ligament (PDL) as a consequence of a history of periodontitis. Moreover, cellular activity in adults is reduced in comparison with younger patients, which may reduce the rate of orthodontic tooth movement (Verna et al. 2000; Ren *et al*. 2002). With the increasing esthetic demands of modern society, a growing number of adult patients are seeking orthodontic treatment for correcting common conditions as anterior tooth diastemas, crowding, uneven gingival margins, or loss of interdental papillae. Furthermore, in patients suffering from severe periodontitis, the combination of attachment and bone loss with tooth loss results in a series of events leading to secondary occlusal trauma, pathological tooth migration, and frequent severe malocclusions and malpositions that severely compromise the patient's masticatory function. In the recent classification of periodontal and peri-implant diseases, stage IV periodontitis defines this clinical situation where severe periodontitis is accompanied by extensive tooth loss and the sequelae of tooth drifting and altered masticatory function. This stage of periodontitis will usually need not only the appropriate treatment of the periodontal condition but also a multidisciplinary rehabilitation including orthodontic tooth movements to restore the patient's functional dentition (Papapanou *et al*. 2018). The

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

multidisciplinary treatment of these patients requires close coordination and collaboration between the orthodontist, the periodontist, and the restorative dentist in order to optimize the treatment outcomes. This chapter specifically reviews how orthodontic therapy can be implemented in adults with periodontally affected dentitions.

Physiological tooth movements are those undertaken by a tooth to attain and maintain its functional position. They take place during the processes of tooth growth, eruption, or when the tooth movement is a consequence of the application of an external force, such as the push from an inclined erupting third molar. Orthodontic tooth movements are those generated by external forces when applied in a controlled manner with the purpose of achieving a predetermined tooth movement. In both types of movements, the basic biological processes are similar; the transmission of a mechanical force from the root to the PDL affecting the homeostasis between the cells and the extracellular matrix, and leading to a series of biological events characterized by the modeling and remodeling processes of the alveolar bone housing, which results in changes in tooth position. The orthodontic forces applied to the tooth crown elicit a series of cell–matrix interactions within the PDL that convert physical distortion into changes in the extracellular, cell membrane, and nuclear transduction mechanisms that alter cell behavior through a chain of biochemical cascades (Masella & Meister 2006). These highly sophisticated biological pathways transforming mechanical forces into controlled active cellular processes represent a controlled inflammatory response (aseptic inflammation), which is regulated by neurotransmitters, growth factors, cytokines, and molecular mediators (Meikle 2006).

Depending on the amount and direction of the mechanical force applied to the tooth, the resulting tooth movement will be different. A mechanical force perpendicular to the longitudinal axis of a tooth will elicit wide areas of pressure on certain parts of the root and corresponding areas of tension on others. In general terms, the tension areas will widen the PDL space by stretching the periodontal fibres, which will distend the blood vessels and increase the fibroblasts orientated in the direction of the applied force. This phenotypic alteration of the fibroblast will induce the differentiation of the osteoblast precursors into functional osteoblasts that will form osteoid leading to bone apposition and reformation of the Sharpey's fibres within the new calcified formation. On the contrary, on the pressure zones, there will be compression of the PDL space, with partial obliteration of the blood vessels and collagen tissue remodeling, leading to a proinflammatory biological cascade with differentiation of bone resorbing cells (osteoclasts), resulting in bone resorption and change of the tooth position towards the force direction. Once the tooth has been displaced and escaped from the physical force, homeostasis will return with new vessel formation, osteoblast recruitment, and reformation of the periodontal fiber attachment to the newly formed bone.

If the mechanical force was located near the center of resistance of the root, there will be an even distribution of pressure and tension areas on both sides of the root, resulting in a horizontal translation of the tooth, also called bodily movement. This movement, however, is impossible in most clinical situations because the root is invested in its alveolar housing and the only available surface to apply the orthodontic force is the crown. Orthodontic forces are, therefore, applied to the tooth crown via some kind of appliance that ensures a two-point contact enabling the necessary couple that transfers the applied force to the tooth center of rotation. The dimensions of such a movement will depend on the site of the force application, the shape of the tooth, and the architecture of the tooth supporting apparatus. Under these circumstances, the ensuing tooth displacement will be a combination of bodily and tilting movements where pressure and tension forces are located everywhere around the root, leading to diverse stress distribution within the PDL (Fig. 47-1).

Because the socket housing is a three-dimensional structure, pressure/tension areas are not clearly defined and will occur simultaneously around the root, usually following a biphasic process with two concomitant sequential phases occurring in the alveolar bone. First, there is a catabolic phase during which osteoclasts resorb bone to adapt to the orthodontic force, followed by an anabolic phase, where bone formation and reorganization of the periodontal fibers will restore homeostasis within the PDL once the tooth has been displaced. Depending on the orthodontic force there will be specific cellular and molecular events establishing the limits for each phase (Alikhani *et al*. 2018).

Application of light mechanical forces (approximately 50–100 g/tooth) on the pressure side is associated with "direct bone resorption". In these situations, the vessels are patent, and the physiology of the cells and tissues is preserved. In contrast, stronger mechanical forces will cause a crushing injury to PDL tissues, with cell death, hyalinization, and the formation of cell-free areas between the PDL and the adjacent alveolar bone, which will interfere with the tooth movement and will slow the biologic processes. Patient variability in the response to similar mechanical forces is common in orthodontic practice and there are many possible reasons for this heterogeneity, such as differences in alveolar bone mineral density, in vascularity, in the number of available bone cells, and in the many inherent cellular and metabolic responses due to differences in the patient's genome that dictate differences in cell recruitment, differentiation, and function, as well as in the expression of the many proteins and regulatory molecules that intervene in bone metabolism.

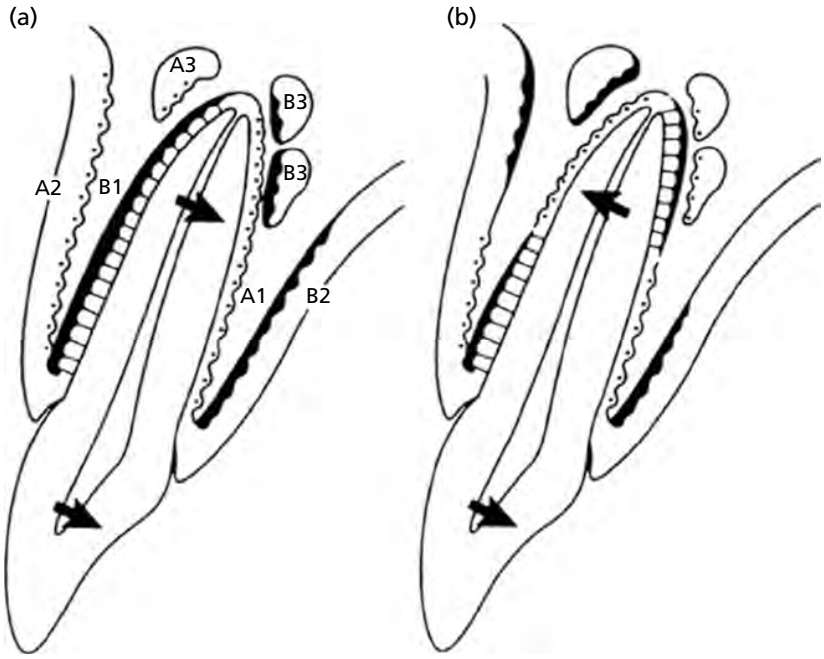


Fig. 47-1 (a) Mechanical force perpendicular to the longitudinal axis of a tooth produces wide areas of pressure on one side of the root and corresponding areas of tension on the other. (b) Direction of the force varies depending on the site of the force application, shape of the tooth, and architecture of the tooth-supporting system. The resulting movement will be a combination of bodily and tilting movements, leading to pressure and tension forces on either side of the root and a varying distribution of the stress along the periodontal ligament.

Periodontal and orthodontic diagnosis

Periodontal health is a prerequisite for any orthodontic tooth movement, and this particularly applies to adult orthodontics. Any adult patient seeking orthodontic therapy must have a comprehensive periodontal diagnosis, including oral examination, periodontal charting, and a complete periapical radiographic series before the start of orthodontic therapy. Periodontal charting should include registration of full mouth probing pocket depths, gingival recessions, bleeding on probing and plaque indexes in 4–6 sites per tooth. Furthermore, presence of tooth mobility, furcation involvements, and mucogingival defects should be evaluated. In conjunction with the periodontal examination, it is important to evaluate carefully the status of the remaining dentition with close attention to the presence of undiagnosed caries or presence of periapical pathology that may interfere with orthodontic therapy. If these pathologies are present, appropriate restorative and/or endodontic therapy should also be performed before the start of orthodontic therapy.

In the diagnosis of the patient's malocclusion, the appropriate intraoral and extraoral examination should be conducted in close collaboration between the orthodontist and the periodontist. The extraoral examination should include a full smile analysis, including the evaluation of the shape and form of the lips, the tooth and gingival exposure in open smiling, as well as the exposure of the posterior corridors. The intraoral examination should also include assessment of the static and dynamic occlusion to detect the presence of prematurities in maximum intercuspidation, or interferences in the protrusive and lateral disclusive movements. The intermaxillar relationships should be studied with the appropriate intraoral and extraoral records. Intraoral models appropriately mounted should reveal the shape of both arches, presence of diastemas, tooth crowding, tooth rotations, anomalies in the size, shape and number of teeth, and their interocclusal relationships. Classically, the combination of orthopantomography (OPG) and cranium lateral radiography will allow a cephalometric analysis leading to the appropriate diagnosis of the patient's malocclusion. The advent of cone-beam computed tomography (CBCT) has improved the diagnostic accuracy for examining the craniofacial complex, including the assessment of buccal alveolar bone height and thickness, transverse dimensions, the presence of impacted, ectopic, supernumerary teeth, as well as the presence of root resorptions. Three-dimensional imaging also allows the assessment of the position of the soft tissues in relation to the bone envelope (Fig. 47-2).

In the treatment of adult patients it is also important to take a detailed medical and drug history because adults may suffer from medical conditions or take regular medications that might interfere with periodontal and/or orthodontic therapy. To assure the appropriate response to periodontal therapy, patients who smoke should be advised to cease and patients who are diabetic or prediabetic should achieve appropriate glycemic control. For orthodontic therapy, the medical history should include details of regular drug-consumption because the use of non-steroidal anti-inflammatory drugs (NSAIDs) may alter the behavior of those cells targeted by the orthodontic forces during tooth movement. These NSAIDs not only effectively reduce inflammation and pain, but also affect the sequence of tooth movement by inhibiting, or at least reducing, the controlled inflammatory and bone resorptive processes. New generation anti-inflammatory drugs such as nabumetone, on the contrary, have been shown to reduce the amount of root resorption in intrusive orthodontic forces, without

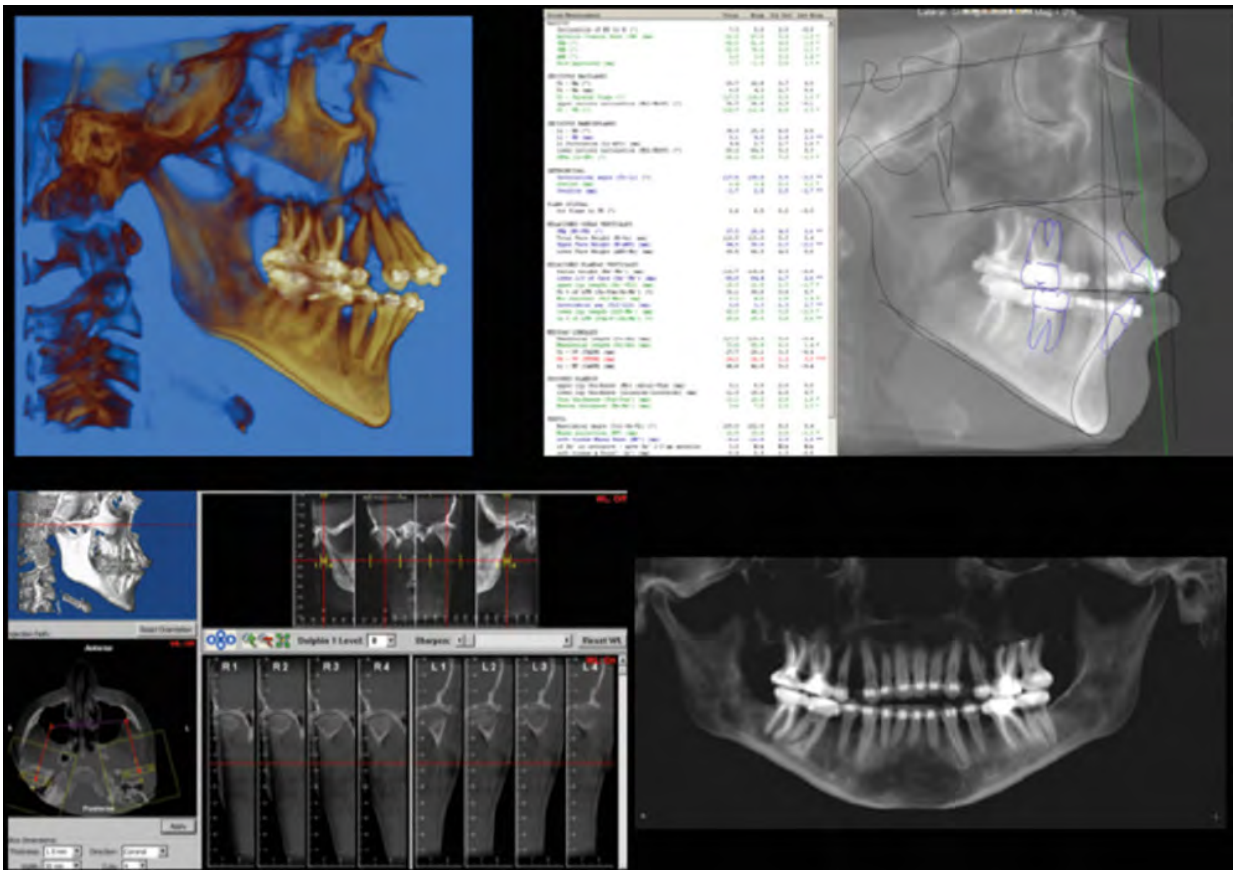


Fig. 47-2 Diagnostic information used in orthodontic treatment planning can now be obtained with cone-bean computed tomography (CBCT) allowing the combination of classical orthopantomography and cranium lateral radiography with 3D information of the craniofacial complex.

affecting the pace of tooth movement (Krishnan & Davidovitch 2006). Another group of drugs that may affect adult patients under orthodontic care are muscle relaxants, such as cyclobenzaprine, and tricyclic antidepressants, such as amitriptyline and benzodiazepines. The main side effect of the latter is xerostomia, which can negatively affect the proper maintenance of oral hygiene, and hence proper periodontal health during orthodontic therapy. Similarly, in patients requiring chronic use of inhalers with steroids, such as those suffering from asthma, oral candidiasis and xerostomia may result. Appropriate measures should be implemented in these patients, such as the use of topical antifungal agents and salivary substitutes before and during orthodontic treatment.

A condition that frequently affects women in adulthood is osteoporosis and most of the current therapies for this disease are antiresorptive (bisphosphonates, selective estrogen receptor modulators, and calcitonin), which may slow the remodeling phase of bone turnover and potentially interfere with orthodontic therapies. Similarly, in patients suffering from rheumatoid arthritis or other chronic inflammatory conditions, therapy aims to block the catabolic cytokine production responsible for the damage to soft tissues and bones (TNF or interleukin antagonists). These immune-modulatory agents might also interfere with orthodontic tooth movement.

Another group of drugs that need special consideration are those associated with gingival hyperplasia, such as phenytoin used for seizure disorders, calcium blockers used as antihypertensive drugs, or cyclosporine-A used in organ transplant patients. These drugs induce gingival hyperplasia, which might prevent the application of certain orthodontic mechanics, as well as interfering with the maintenance of proper oral hygiene and periodontal health.

Tooth movement might also be affected in patients who have recently received chemotherapy with busulfan/cyclophosphamide (<2 years of disease-free life), because these drugs are known to produce damage to the precursor cells involved in the bone remodeling processes.

Treatment planning

Once the patient has completed the required dental and periodontal treatments leading to oral and periodontal health, the multidisciplinary treatment, including orthodontic tooth movements, should be planned, always taking into consideration the patient's main concerns and expectations, and the foreseen realistic functional and aesthetic objectives. The sequence of planned interventions must be customized to the patient's pattern of bone loss, type of malocclusion, and periodontal disease severity

(Geisinger *et al*. 2014). One important complication during the orthodontic treatment of periodontal patients is the occurrence of root resorption, which may be associated with the presence of periodontal inflammation, the dimension of the orthodontic forces, or the individual relative expression of inflammatory/osteoclast marker genes (Kirshneck *et al*. 2017).

Periodontal considerations

Although the effects of orthodontic forces on the periodontium have been studied extensively, there are contradictory findings in the scientific literature on the impact of orthodontic therapy on periodontal health. A recent systematic review assessing the effect of orthodontic treatment on periodontal outcomes concluded that orthodontic treatment with fixed appliances has little to no clinically relevant effect on periodontal clinical attachment levels (Papageorgiou *et al*. 2018a). In fact, many clinical studies have clearly shown that with adequate plaque control, orthodontic treatment in patients with a reduced but healthy periodontium achieves the orthodontic objectives without aggravating their periodontal condition and the risk of periodontal recurrence in these patients is not increased during orthodontic therapy (Re *et al*. 2000). When periodontal inflammation is not fully controlled during orthodontic treatment, however, these inflammatory processes may accelerate the progression of periodontal destruction leading to further loss of attachment (Fig. 47-3).

In some clinical studies, a mean increase in probing depth of about 0.5 mm during orthodontic treatment has been reported, and this increase has been interpreted as caused by marginal inflammatory changes rather than by periodontal attachment loss (Ristic *et al*. 2007; van Gastel *et al*. 2008). Clinical trials comparing molars with bands versus brackets have shown that bands exhibit greater gingival inflammation and loss of attachment (Boyd & Baumrind 1992). Other studies, however, have reported the presence of gingival inflammation as a result of accumulation of subgingival plaque around the bands, but without loss of attachment (Diamanti-Kipioti *et al*. 1987; Huser *et al*. 1990) or without demonstrating significant differences in other clinical periodontal parameters when comparing banding and bonding procedures (Sinclair *et al*. 1987; van Gastel *et al*. 2008).

It is, therefore, critical that accumulation of dental biofilm during orthodontic treatment is prevented and closely monitored. This is particularly relevant when using fixed orthodontic appliances that may facilitate plaque accumulation and hinder a patient's oral hygiene practices. Although changes in the subgingival microbiota after the insertion of orthodontic appliances have been reported, they appear to be a transient and usually revert to a healthy microbiota in the first months after appliance removal (Papageorgiou *et al*. 2018b).

Patients preparing for orthodontic therapy must demonstrate not only gingival and periodontal health but also excellent oral hygiene. Patients should be informed that the lack of adequate oral hygiene poses a significant risk of periodontal breakdown that will entail the discontinuation of orthodontic treatment until low plaque scores have been re-established.

In some patients with poor oral hygiene, the fixed orthodontic appliances may promote gingival enlargement, which further enhances plaque accumulation. In these situations, orthodontic therapy should be stopped, and the orthodontic appliance removed until the inflammation is resolved, and efficient oral hygiene practices are reinstated (Davis *et al*. 2014). Sometimes the marginal tissues do not revert to their appropriate position with only subgingival instrumentation and surgical removal of the excessive gingival tissue is needed (Graber & Vanarsdall 1994; Sanders 1999).

The timing of initiating orthodontic treatment after periodontal therapy is still controversial. A recent clinical trial compared starting orthodontic therapy immediately after basic periodontal therapy versus 3–6 months after the surgical therapy and showed no differences in attachment levels (Zasciurinskiene *et al*. 2018). However, there is no consensus on the optimal timing for initiating orthodontic tooth movements after periodontal surgery, although it is mandatory to start orthodontic therapy once periodontal health has been achieved. In consideration of the previously described biological bases of orthodontic tooth movements, once proper infection control has been implemented and the endpoints of periodontal therapy achieved (no pockets of ≥6 mm and no probing pocket depth >4 mm with bleeding on probing), it is advisable to start the orthodontic treatment as soon as possible in order to benefit from the high bone turnover secondary to the healing of the periodontal interventions, which may accelerate orthodontic tooth movements (Frost 1989).

During orthodontic therapy, the periodontal condition and oral hygiene compliance of patients should be closely monitored. It is advisable that during the monthly orthodontic appointment, the periodontal status is verified and professional plaque removal should be implemented if required.

Orthodontic considerations

Orthodontic tooth movements *per se* do not cause periodontal attachment loss and/or gingival recession (Wennstrom 1996). However, in areas of thin buccal cortical bone, labial or proinclination orthodontic tooth movements can result in bone dehiscence defects, which when accompanied by a thin gingival phenotype in conjunction with presence of plaque derived gingival inflammation and/or toothbrush trauma may lead to attachment loss and the development of localized gingival recessions (Coatoam *et al*. 1981; Artun & Krogstad 1987; Maynard 1987;

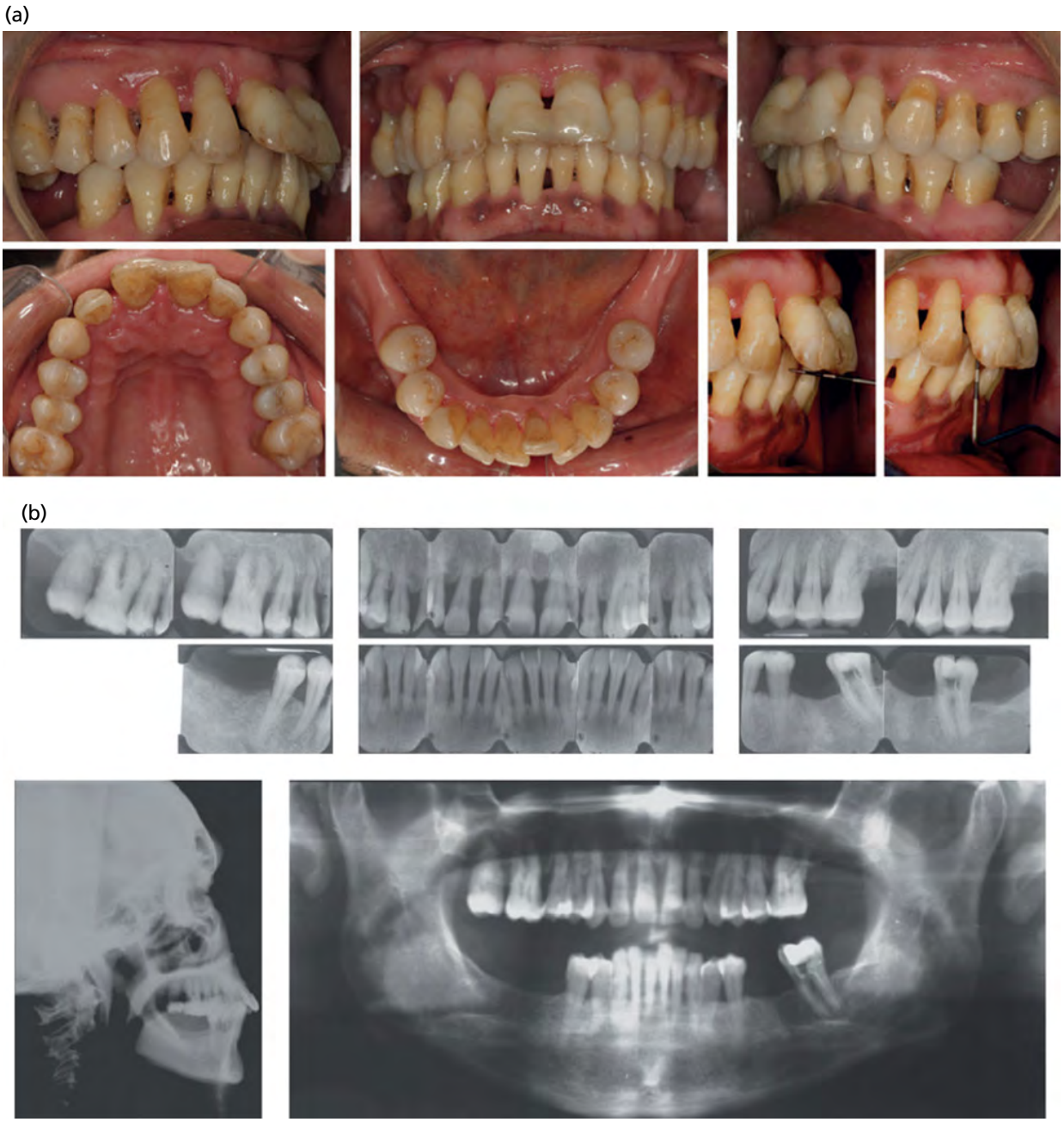


Fig. 47-3 Patient with severe chronic periodontitis, together with pathologic tooth migration, secondary occlusal trauma, and severe esthetic and functional impairment. (a) Intraoral initial clinical pictures. (b) Initial orthopantomogram (OPG), lateral cephalogram, and periapical series.

Wennstrom 1996). In the presence of thick gingival tissues, gingival marginal tissue recessions will not occur, even when labial or expansive tooth movements are carried out (Coatoam *et al*. 1981; Artun & Krogstad 1987; Maynard 1987; Wennstrom 1996).

In children and adolescents, prospective and retrospective clinical studies have not found a correlation between orthodontic labial inclination of mandibular central incisors with the development of gingival recessions (Ruf *et al*. 1998; Artun & Grobety 2001; Djeu *et al*. 2002). In adults, however, a prospective study showed a significant correlation between the incidence and the severity of recession lesions with excessive proinclination (>10°) of the mandibular incisors (Artun & Krogstad 1987). However, other studies in patients with mandibular prognathism subjected to orthognathic surgery reported that in spite of extensive labial tipping the mandibular incisors, there were no negative outcomes in the periodontal tissues (Ari-Demirkaya & Ilhan 2008). It is the combination of the final tooth inclination and the thickness of the marginal gingival tissues (<1 mm) that has been associated with the occurrence of recessions in mandibular central incisors after orthodontic treatment (Yared

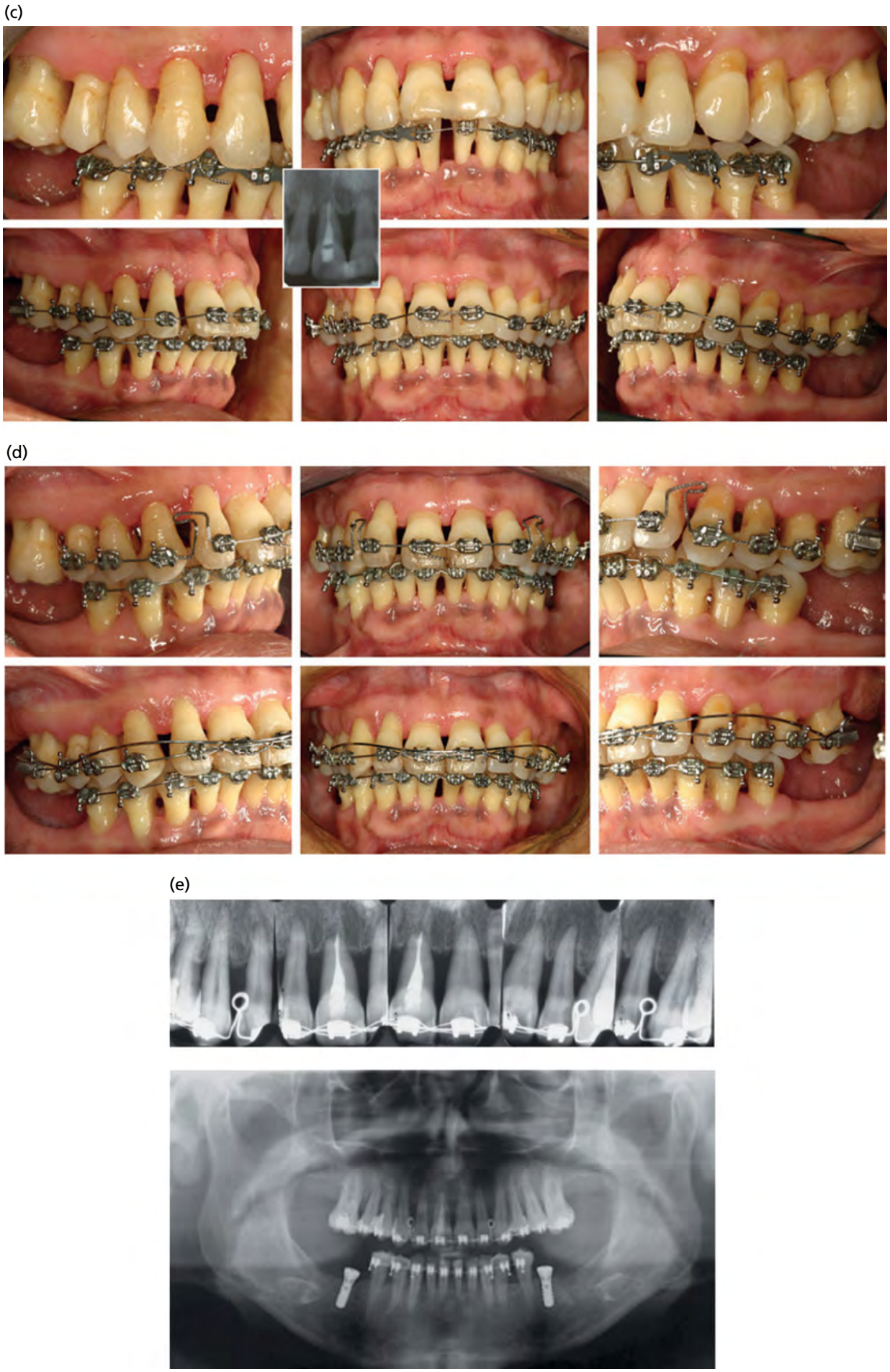


Fig. 47-3 *(Continued).* (c) Orthodontic treatment progress, lower arch appliances first and preventive root canal treatment prior to upper arch appliances. (d) Orthodontic treatment progress. (e) Follow-up periapical series and OPG.

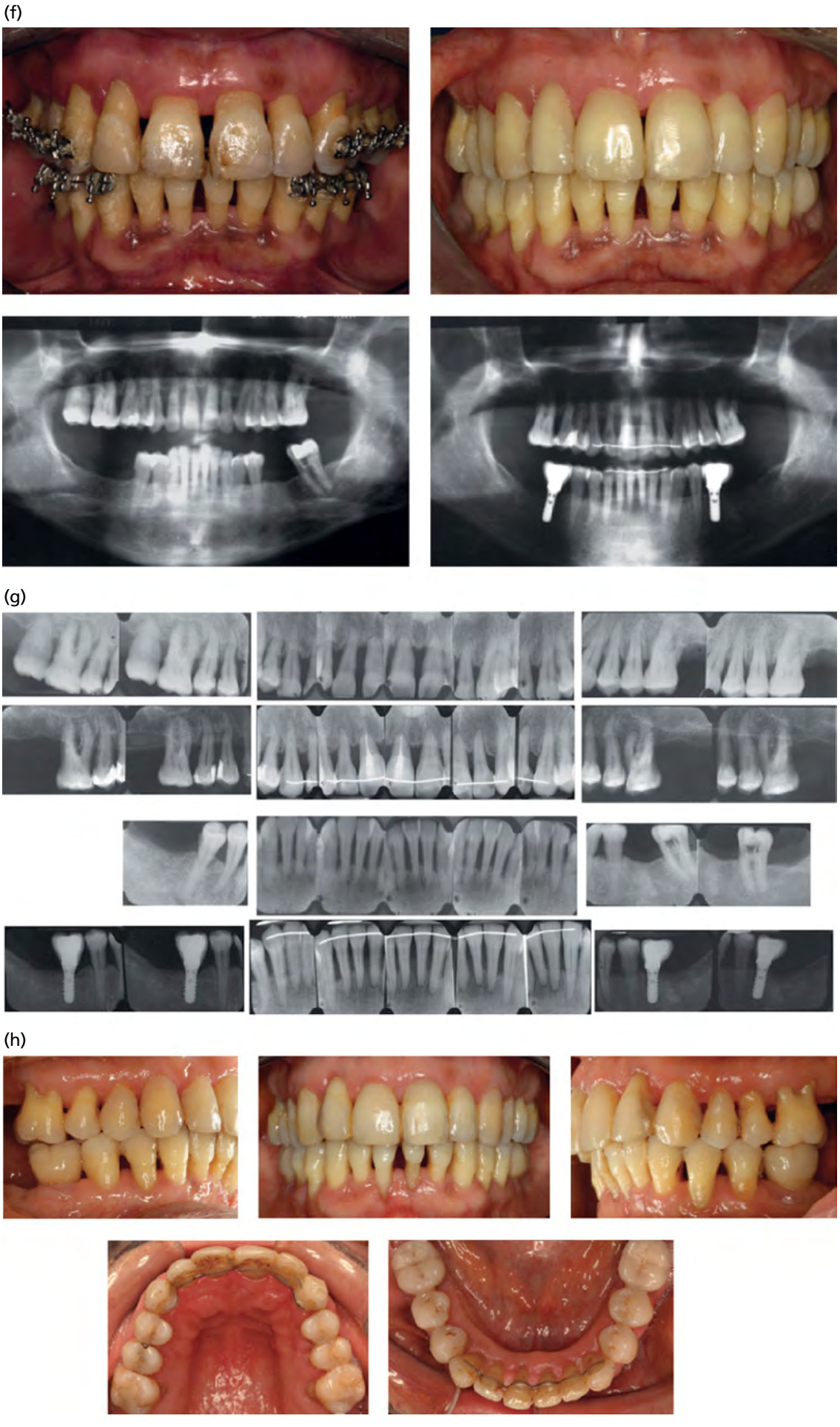


Fig. 47-3 *(Continued)*. (f) Composite veneers and initial/final OPG. (g) Initial/final periapical series. (h) Five-year post-retention intraoral clinical photographs.

et al. 2006) and, therefore, the main risk factors associated with the development or the aggravation of gingival recession lesions after adult orthodontic therapy is the presence of a thin gingival phenotype combined with an insufficient width of keratinized gingiva, and/or presence of gingival inflammation (Melsen & Allais 2005). In these risk situations, the orthodontist should consult with the periodontist and consider a gingival augmentation or root coverage procedure before attempting to move the affected tooth or root labially (Pini-Prato *et al*. 2014). On the contrary, if a labially positioned tooth is orthodontically moved lingually, the bone dehiscence may disappear and the gingival thickness increase (Steiner *et al*. 1981; Karring *et al*. 1982; Wennstrom *et al*. 1987). In these situations, the mucogingival conditions should be closely monitored during the orthodontic therapy and the possible indication of a mucogingival surgical procedure should be evaluated during and after orthodontic treatment (Fig. 47-4).

Some authors have also reported the risk of gingival recessions in the area of maxillary premolars and molars when rapid maxillary expansion movements are carried out after mid-palatine suture fusion (after 20 years of age) (Graber & Vanarsdall 1994). Similarly, the movement of teeth into edentulous spaces (areas of reduced buccolingual bone dimension) is often possible with slow, light orthodontic forces, depending on the tooth-to-bone width ratio, although in spite of these measures, loss of alveolar bone and presence of dehiscence defects have been reported in these clinical situations (Stepovich 1979; Hom & Turley 1984; Pontoriero *et al*. 1987; Goldberg & Turley 1989; Fuhrmann *et al*. 1995; Wehrbein *et al*. 1995). This complication may be even more frequent when orthodontic tooth movements are aimed through atrophic and narrow alveolar ridges (Ramos *et al*. 2019). In these situations, the orthodontist, together with the periodontist, should consider a lateral bone augmentation procedure to increase the width of the ridge prior to the orthodontic treatment (Kaminishi *et al*. 1986).

Goldberg and Turley (1989) studied the periodontal changes associated with orthodontic space closure of edentulous maxillary first molar areas in adults. With a space closure averaging 5.3 mm, the resulting vertical bone loss averaged 1.2 mm in the second molar and 0.6 mm in the second premolar, with 60% of the teeth showing ≤1.5 mm of bone loss. Although space closure can be considered a potential solution in the absence of the first permanent molar, attachment loss and space reopening can be common complications.

Orthodontic treatment

Once orthodontic therapy starts; periodontal patients should be closely monitored for any signs of recurrence of their previous periodontal pathology and they should be frequently recalled for professional infection control. These recall visits should be customized according to the severity of the reduced periodontium and the associated patient risk factors (smoking, diabetes, etc.). At these visits, probing pocket depths and gingival bleeding scores should be monitored and when present, appropriate professional plaque removal or subgingival root instrumentation, together with other adjunctive therapies (adjunctive antiseptics, such as chlorhexidine, cetyl pyridinium chloride, or phenolic compounds) should be implemented.

In patients with a reduced periodontium, the total surface of the PDL that receives the orthodontic forces is significantly less and the tooth's center of resistance is displaced apically, which results in the expression of greater moments of force. In these cases, orthodontic treatment should be carefully planned and monitored to achieve as much as possible bodily, instead of tipping, tooth movements (Melsen 1988). In terms of orthodontic appliances, it is always advisable to use the simplest orthodontic system with the goal of facilitating oral hygiene practices and thus reducing plaque accumulation. It has been shown, although in the short term, that the design of the bracket may influence significantly bacterial accumulation and gingival inflammation (van Gastel *et al*. 2007). In this context, self-ligating brackets or wire ligatures are considered better than elastomeric ligatures (Turkkahraman *et al*. 2005; Alves de Souza *et al*. 2008). Although the use of clear aligners in the treatment of periodontal patients has shown no differences in terms of plaque levels or gingival scores, when compared with fixed orthodontic appliances, patients in the group with fixed appliances had significantly shallower pockets and the duration of the treatment was shorter (Han 2015). When using aligners, the placement of attachments on tooth surfaces with a reduced bone support should be avoided, because these teeth may be traumatized when inserting the appliances.

Reduced periodontal support also implies a reduction in the anchorage required to undertake orthodontic tooth movements and in patients with severe periodontal destruction, the use of skeletal anchorage devices, such as orthodontic mini-screws, mini-plates, or conventional dental implants is recommended to assure better control of three-dimensional tooth movements (Fig. 47-5).

Once orthodontic treatment is finished after achieving the desired tooth position, a permanent retention is recommended in patients with a reduced periodontium. Retainers bonded to both canines and incisors are usually the preferred retention method, although in some studies these lingually fixed retainers have resulted in negative periodontal outcomes (Pandis *et al*. 2007; Levin *et al*. 2008), whereas in others no significant long-term periodontal changes were shown (Reitan 1969). In some severe cases, a two-retainer approach is chosen, combining a conventional lingual retainer and a segmented retainer inserted within the crowns of two adjacent teeth and covered with composite resin. Removable retainers should be avoided to prevent jiggling movements on the periodontally compromised teeth.

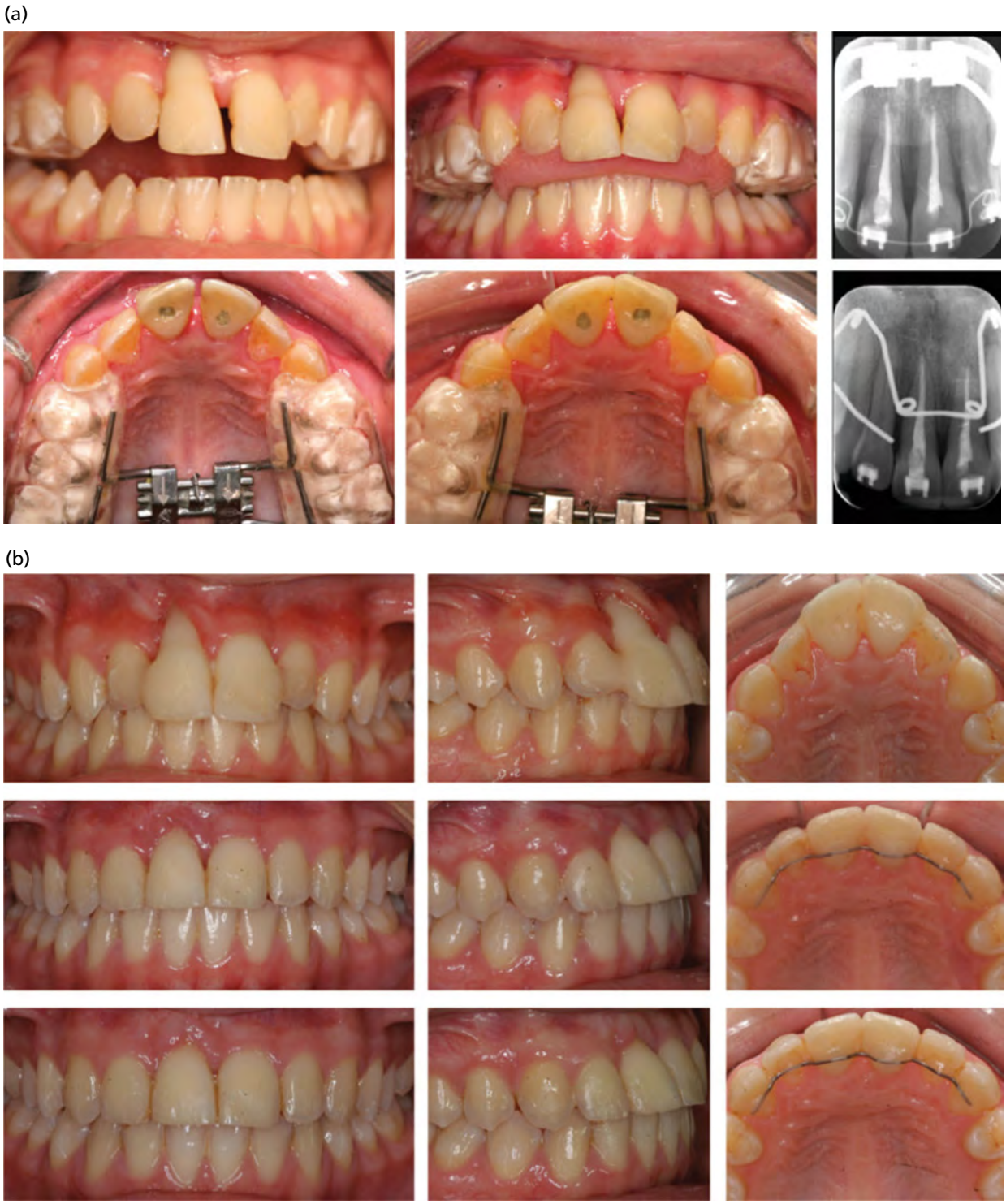


Fig. 47-4 Patient with localized gingival recession and absence of keratinized tissue in a central incisor prior to orthodontic therapy. (a) Orthodontic therapy was initiated by rapid palatal expansion. (b) Prior to expansion and retraction of upper central incisors, an autogenous gingival graft was placed. The final intraoral images demonstrate the root coverage of the recession by a combination of grafting and lingual tooth movements.

Specific orthodontic tooth movements

Extrusion movements

Tooth extrusion is a predictable tooth movement to level bone margins or to lengthen the clinical crown in cases of tooth fracture or when indicated for restorative purposes. Mainly in situations of compromised periodontal support, orthodontic eruption is a valuable alternative to surgical crown lengthening, because in these surgical interventions, resective osseous surgery will further compromise the attachment apparatus. When malocclusion or malalignment affects the aesthetic areas, tooth extrusion movements can also be considered to align gingival margins and correct incisor edges, thus

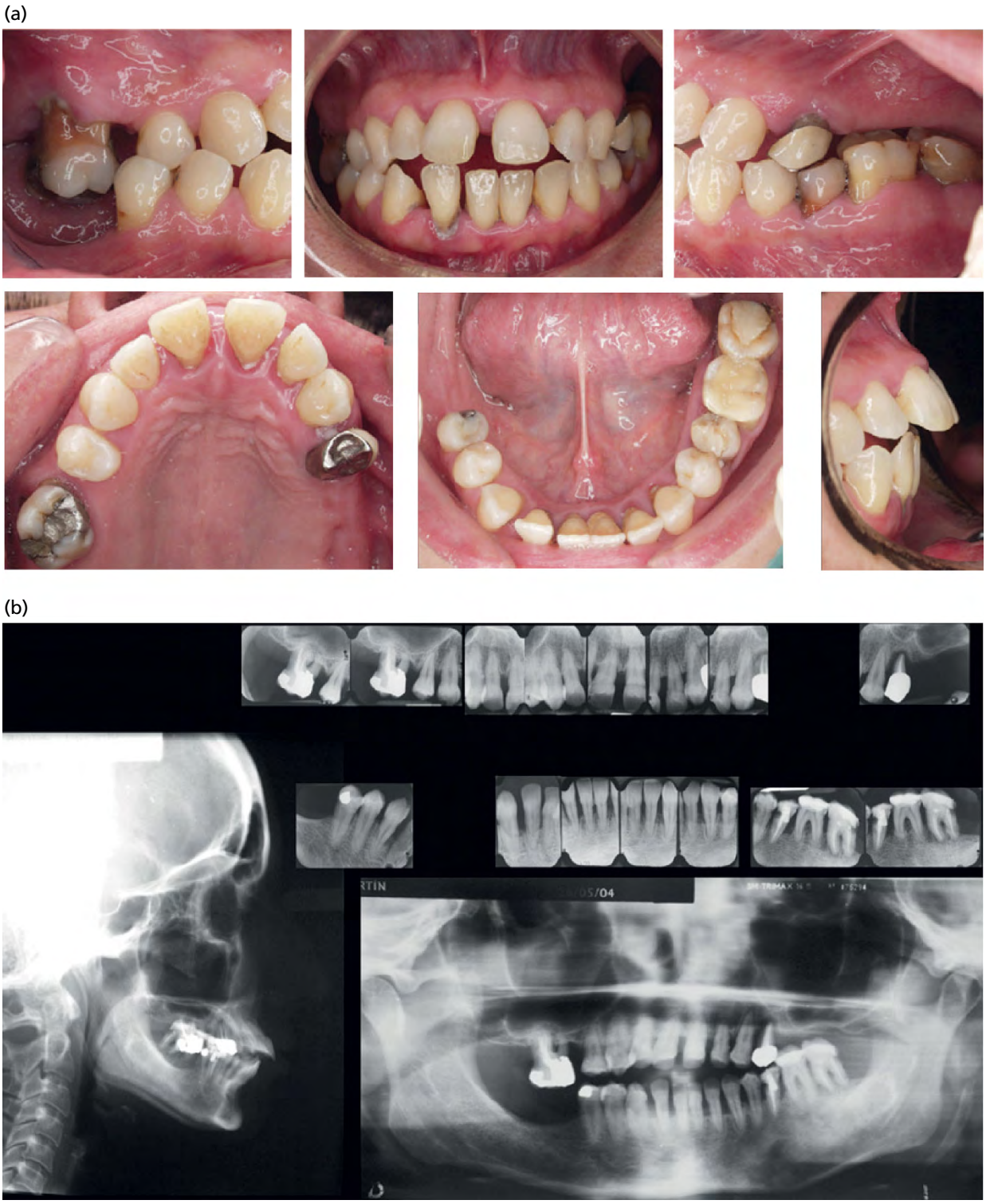


Fig. 47-5 Patient with severe chronic periodontitis, together with pathologic tooth migration, open anterior bite, and posterior bite collapse. (a) Intraoral images before periodontal and orthodontic therapy. (b) Radiographic images demonstrating the severe bone loss and posterior bite collapse.

reducing the need for periodontal and/or restorative therapy (Majzoub *et al*. 2014).

When extruding teeth with a healthy periodontium, a concomitant displacement of the gingival margin and the mucogingival junction occurs in 80% and 52.5% of cases, respectively (Pikdoken *et al*. 2009). Similar results have been reported in experimental studies where the free and attached gingiva followed the tooth movement in 90% and 80% of cases, respectively, while the mucogingival junction remained in the same position (Berglundh *et al*. 1991; Kajiyama *et al*. 1993). In the presence of intrabony

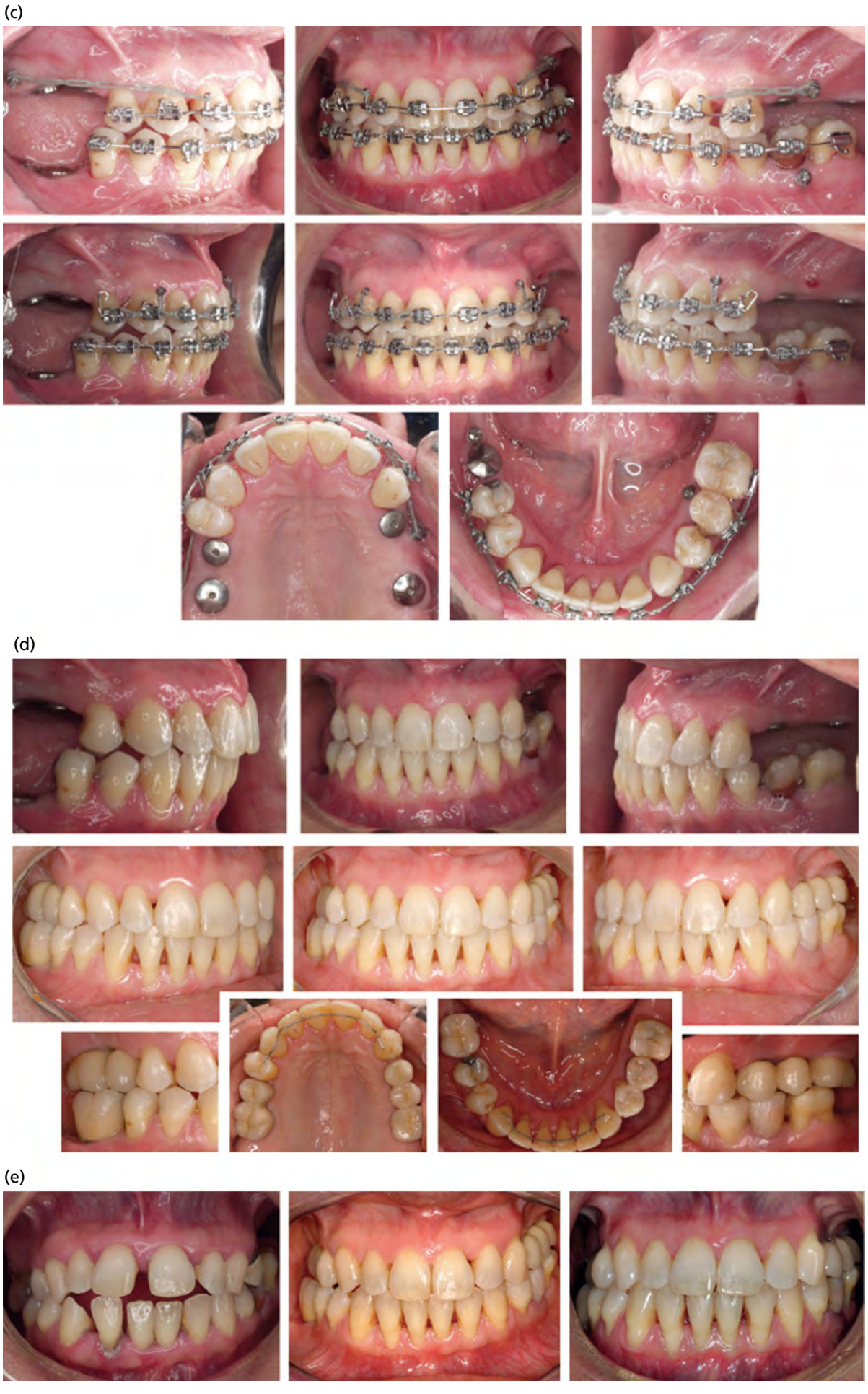


Fig. 47-5 *(Continued)*. (c) Orthodontic therapy accomplished by using microimplants as anchorage. Posterior dentition was restored by dental implants. (d) Final retention and esthetic treatment was accomplished with composite veneers. Posterior function was restored with implant-supported restorations. (e) Patient before treatment, after restorative therapy, and 3 years post retention.

defects, orthodontic extrusive movements will predictably eliminate the angular bony defect, but the periodontal attachment levels will remain unaltered. This treatment option is particularly indicated in the presence of one-wall intrabony defects because in these lesions periodontal regenerative techniques do not have a favorable prognosis and once the extrusive orthodontic movement has been completed the unaltered connective-tissue attachment will be positioned in a more coronal position (Ingber 1974).

Orthodontic extrusion of "hopeless" teeth for alveolar site preparation prior to implant placement has been proposed with the objective of displacing the bone crest coronally and thus facilitating implant placement levelled with the rest of the bone crest, what may reduce the need for complex bone augmentation procedures. The efficacy of this intervention has been evaluated in a systematic review, which reported improvements in alveolar bone availability with varied qualitative and quantitative gains in hard and soft tissues, although most of the identified studies were case reports or case series (Korayem *et al*. 2008). In spite of this heterogeneity and the different orthodontic methods reported in the different studies, the authors recommended: (1) the use of light, constant, extrusive forces of 15 g for the anterior teeth to 50 g for the posterior teeth; (2) the rate of extrusion should be maintained at a slow and steady rate of no more than 2.0 mm per month; (3) a buccal root torque component may be applied concomitantly to increase the buccolingual bulk of alveolar bone; (4) a retention and stabilization period of no less than 1 month for every month of active extrusion is recommended prior to extraction; and (5) overlay wires (anchorage wires) are recommended to reinforce anchorage and avoid tipping of adjacent teeth toward the tooth undergoing active extrusion (Fig. 47-6).

Depending on the amount of periodontal attachment, there will be either coronal displacement of the gingival margin when extruding the affected teeth or in cases of teeth affected with deep periodontal pockets, the marginal tissue will not move coronally until there is complete elimination of the pocket (Hochman *et al*. 2014)

Limited orthodontic extrusion has also shown an additional benefit in the correction of infrabony defects when combined with periodontal regenerative interventions. The addition of orthodontic extrusive forces attained significantly higher attachment level gains at 6 months, when compared with the same regenerative interventions without the orthodontic movements (Ogihara & Wang 2010)

Molar up-righting

The orthodontic up-righting of mesially tilted molars is particularly indicated when an angular bony defect is formed in the mesial aspect of the affected molar. This orthodontic movement will level the bone crest and eliminate the bone defect, although the periodontal attachment level will be unaltered. In these clinical situations, the recommended movement is to displace the tooth away from the defect in a disto-occlusal direction, which may increase the tension in the collagen fibers of the PDL, thus stimulating new bone formation and levelling the alveolar crest contours (Diedrich 1996). Even though the level of the connective tissue attachment remains unchanged, the new anatomical position of the molar usually translates into an improvement in probing depth levels and the crown–root ratio (Brown 1973) (Fig. 47-7).

When the mesially tilted molar has a furcation involvement, the orthodontic tooth movement may exacerbate the periodontal lesion, unless strict infection control measures prevent the development of inflammation (Burch *et al*. 1992). A valid alternative in these clinical situations is to treat the furcation lesion with either regenerative or resective approaches and then carry out the orthodontic movement subsequently in order to attain the ideal tooth position before the final restorative therapy (Muller *et al*. 1995).

Orthodontic tooth movements through cortical bone

Alveolar ridge contraction is the physiologic consequence of tooth extraction. In fact. most of the buccolingual crest reduction will occur within the first 3 months after tooth extraction (Schropp *et al*. 2003), although the resorptive process will continue, albeit at a slower pace (Carlsson *et al*. 1967). When the alveolar bone housing is thin and there is minimum trabecular bone between the buccal and lingual cortical plates, the orthodontic tooth movement may be slowed or result in bone dehiscence defects in these areas. To avoid these unwanted consequences, surgical interventions aimed at bone augmentation width have been suggested before the orthodontic movement (Diedrich 1996). Other authors have recommended undertaking orthodontic tooth movement immediately after tooth extraction to counteract this resorptive process and thus develop an appropriately sized alveolar ridge. A prospective case series in a sample of 20 patients demonstrated that orthodontic tooth movement through fresh extraction sockets maintained the profile of the ridge with less than 1% of bone contraction at 4 years (Ostler & Kokich 1994). Similar results were reported in an experimental study on dogs where the pressure side (towards the socket) showed increased bone height, while in the tension side the bone level remained unaltered (Lindskog-Stokland *et al*. 1993).

The orthodontic movement of teeth with a reduced but healthy periodontium through edentulous areas is usually possible with minimal loss of bone, provided the movement is parallel to the ridge and slight orthodontic forces are used (Hom & Turley 1984). However, experimental studies have shown that

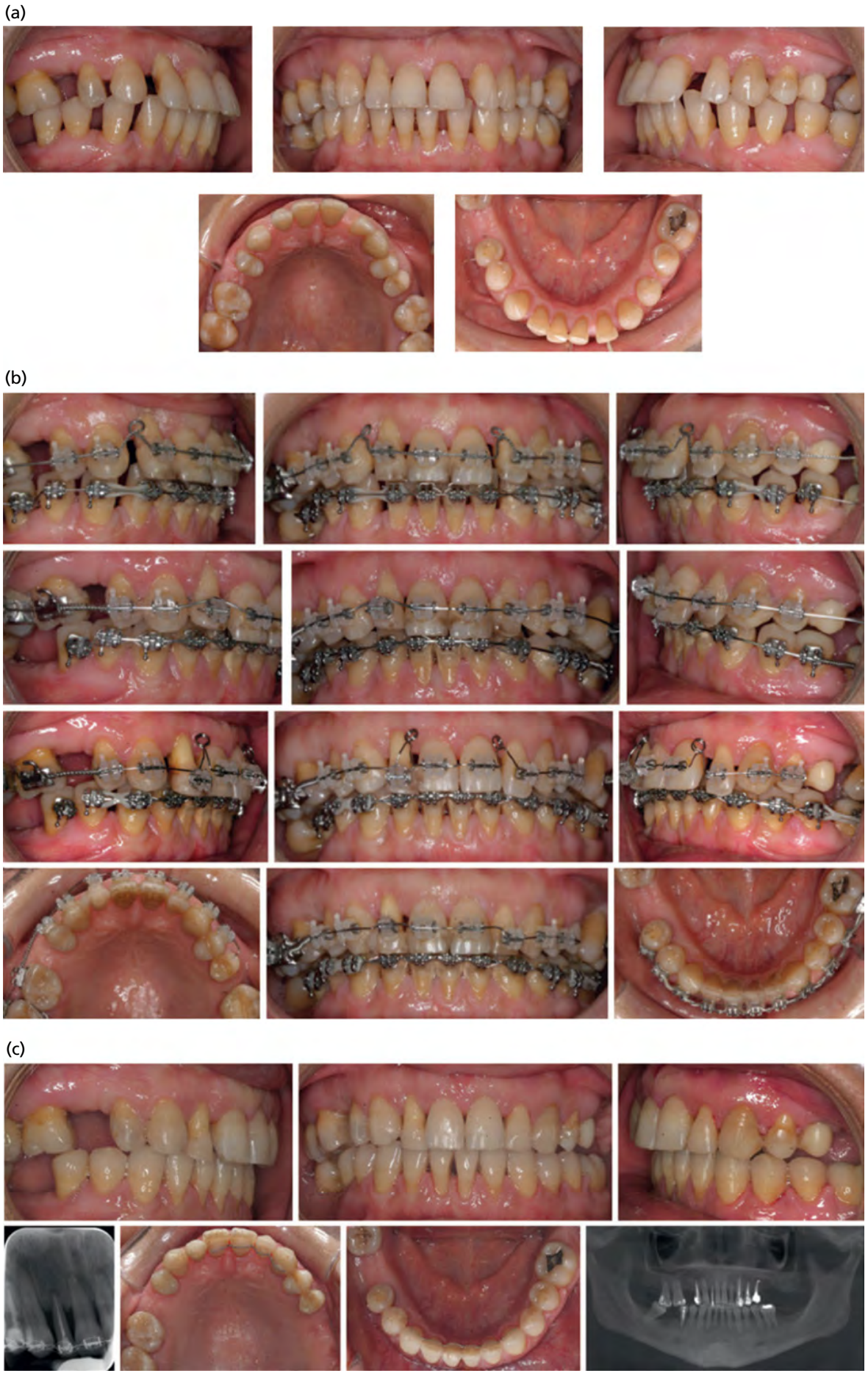


Fig. 47-6 Patient with severe chronic periodontitis, presence of diastemata, and pathologic tooth migration, together with a hopeless prognosis for tooth 12. (a) Intraoral images before orthodontic therapy. (b) Orthodontic therapy was aimed at closing the diastemata, distributing spaces, and controlling forced extrusion of tooth 12 in order to create bone and soft tissue prior to implant placement. (c) End of orthodontic therapy prior to tooth extraction and implant placement. Note the position of the gingival margin in relation to the adjacent teeth.

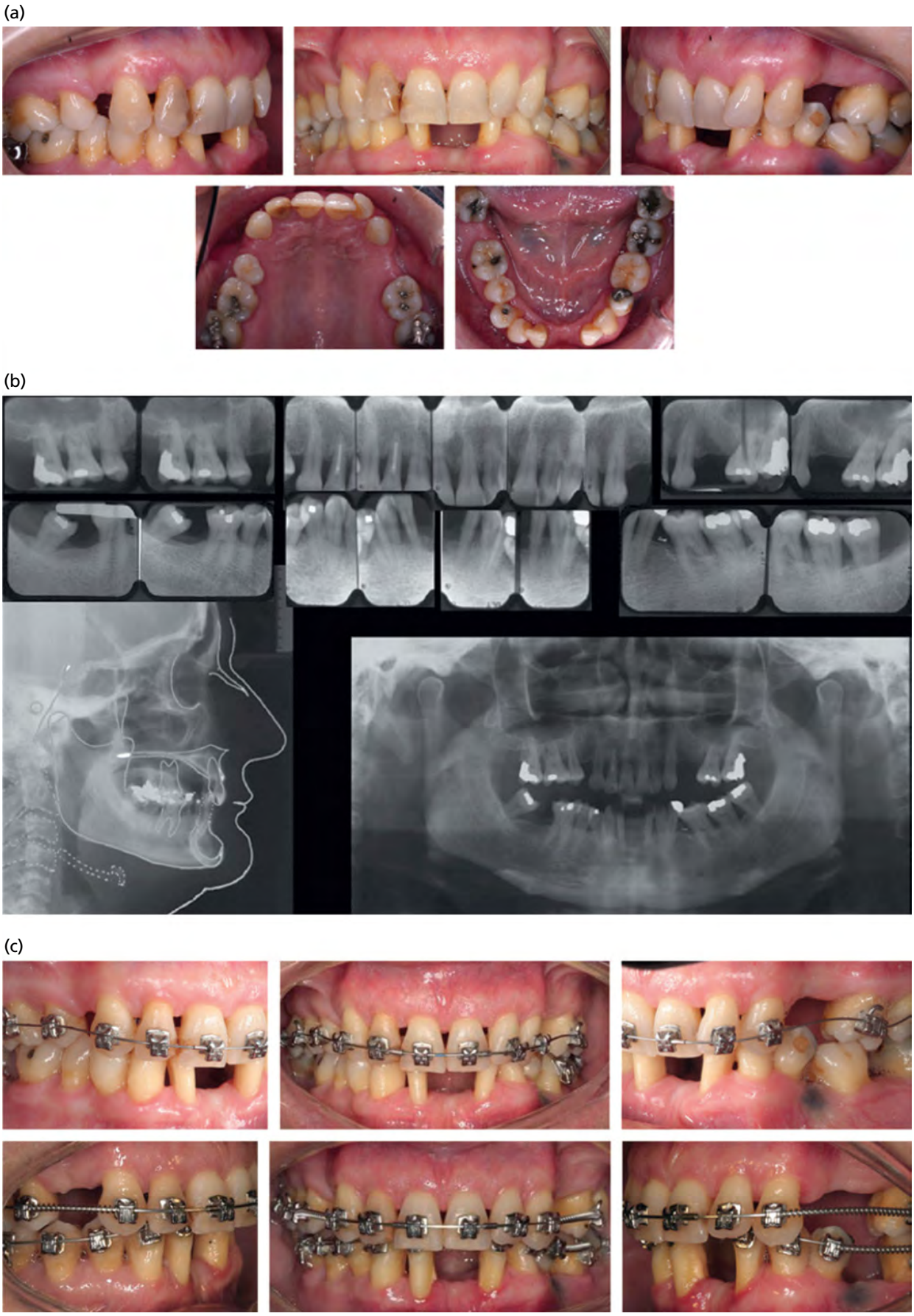


Fig. 47-7 Patient with severe chronic periodontitis, partial edentulism, and collapsed posterior bite. (a) Intraoral images of the patient before orthodontic therapy. (b) Initial panoramic, lateral cephalogram, and periapical radiographic series depicting the patient's bone loss and presence of mesially inclined first lower molars. (c) Orthodontic therapy was aimed at uprighting lower molars and distributing the spaces prior to implant therapy to restore lost dentition.

(d)

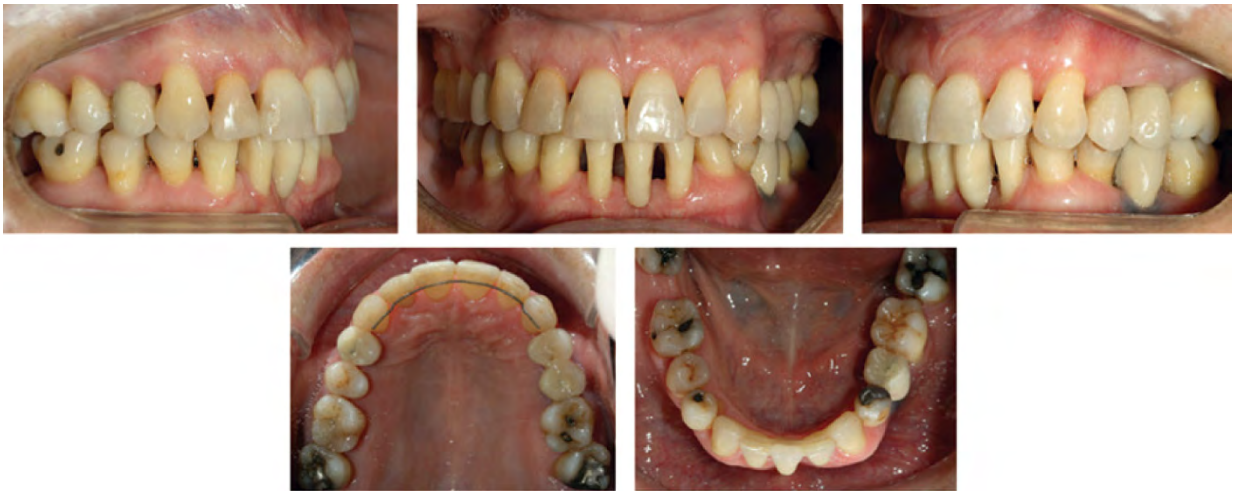


Fig. 47-7 *(Continued)*. (d) End of orthodontic therapy with restoration of the posterior occlusal plane and alignment of upper incisors. Note the position of the lower mandibular molars.

when bodily movements are carried out through cortical bone in a labial direction there is no bone formation in the buccal aspect of the tooth and a dehiscence defect occurs (Steiner *et al*. 1981). The orthodontic movement *per se* will not cause attachment loss and gingival recession, but the resulting bone dehiscence in combination with thin soft tissues will be a predisposing factor for attachment loss in presence of inflammation and/or trauma (Wennstrom 1996). On the contrary, lingual movements of labially displaced teeth showing dehiscence defects will result in new bone formation in the buccal aspect of the root, with concomitant soft tissue augmentation (Karring *et al*. 1982; Wennstrom *et al*. 1987). Wennstrom (1996) recommended the treatment of localized gingival recessions with orthodontic movements, whenever the affected tooth was labially displaced and lingual orthodontic movements were possible. Pini-Prato *et al*. (2000), however, recommended the placement of a gingival autograft prior to orthodontic therapy in these situations in order to prevent periodontal attachment loss and the occurrence of recession defects, because pure lingual root movements through cortical bone are difficult and in most cases crown tipping or rotation components will occur, hence moving the root buccally and causing further bone dehiscence and soft tissue loss (Fig. 47-8).

Intrusive tooth movements

Intrusive tooth movements can be attempted even in situations of reduced periodontal support provided the periodontal tissues do not have inflammation and plaque control is excellent. Melsen *et al*. (1989) recommended the use of light forces during these intrusive movements (5–15 g per tooth) to prevent root resorption, mainly in teeth with an increased crown–root ratio due to reduced periodontal support. There is controversy whether this orthodontic tooth movement should be recommended in the presence of angular bony lesions and intrabony defects. In experimental studies, when intrusive movements have been carried out in the presence of plaque, formation of periodontal pockets and infrabony defects has occurred (Ericsson *et al*. 1977; Polson *et al*. 1984). On the contrary, in the absence of inflammation, other experimental studies have shown the resolution of the intrabony defect when teeth are moved bodily into bone, although the periodontal attachment levels did not change and the healing was reparative, mainly through the formation of a long junctional epithelium. These results were contradicted by Melsen *et al*.(1988), who demonstrated in monkeys the resolution of bone defects by intrusive movement, but healing occurred through the formation of a new connective tissue attachment and periodontal regeneration. In humans, several clinical studies have also shown gains in clinical attachment levels with intrusive tooth movements in absence of periodontal inflammation (Melsen *et al*. 1989; Cardaropoli *et al*. 2001). Corrente *et al*. (2003) recommended the treatment of infrabony defects in anterior teeth by combining surgical periodontal therapy (access flaps) with intrusive orthodontic movements and reported significant attachment gains and radiographic bone fill. Similarly, Re *et al*. (2004) showed a 50% reduction in recession after intrusion of periodontally comprised teeth. These movements, however, are not always predictable and some authors have recommended that intrabony defects are first treated with surgical periodontal regenerative procedures, followed by intrusive tooth movement (Diedrich 1996; Re *et al*. 2002a). In the presence of shallow circumferential bony lesions, orthodontic intrusive movements may resolve the defect, but if these defects are deep they should be treated first with periodontal regenerative procedures. When these defects are too wide, orthodontic intrusive movements have been

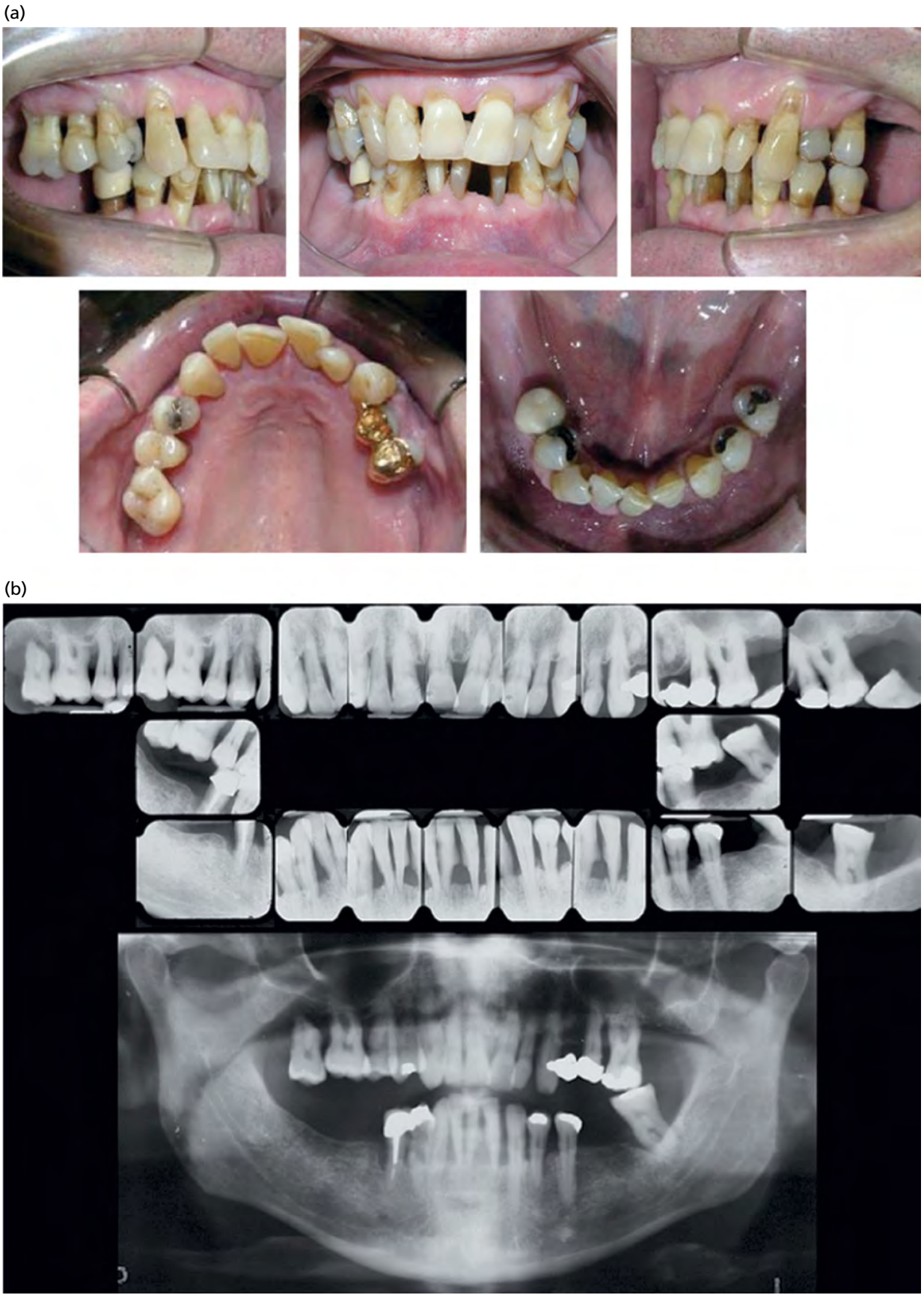


Fig. 47-8 Patient with severe chronic periodontitis, partial edentulism, and severe malocclusion. (a) Intraoral images after periodontal therapy and before orthodontic therapy. (b) Initial panoramic and periapical radiographic series depicting the bone loss and tooth malposition.

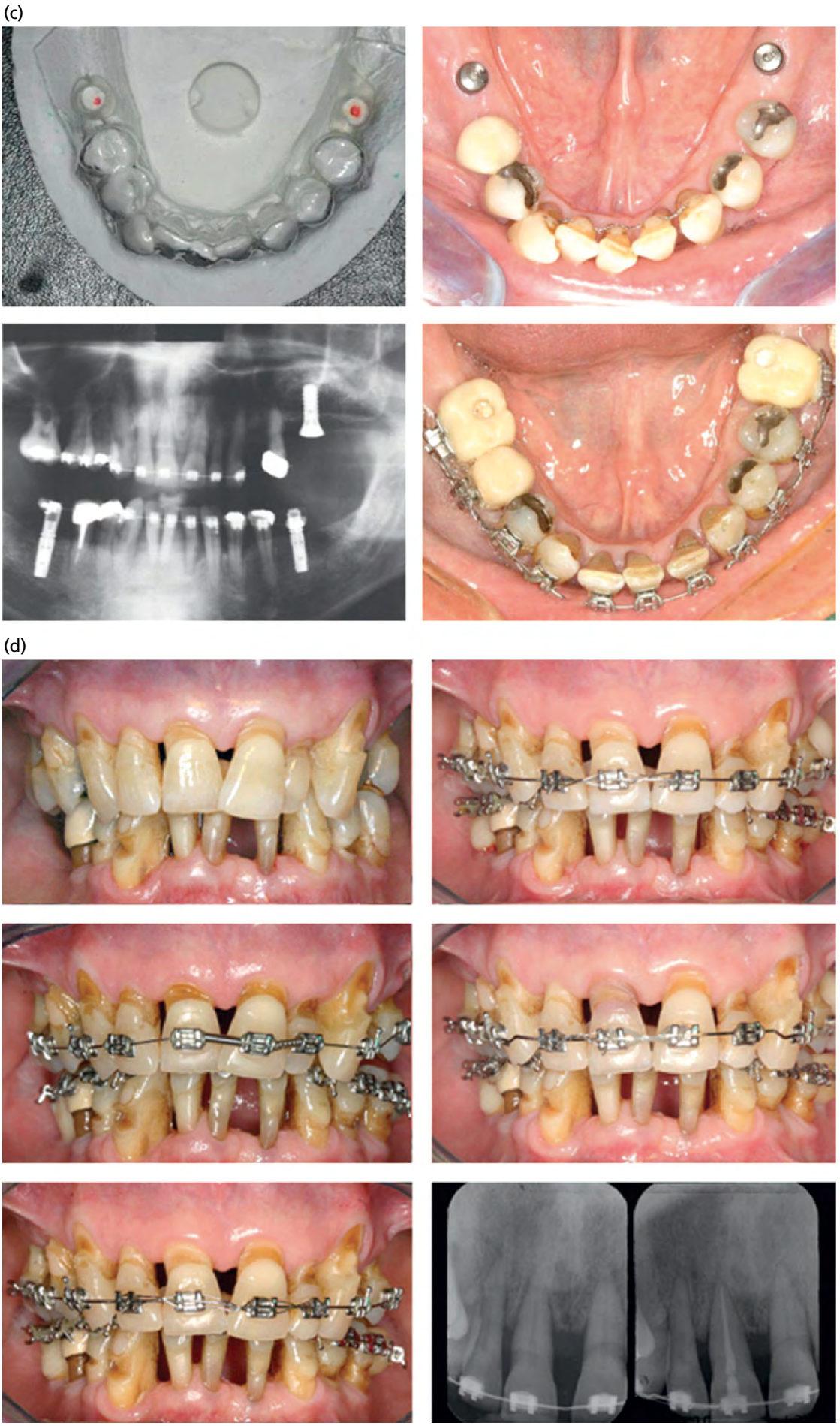
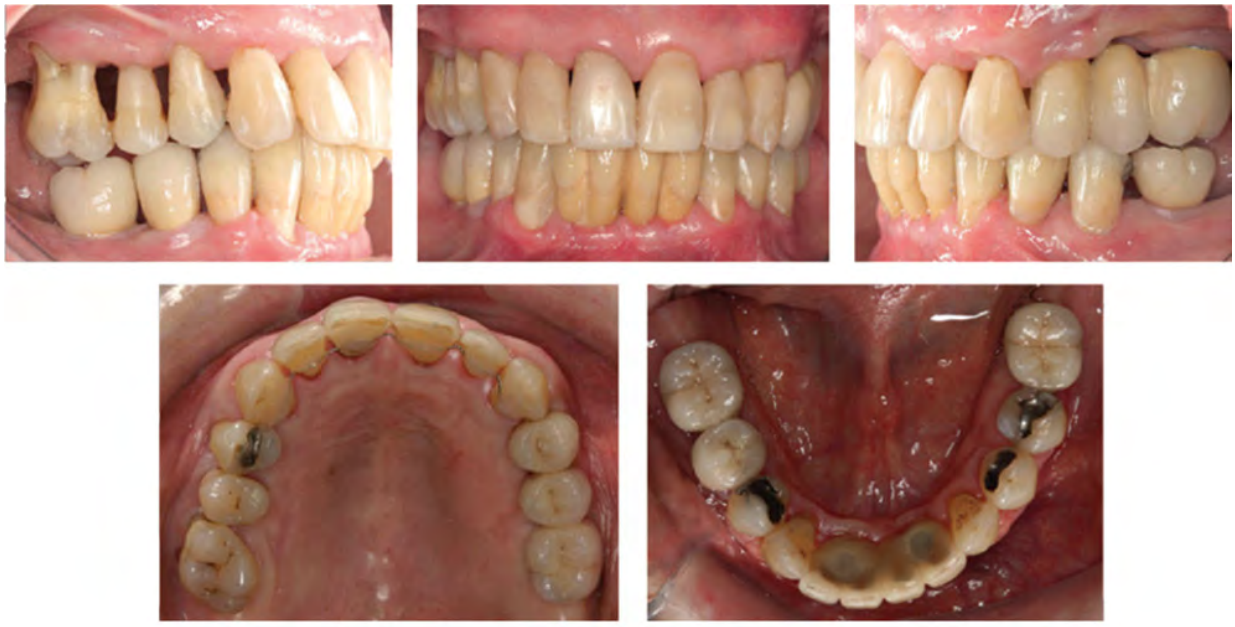


Fig. 47-8 *(Continued)*. (c) Dental implants were placed in the posterior mandible before the orthodontic therapy to serve as anchorage for the orthodontic tooth movements. (d) Orthodontic therapy was aimed at aligning the teeth and distributing the spaces prior to implant therapy to restore the lower anterior teeth. Note the gingival recessions and severe abrasion in the upper cuspids.

(e)



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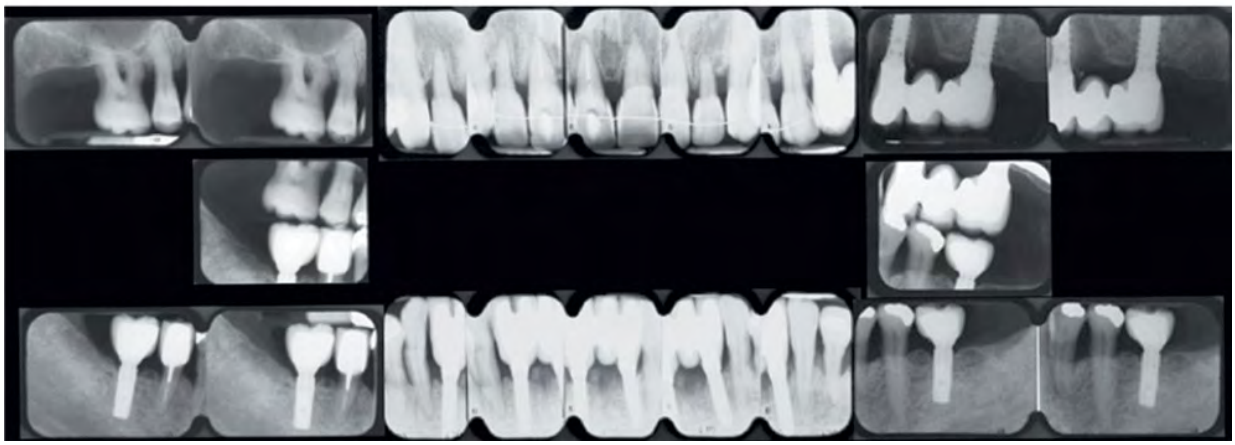


Fig. 47-8 *(Continued)*. (e) End of orthodontic therapy with restoration of the posterior occlusal plane and alignment of the upper incisors. Note that the recessions were treated by means of connective tissue autografts and the open papillae have been filled with composite veneers. (f) Final radiographs depicting stable bone levels and restoration of the posterior occlusal plane.

recommended to improve the defect anatomy before carrying out the regenerative procedure (Rabie *et al*. 2001; Passanezi *et al*. 2007) (Fig. 47-9).

Orthodontic intrusion movements have also been recommended for leveling gingival margins with the adjacent teeth when treating extruded and misaligned teeth, since the gingival margin will move apically together with the tooth (Erkan *et al*. 2007).

Orthodontic tooth movements and periodontal regeneration

Periodontal regenerative procedures are frequent in the treatment of chronic periodontitis, particularly in the presence of infrabony defects and furcation lesions. These surgical techniques aim for the establishment of a new periodontal attachment apparatus to a root surface previously affected by periodontitis. Histologically, periodontal regeneration requires the formation of new cementum on the affected root and the establishment of new connective tissue attachment between newly formed cementum and the alveolar bone. Several regenerative technologies have demonstrated these regenerative outcomes in experimental studies, such as guided tissue regeneration (GTR), use of bone graft materials, and application of enamel matrix derivatives (EMDs). They have also evidenced clinical efficacy, as reported in several systematic reviews (for details see Chapter 38). In clinical situations where orthodontic tooth movements were planned in patients where periodontal regenerative surgeries were part of the periodontal treatment plan, there has been controversy whether these orthodontic tooth movements might be different when applied through regenerated periodontium or whether these movements might create unwanted effects (root resorption, bone loss, ankylosis, etc.). There has also been controversy on the optimum timing for starting the orthodontic therapy after the regenerative procedure, as well as the necessary stability once the teeth have been moved into regenerated areas.

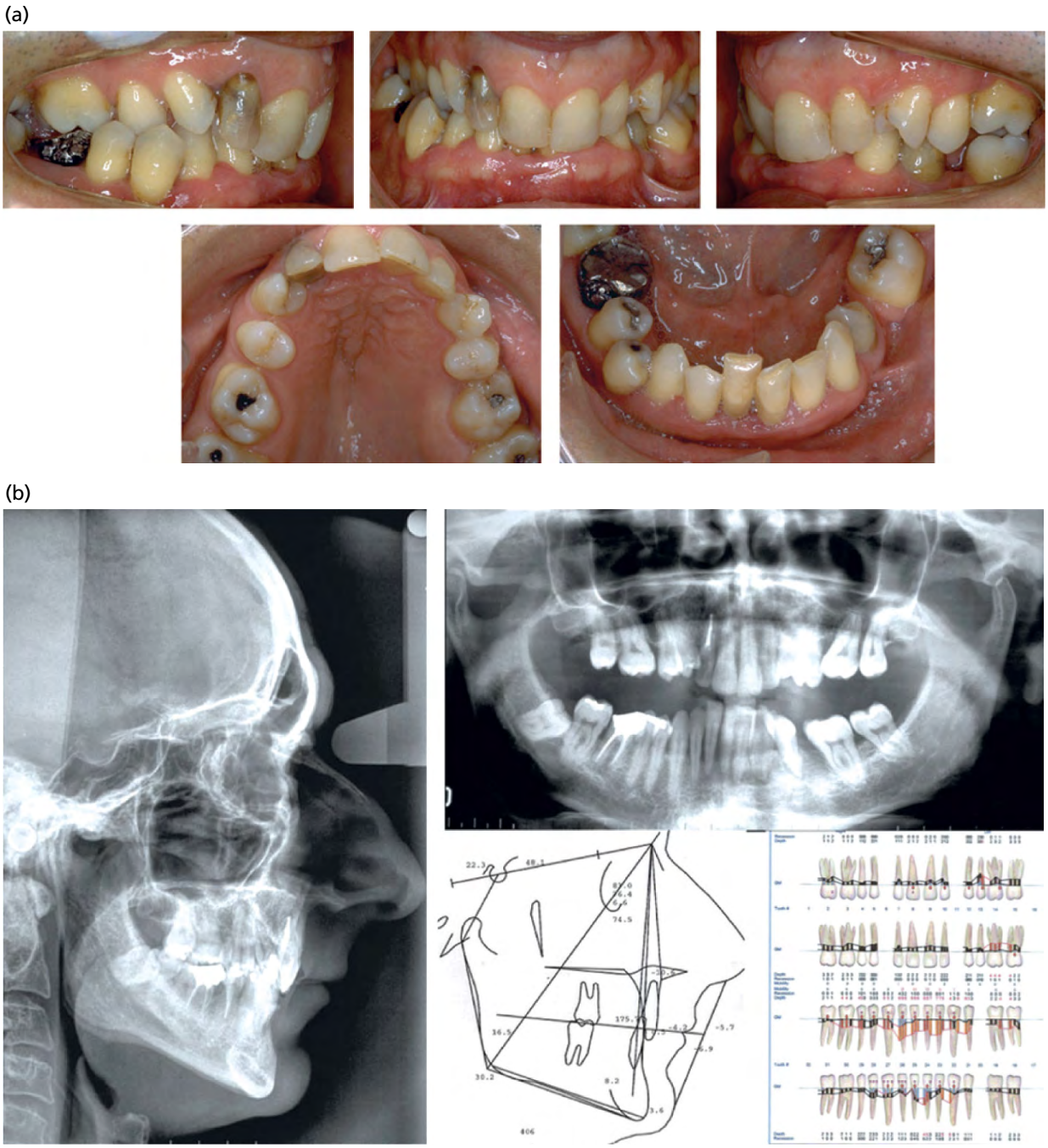


Fig. 47-9 Patient with severe chronic periodontitis and severe overbite. (a) Intraoral images before orthodontic therapy. Note the posterior bite collapse and severe overbite. (b) Initial panoramic and lateral cephalogram depicting the bone loss. The periodontal charting after therapy shows lack of periodontal pockets except in the lower anterior region, with tooth 41 having a hopeless prognosis.

Diedrich (1996) conducted a series of experimental studies evaluating the impact of orthodontic treatment on regenerated tissue after GTR procedures and demonstrated that the newly regenerated tissue was not negatively affected by the orthodontic treatment. Several case reports in humans have corroborated these experimental results, demonstrating the long-term stability of these regenerated periodontal structures subjected to orthodontic therapy (Stelzel & Flores-de-Jacoby 1995, 1998; Efeoglu *et al*. 1997).

Barrier membranes have also been utilized on fresh extraction sockets aiming to preserve the alveolar ridge and when teeth subsequently moved into these regenerated areas, the orthodontic therapy was uneventful and without complications (Tiefengraber *et al*. 2002). Also, membranes have been used to protect bone replacement grafts in corticotomy surgical procedures in combination with orthodontic therapy. Even though the membrane did not show a significant added value in the amount of tipping and new

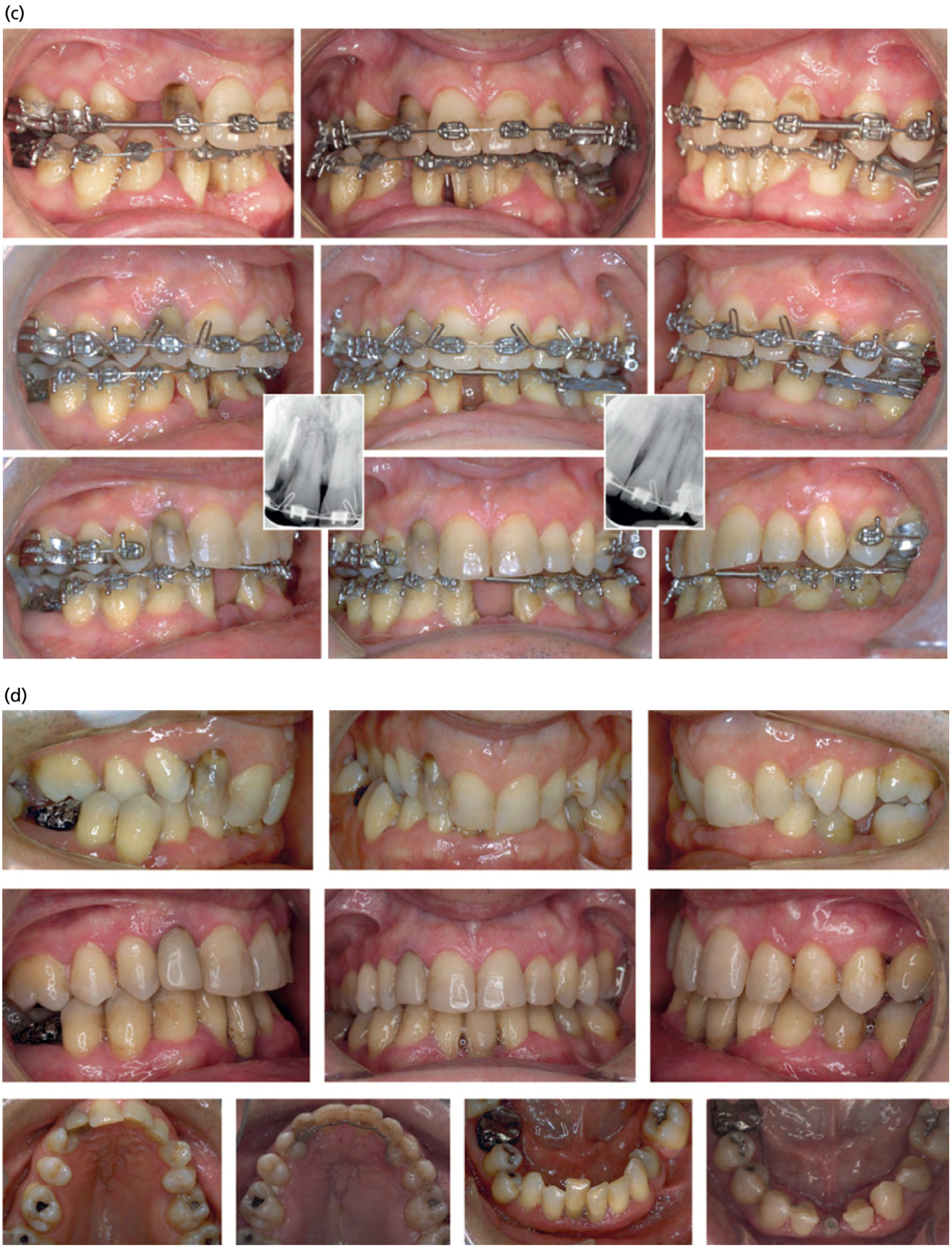


Fig. 47-9 *(Continued)*. (c) Orthodontic therapy was aimed at aligning the teeth by intrusion of maxillary teeth. Note the slight root resorption of the upper laterals after the orthodontic tooth movement. (d) End of orthodontic therapy with proper alignment of the upper incisors and re-establishment of an occlusal plane. Note the resolution of the deep overbite by orthodontic tooth intrusion.

bone formation in the buccal wall, the use of membranes promoted the augmentation of the buccal contour (Lee *et al*. 2014).

The regenerative periodontal treatment of non-contained infrabony defects usually combines bioabsorbable barrier membranes with bone grafts. These bone replacement grafts can be autologous, allogeneic, xenogeneic, and synthetic with similar outcomes, although with lesser morbidity and complications when using xenogeneic or allogenic

grafts. Orthodontic tooth movements through regenerated bone after using xenografts of bovine origin has been investigated in animal studies (Araújo *et al*. 2001; Kawamoto *et al*. 2002, 2003; da Silva *et al*. 2006; Zhang *et al*. 2006). Araújo *et al*. (2001) showed that these orthodontic tooth movements were possible without any complication. The xenogeneic deproteinized bovine bone material (DBBM) was partially resorbed on the pressure side, whereas there was no sign of resorption in the tension side. These findings are explained by the enhanced osteoclastic activity during tooth movement. Similar observations were made when implanting xenogeneic grafts into furcation defects (da Silva *et al*. 2006). When comparing the healing after the application of orthodontic tooth movements in regenerated defects with xenogeneic bone substitutes versus in non-regenerated teeth, they found no differences in the amount of newly developed bone and no signs of root resorption. Similar results were reported with the use of synthetic biomaterials and bioglasses in rats (Hossain *et al*. 1996; Kawamoto *et al*. 2002; Zhang *et al*. 2006). When comparing the behavior of different biomaterials used as bone replacement grafts after orthodontic tooth movements, the rate and amount of movement depended on the biomaterial bioabsorbability (Ru *et al*. 2016). For example, when comparing synthetic bone grafts made of hydroxyapatite and ß-tricalcium phosphate (ß-TCP) with DBBM in experimental studies, the slower rate of bioabsorbability of DBBM resulted in a slower and lesser amount of tooth movement, although the resulting orthodontic outcomes were similar (Machibya *et al*. 2018; Klein *et al*. 2019; Klein *et al*. 2020)

The results from these experimental studies have been corroborated with several clinical case series in humans where orthodontic movements were carried out in teeth previously treated with allogeneic and xenogeneic grafts in combination with collagen barrier membranes. These cases showed stable bone levels 12–18 months after the end of the orthodontic therapy, without evidence of any unwanted side effects (Yilmaz *et al*. 2000; Ogihara & Marks 2002, 2006; Re *et al*. 2002b; Naaman *et al*. 2004; Maeda *et al*. 2005; Cardaropoli *et al*. 2006; Pinheiro *et al*. 2006). There are, however, no clinical trials comparing the outcome of orthodontic therapy in teeth with and without previous regenerative therapy (Fig. 47-10).

The application of biological agents in periodontal regeneration, such as enamel matrix proteins (EMDs), has also been evaluated in relation to orthodontic tooth movements demonstrating uneventful results in both experimental studies (Diedrich 1996) and human clinical case reports (Juzanx & Giovannoli 2007). However, the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for bone regeneration has shown complications, mainly root resorption on the pressure side (Kawamoto *et al*. 2003)

With regard to the timing of orthodontic tooth movements in relation to regenerative interventions, Ahn *et al*. (2014) evaluated the outcome of alveolar osteotomies and orthodontic tooth movements with grafting with DBBM immediately, 2 weeks, or 12 weeks after bone surgery. They concluded that application of immediate orthodontic forces accelerated the orthodontic tooth movement with favorable periodontal regeneration, and fewer complications. The effect of low-level laser therapy on orthodontic tooth movement into bone-grafted alveolar defects also demonstrated enhanced defect healing and maturation, with a decreased rate of orthodontic tooth movements, mainly when these were delayed (Kim *et al*. 2015).

Pathologic tooth migration

Pathologic tooth migration (PTM) is a common complication of periodontitis and is often the motivation for patients to seek orthodontic therapy. It is characterized by significant changes in tooth position as a consequence of the severe attachment loss and the subsequent disruption of the forces that maintain teeth in position. Its clinical presentation is characterized by extrusion and drifting out of the anterior maxillary teeth, resulting in diastemas and increased overbite. Prevalence of PTM among periodontal patients has been reported to range between 30% and 55%. The etiology of PTM appears to be multifactorial, although the destruction of periodontal supporting tissues seems to be the major factor, because in these teeth with reduced periodontal support, application of non-axial occlusive forces contributes to the abnormal migration of teeth. The soft tissue forces of the tongue, cheeks, and lips can also play a role in these unwanted tooth migrations, mostly resulting in the extrusion and flaring of the anterior teeth.

When posterior teeth are lost and there is lack of arch integrity, PTM is usually combined with posterior bite collapse and loss of vertical dimension. Treatment of this complex anatomical and functional condition will require a multidisciplinary approach with complete periodontal therapy to eliminate the infection and fully arrest inflammation, followed by orthodontic therapy and restoration of the lost dentition with dental implants and/or prosthetic restorations (Fig. 47-11).

Multidisciplinary treatment of esthetic problems

During the course of orthodontic therapy in periodontally affected dentitions the advent of unesthetic complications are relatively frequent, mainly related to loss of interdental papillae, gingival margin discrepancies, or excessive gingival exposure (Kokich 1996; Gkantidis *et al*. 2010). Kurth and Kokich

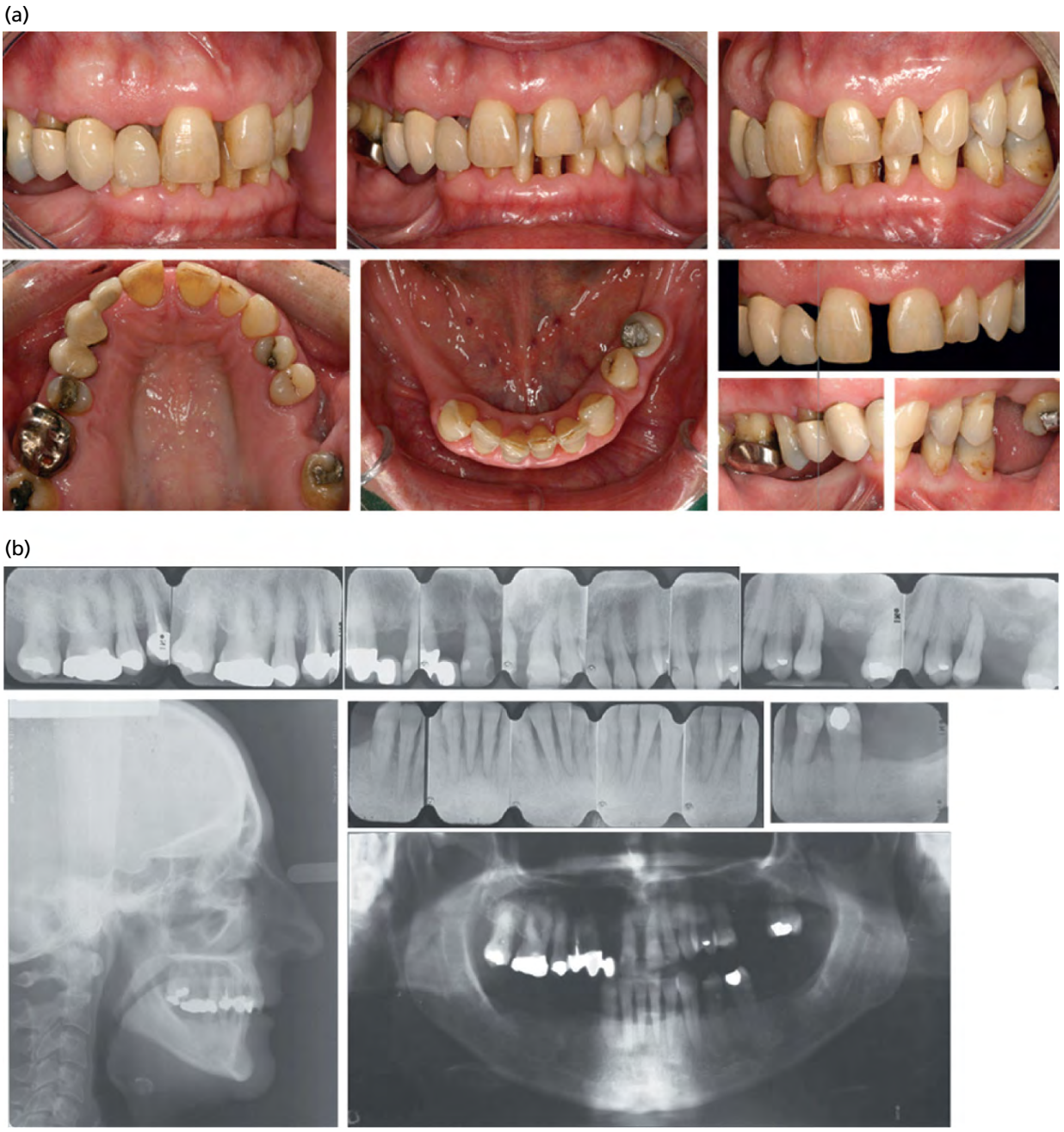


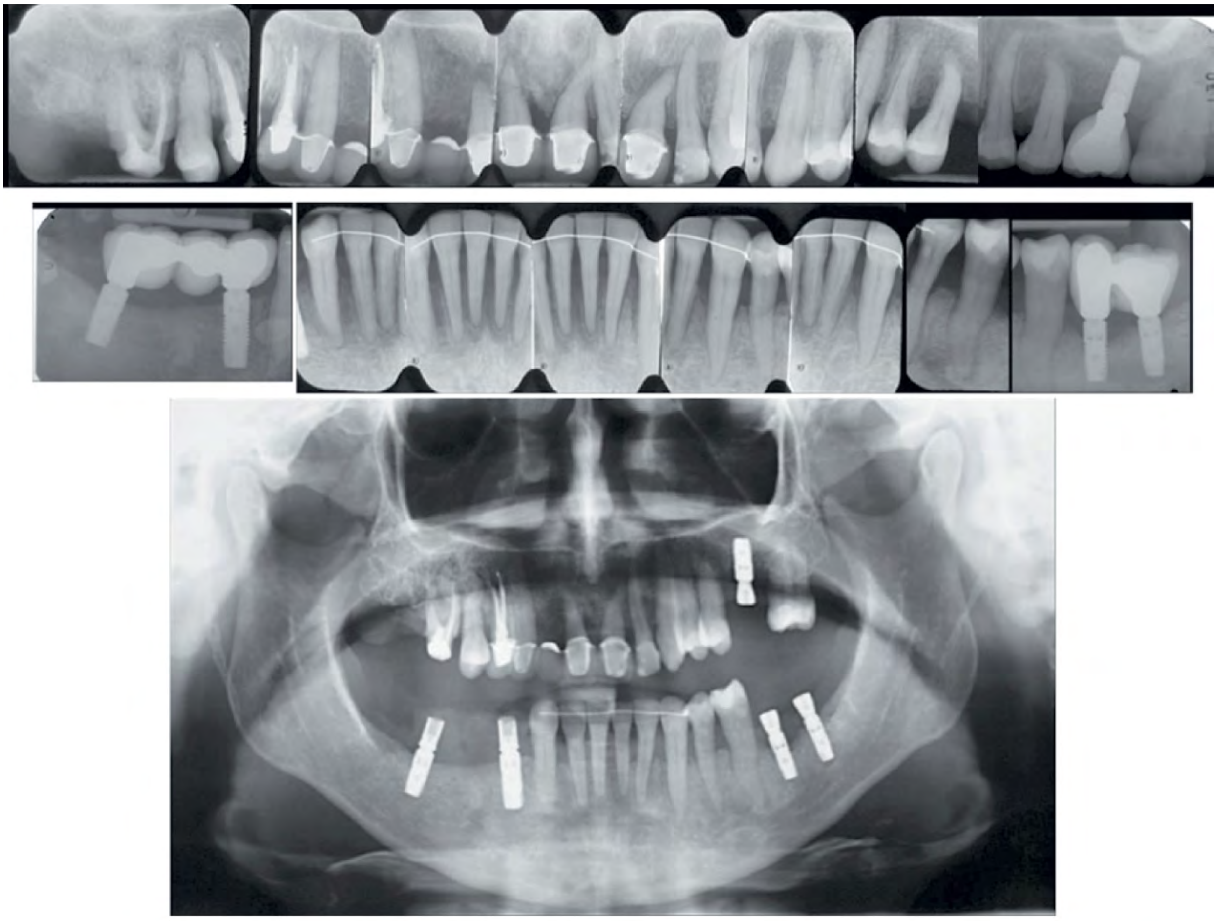
Fig. 47-10 Patient with severe chronic periodontitis, presence of deep intrabony defects in maxillary teeth, and severe malocclusion. (a) Intraoral images before orthodontic therapy. Note the anterior diastema, severe extrusion of maxillary right posterior teeth, and presence of edentulous spaces. (b) Initial panoramic, lateral cephalogram, and periapical radiographic series depicting the bone loss and presence of deep intrabony defects in the upper incisors and the upper and lower left premolars.

(2001) reported a 38% prevalence of open gingival embrasures in the region of the maxillary incisors after adult orthodontics.

Improper root angulation, divergent or triangular-shaped crown forms, and periodontal bone loss are factors associated with this unwanted effect. Burke *et al*. (1994) correlated the incidence and size of pretreatment tooth crowding with the post-treatment gingival embrasure space between maxillary central incisors in adult orthodontic patients. Another important factor in the loss of the interdental papilla is bone loss. Tarnow *et al*. (1992) correlated the distance from the contact point to the crest of bone with the presence or absence of the interproximal dental papilla. When this distance was 5 mm or less, the papilla was present in almost 100% of cases, when the distance was 6 mm, it was present in 56%, and when the distance was 7 mm or more, only in 27%. In the clinical situations where there is a combination of severe anterior crowding and periodontal bone loss, orthodontic therapy should be aimed not only at attaining the proper tooth alignment, but also at reducing the interdental space in order to compress the interdental soft tissues to force the formation of a new papilla. In these situations, orthodontic tooth movement should be combined with restorative

Fig. 47-10 *(Continued)*. (c) Regenerative surgical procedure using guided tissue regeneration with a xenogeneic bone graft and a collagen resorbable membrane to treat the deep one-two wall defect in tooth 21. Dental implants were placed in the posterior mandible for anchorage during orthodontic therapy. Similarly, microscrews were placed in the maxillary right posterior tooth for anchorage for the intrusive movements. (d) Orthodontic therapy was aimed at intruding the upper posterior right segment, aligning the teeth, closing the diastema, and distributing the spaces prior to final implant therapy in the posterior maxilla. The orthodontic tooth movements in the maxilla were carried out 9 months after the periodontal regenerative procedure.

(e)



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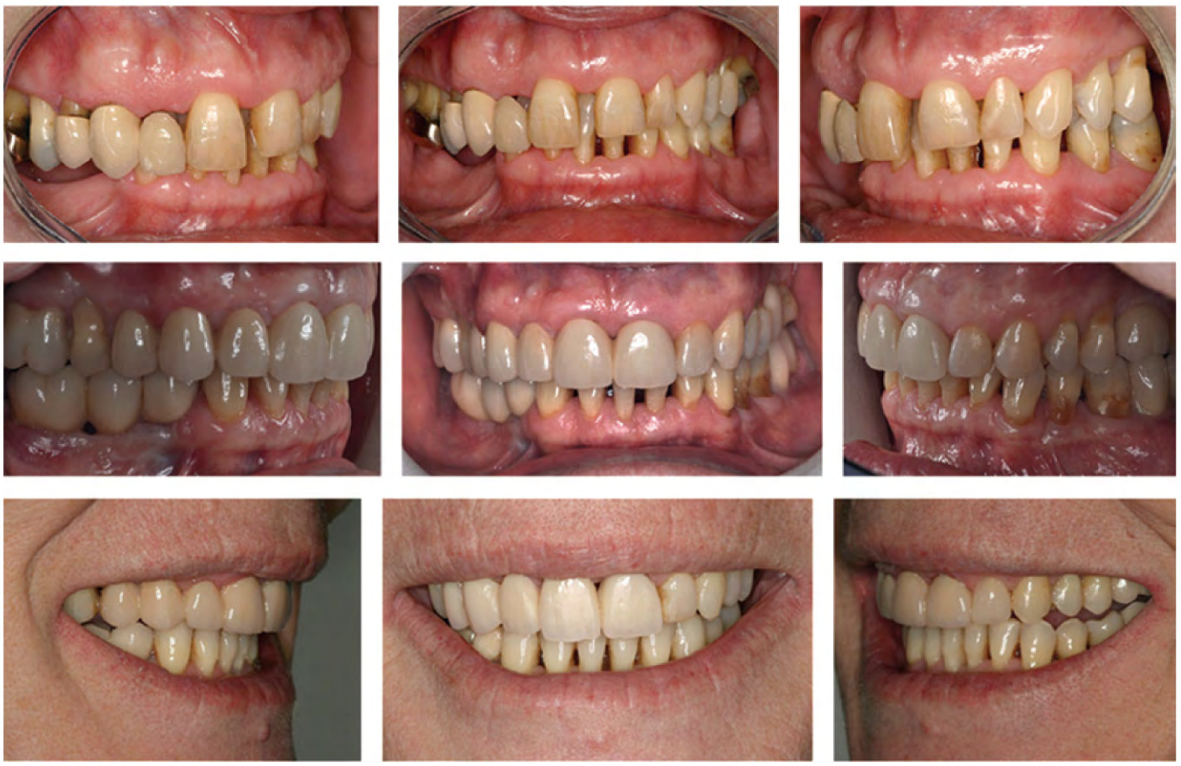

Fig. 47-10 *(Continued).* (e) Final radiographs depicting stable bone levels and resolution of the intrabony defects. (f) End of orthodontic therapy with proper alignment of the upper incisors and re-establishment of an occlusal plane. Final restorations were performed using full ceramic crowns.

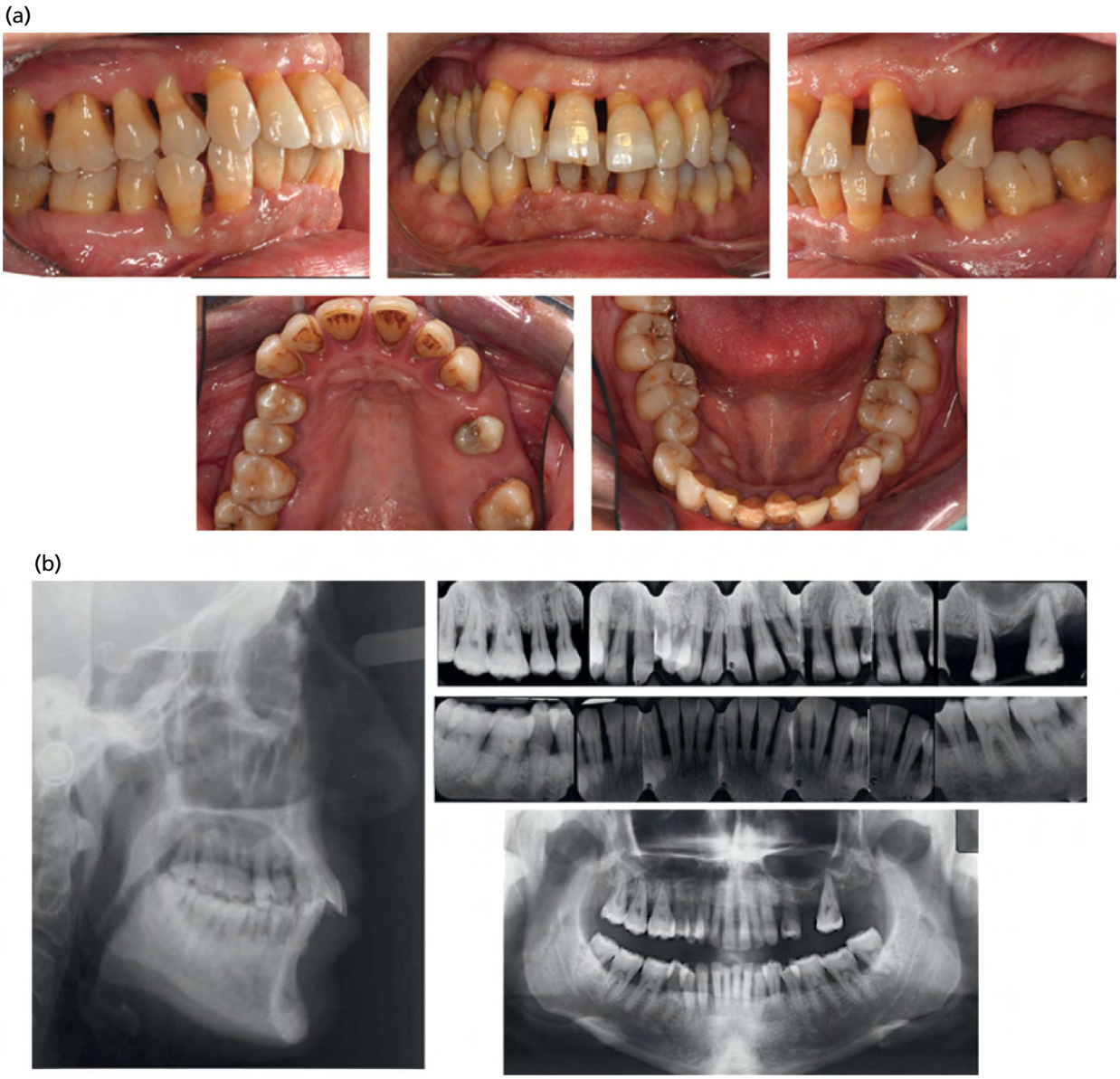

Fig. 47-11 Patient with severe chronic periodontitis, together with pathologic tooth migration, posterior right cross-bite, and posterior bite collapse. (a) Intraoral images after periodontal and before orthodontic therapy. (b) Radiographic images demonstrating the severe bone loss. Note the hopeless prognosis of tooth 26.

procedures aimed at raising the contact point, thus creating the illusion of a healthy interdental papilla.

The gingival marginal relationships of the upper anterior teeth play an important role in the aesthetic appearance of the smile. These gingival marginal contours should mimic the natural anatomy of the tooth cementoenamel junction (CEJ), providing an adequate scalloping with thin marginal tissues and papillae filling the interdental space. When orthodontic therapy is applied to periodontally affected dentitions, the occurrence of gingival marginal discrepancies is frequent and should be treated orthodontically with minor intrusive or extrusive tooth movements until the correct marginal alignment is reached. In situations with localized gingival recessions, the appropriate mucogingival surgical techniques for root coverage should be implemented before the orthodontic tooth movement (see Figs. 47-3, 47-5, 47-11).

During treatment planning it is very important to evaluate the length of the clinical crowns, the patient's gingival exposure, and the presence of gingival marginal discrepancies during smiling (Kokich 1996). Depending on these factors, different combinations of periodontal plastic surgical techniques and orthodontic tooth movements will be indicated. In some situations, the indication will be the extrusion of the longer tooth and subsequent grinding of its incisal edge, whereas in others, it will be intrusion and treatment of the resulting shorter tooth reconstruction of the incisal edge.

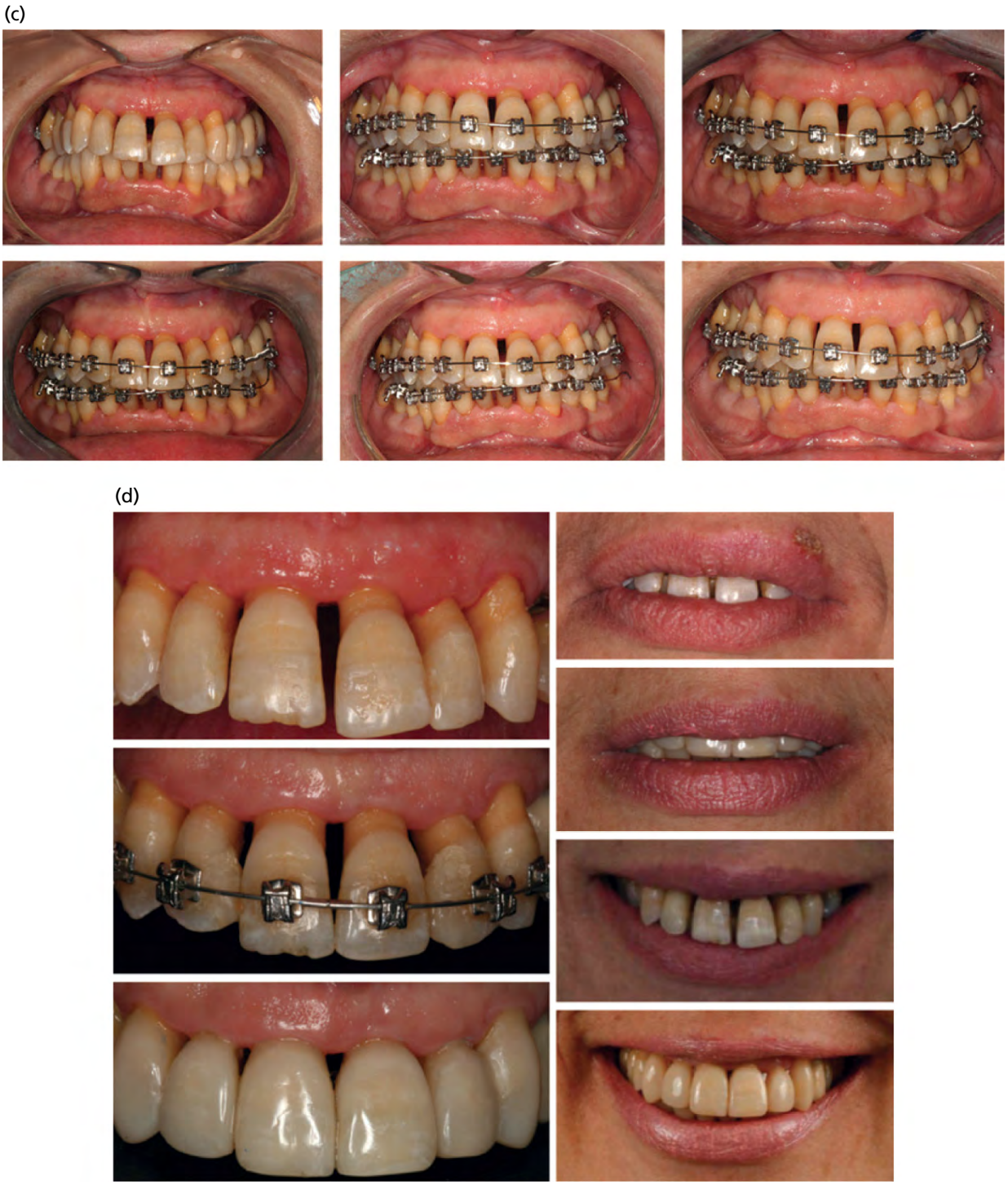

Fig. 47-11 *(Continued).* (c) Orthodontic therapy was aimed at intruding the upper anterior segment, aligning the teeth, and distributing the spaces prior to final implant therapy in the posterior left maxilla. (d) Final retention and esthetic treatment was accomplished with composite veneers. Note the improvement in the esthetic result and the lack of interdental papillae following the restorative work.

The problem of excessive gingival exposure (a gummy smile) can also be found frequently in adults requiring adult orthodontics. This condition may be caused by: excessive maxillary growth, tooth extrusion in deep anterior overbites, and delayed apical migration of the gingival margin over the maxillary anterior teeth. Its esthetic correction largely depends on its etiology.

If the cause of the gummy smile is the extrusion of the upper anterior teeth, orthodontic intrusion will solve the excessive gingival display. In contrast, the retardation of the physiological apical migration of gingival margins will require a mucogingival excisional surgical correction. In situations with a clear skeletal cause, an orthognathic surgical approach is the only corrective solution.

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Part 18: Supportive Care

Chapter 48

Supportive Periodontal Therapy

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Introduction

Clinical trials on the long-term effects of the treatment of periodontitis have clearly demonstrated that post-therapeutic professional maintenance care is an integral part of this treatment. This also constitutes the only means of assuring the maintenance of long-term beneficial therapeutic effects. Re-infection could be prevented or kept to a minimum in most patients, mainly through rigid surveillance involving visits to professionals at regular intervals. However, the maintenance systems presented in the various studies do not give a clear concept with general validity for the frequency of maintenance visits to professionals and the mode of maintenance therapy. In some patients there may be a danger that re-infection and recurrent disease are neglected, while in others there may be a tendency to overtreat.

Objective criteria for assessing the patient's individual risk for recurrent disease have been the focus of attention in recent years. However, this evaluation still has to be based on a probability estimate derived from the assessment of the patient, tooth, or tooth-site risks.

The purpose of this chapter is to discuss the basics of continuous patient monitoring following active periodontal and implant therapy in order to prevent re-infection and progression of periodontal disease following therapy. The mode and extent of interceptive therapeutic measures needed to achieve this goal will also be evaluated.

Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

Definition

Periodontal treatment includes:

1. Systemic evaluation of the patient's health
2. Cause-related therapeutic phase
3. Corrective phase involving periodontal surgical procedures, and
4. Maintenance phase.

The 3rd World Workshop of the American Academy of Periodontology (1989) renamed the collective periodontal treatment procedures to supportive periodontal therapy (SPT). This term expresses the essential need for therapeutic measures to support the patient's own efforts to control periodontal infections and to avoid re-infection. Regular visits to the therapist should serve as a positive feedback mechanism between the patient and the therapist with the purpose of ensuring that patients can maintain their dentitions in a healthy status for the longest possible time. An integral part of SPT is the continuous diagnostic monitoring of the patient in order to intercept with adequate therapy and to optimize the therapeutic interventions tailored to the patient's needs.

Basic paradigms for the prevention of periodontal disease

Periodontal maintenance care, or SPT, follows the paradigms of the etiology and pathogenesis of periodontal and peri-implant diseases and must consider the fact that these diseases represent opportunistic infections.

Almost 60 years ago, a cause–effect relationship between the accumulation of bacterial biofilm on teeth and the development of gingivitis was proven (Löe *et al*. 1965). This relationship was also documented by the restoration of gingival health following biofilm removal. The same cause–effect relationship has been demonstrated for the peri-implant tissues between the biofilm and the development of mucositis (Salvi *et al*. 2012). This causal relationship was further characterized when loss of connective tissue attachment and resorption of alveolar bone with biofilm accumulation and the development of periodontal disease was shown in laboratory animals (Lindhe *et al*. 1975). Because some of these animals did not develop periodontal disease despite a persistent biofilm accumulation for 48 months, it must be considered that the composition of the microbiota or the host's defense mechanisms or susceptibility to disease may vary from individual to individual. Nevertheless, in the study mentioned, the initiation of periodontal disease was always preceded by obvious signs of gingivitis. Hence, it seems reasonable to predict that the elimination of gingival inflammation and the maintenance of healthy gingival tissues will prevent both the initiation and the recurrence of periodontal and peri-implant disease. In fact, as early as 1746, Fauchard stated that "little or no care as to the cleaning of teeth is ordinarily the cause of all diseases that destroy them".

From the clinical point of view, the abovementioned results must be translated into the necessity for proper and regular personal biofilm removal, at least in patients treated for or susceptible to periodontal disease. This simple principle may be difficult to implement in all patients; however, interceptive professional SPT at regular intervals may, to a certain extent, compensate for the lack of personal compliance with regard to oral hygiene standards.

These aspects have been imitated in a Beagle dog model with naturally occurring periodontal disease (Morrison *et al*. 1979). Two groups of animals were used. The test group was subjected to initial scaling and root planing and, subsequently, biofilm was eliminated by daily toothbrushing and biweekly polishing with rubber cups for a period of 3 years. In the control group, no initial scaling and no oral hygiene practices were performed during the same period of time. Every 6 months, however, the teeth in two diagonally opposed jaw quadrants in both test and control animals were scaled and root planed. The results showed that the reduction of probing pocket depth (PPD) and the gain of probing attachment obtained after the initial scaling and root planing in the test animals were maintained throughout the entire course of the study irrespective of whether or not repeated scaling and root planing had been performed. The control animals, on the other hand, continued to show increasing PPD and loss of attachment in all quadrants irrespective of whether or not repeated scaling and root planing had been performed. However, in the jaw quadrants where the teeth were repeatedly instrumented every 6 months, the progression of the periodontal destruction was significantly less pronounced (Fig. 48-1). These results indicate that professional SPT, performed at regular intervals, may, to a certain extent, compensate for a "suboptimal" personal oral hygiene standard. In this respect, it has been demonstrated that following root instrumentation, the subgingival microbiota is significantly altered in quantity and quality (Listgarten *et al*. 1978), and that the re-establishment of a disease-associated, subgingival microbiota may take several months (Listgarten *et al*. 1978; Slots *et al*. 1979; Mousquès *et al*. 1980; Caton *et al*. 1982; Magnusson *et al*. 1984).

In a number of longitudinal clinical studies on the outcome of periodontal therapy, the crucial role of SPT in maintaining successful results has been documented (Ramfjord *et al*. 1968; Lindhe & Nyman 1975; Ramfjord *et al*. 1975; Rosling *et al*. 1976; Nyman *et al*. 1977; Knowles *et al*. 1979, 1980; Badersten *et al*. 1981, Hill *et al*. 1981; Lindhe *et al*. 1982a, b; Pihlström *et al*. 1983; Westfelt *et al*. 1983a; Lindhe & Nyman 1984; Westfelt *et al*. 1985; Isidor & Karring 1986; Badersten

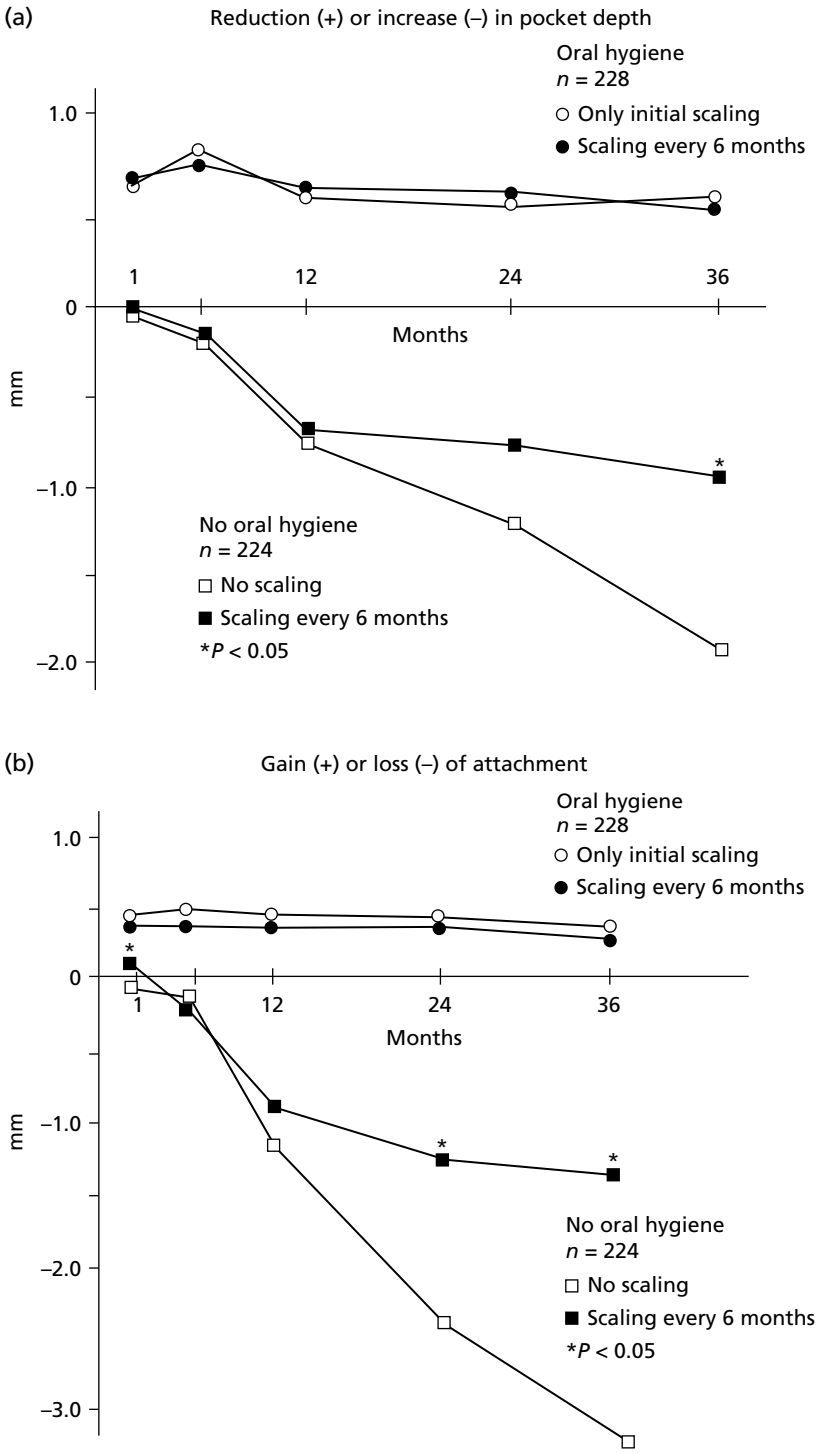

Fig. 48-1 (a) Mean probing depth reduction (+) or increase in probing depth (–) in millimeters with or without repeated scaling and root planing in experimental (oral hygiene) and control (no oral hygiene) animals relative to baseline means. (b) Mean gain (+) or loss (–) of probing attachment with or without repeated scaling and root planing in experimental (oral hygiene) and control (no oral hygiene) animals relative to baseline means. (Source: Data from Morrison *et al*. 1979. Reproduced with permission from John Wiley & Sons.)

et al. 1987; Kaldahl *et al*. 1988). In all these studies, PPD and clinical attachment levels were maintained as a result of a well-organized professional maintenance care program (SPT intervals varying between 3 and 6 months), irrespective of the initial treatment modality performed.

In one of the studies (Nyman *et al*. 1977), an alarming result was that patients treated for advanced periodontal disease involving surgical techniques, but not enrolled in a supervised maintenance care program, exhibited recurrent periodontitis, including loss of attachment, at a rate three to five times higher than documented for natural progression of periodontal disease in population groups with high disease susceptibility (Löe *et al*. 1978, 1986). Within this area, the effect of negligence in providing adequate SPT following periodontal treatment was studied over a 6-year period by Axelsson and Lindhe (1981a). Following presurgical root instrumentation and instruction in oral hygiene practices, all study patients were subjected to modified Widman flap procedures. During a 2-month healing period, professional tooth cleaning was performed every 2 weeks. Following this time period, baseline clinical data were obtained and one in every three patients was dismissed from the clinic, while the other two were enrolled in a professionally conducted maintenance program with an SPT visit once every 3 months.

These patients maintained excellent oral hygiene and consequently yielded a very low frequency of bleeding sites. In addition, PPD and probing attachment levels were maintained unchanged over the 6-year period. In contrast, the non-recalled patients demonstrated obvious signs of recurrent periodontitis at the 3-year and 6-year re-examinations. Further evidence for the likelihood of recurrent disease in patients not subjected to professional maintenance care was presented by Kerr (1981). Five years after successful treatment, 45% of the patients presented with periodontal conditions similar to their status before treatment. SPT had only been provided at intervals varying between 9 and 18 months. Similar results were obtained from a systematic review by Farooqi *et al*. (2015). Their analysis revealed that shorter intervals were positively associated with reduced tooth loss while available evidence for the indication of specific intervals (e.g. 3 months) remains scarce (Farooqi *et al*. 2015).

Even though the number of well-controlled longitudinal clinical trials is rather limited for patients who, in addition to periodontal treatment, have undergone extensive reconstructive therapy, it should be realized that the concept of professional maintenance care has unrestricted validity. In a longitudinal study of combined periodontal and prosthetic treatment of patients with advanced periodontal disease, periodontal health could be maintained over a study period of 5–8 years with regular SPT appointments scheduled every 3–6 months (Nyman & Lindhe 1979). Similar results have been presented by Valderhaug and Birkeland (1976) and by Valderhaug (1980) for periods of up to 15 years. Another study of 36 patients who received extensive poly-unit cantilevered bridgework following periodontal therapy, confirmed the maintenance of periodontal health over 5–12 years (Laurell *et al*. 1991). More recent studies on the long-term maintenance of periodontal patients who, following successful treatment of periodontitis, were reconstructed with extensive fixed reconstructions, revealed that regularly performed SPT resulted in periodontal stability. Only 1.3% (Hämmerle *et al*. 2000) and 2.0% (Moser *et al*. 2002) of the abutments showed some minor attachment loss during these long periods of observation (10 and 11 years, respectively). In contrast, a report of insurance cases who were not regularly maintained by SPT yielded a recurrence rate for periodontitis of almost 10% after an observation of 6.5 years (Randow *et al*. 1986).

Summary: The etiology of gingivitis and periodontitis is fairly well understood. However, the causative factor, that is the microbial challenge which induces and maintains the inflammatory response, may not be completely eliminated from the dentogingival and peri-implant environment for any length of time. This requires the professional removal of all microbial deposits in the supragingival and subgingival areas at regular intervals, because recolonization will occur following the debridement procedures, leading to a re-infection of the ecologic niche and, hence, further progression of the disease process. Numerous well-controlled clinical trials, however, have documented that such a development can be prevented over very long periods of time only by regular interference with the subgingival environment aimed at removal of the subgingival bacteria.

Patients at risk for periodontitis without regular supportive periodontal therapy

The effect of omission of SPT in patients with periodontitis may best be studied either in untreated populations or patient groups with poor compliance.

One of the few studies documenting untreated periodontitis-susceptible patients reported on the continuous loss of periodontal attachment as well as teeth in Sri Lankan tea plantation workers receiving no dental therapy (Löe *et al*. 1986; Ramseier *et al*. 2017). In this – for the Western world – rather unique model situation, an average loss of 0.3 mm per tooth surface and per year was encountered. Also, the laborers lost between 0.1 and 0.3 teeth per year as a result of periodontitis. In another untreated group in the USA, 0.61 teeth were lost per year during an observation period of 4 years (Becker *et al*. 1979). This is in dramatic contrast to reports on tooth loss in well-maintained patients treated for periodontitis (e.g. Hirschfeld & Wasserman 1978; McFall 1982; Becker *et al*. 1984; Wilson *et al*. 1987, Ng *et al*. 2011; Costa *et al*. 2012, 2014). Such patients were either completely stable and lost no teeth during maintenance periods ranging up to 22 years or lost only very little periodontal attachment and only 0.03 teeth (Hirschfeld & Wasserman 1978) or 0.06 teeth (Wilson *et al*. 1987).

Non-complying but periodontitis-susceptible patients receiving no SPT following periodontal surgical interventions continued to lose periodontal attachment at a rate of approximately 1 mm per year regardless of the type of surgery chosen (Nyman *et al*. 1977). This is almost three times greater than would be expected as a result of the "natural" course of periodontal disease progression (Löe *et al*. 1978, 1986; Ramseier *et al*. 2017).

In a British study of a private practice situation (Kerr 1981) where the patients were referred back to the general dentist after periodontal therapy, 45% of the patients showed complete re-infection after 5 years.

Similar results have been described for private practice patients who decided not to participate in an organized maintenance care program following active periodontal therapy (Becker *et al*. 1984). Subsequent examinations revealed clear signs of recurrent periodontal disease, including increased PPD and involvement of furcations of multirooted teeth concomitant with tooth loss. Also, loss of alveolar bone observed on radiographs and tooth loss have been reported for a group of patients in whom

SPT was provided less frequently than once every 12 months (De Vore *et al*. 1986).

From all these studies, it is evident that periodontal treatment is ineffective in maintaining periodontal health if SPT is neglected, denied, or omitted.

The most impressive documentation of the lack of SPT in disease-susceptible individuals is probably that from a clinical trial in which one-third of the patients had been sent back to the referring general practitioner for maintenance, while two-thirds of the patients received SPT in a well-organized maintenance system (Axelsson & Lindhe 1981a). The 77 patients were examined before treatment, 2 months after the last surgical procedure, and 3 and 6 years later. The 52 patients on the carefully designed SPT system visited the program every 2 months for the first 2 years and every 3 months for the remaining 4 years of the observation period. The results obtained from the second examination (2 months after the last surgery) showed that the effect of the initial treatment was good in both groups. Subsequently, the patients on SPT were able to maintain proper oral hygiene and unaltered attachment levels. In the non-SPT group, plaque-index scores increased markedly from the baseline values, as did the number of inflamed gingival units (Fig. 48-2a). Concomitantly, there were obvious signs of recurrent periodontitis. The mean values for pocket depth and attachment levels at the 3-year and 6-year examinations were higher than at baseline (Fig. 48-2b). In the SPT group, approximately 99% of the tooth surfaces showed either improvement, no change or <1 mm loss of attachment, compared with 45% in the non-SPT group (Table 48-1). In the latter patients, 55% of the sites showed a further loss of attachment of 2–5 mm at the 6-year examination, and 20% of the pockets were 4 mm deep or more (Tables 48-1, 48-2).

Summary: Patients susceptible to periodontal disease are at high risk for re-infection and progression of periodontal lesions without meticulously organized and performed SPT. Since all patients who are treated for periodontal disease belong

Table 48-1 Percentage of sites showing various changes in probing attachment level between baseline examination, 2 months after completion of active periodontal therapy, and at follow-up examination 6 years later.

Site level	Periodontal probing depths (mm)	
	SPT	Non-SPT
Attachment level improved	17	1
No change	72	10
Attachment level worse by:		
≥1 mm	10	34
2–5 mm	1	55

SPT, supportive periodontal therapy. (Source: Adapted from Axelsson & Lindhe 1981b. Reproduced with permission from John Wiley & Sons.)

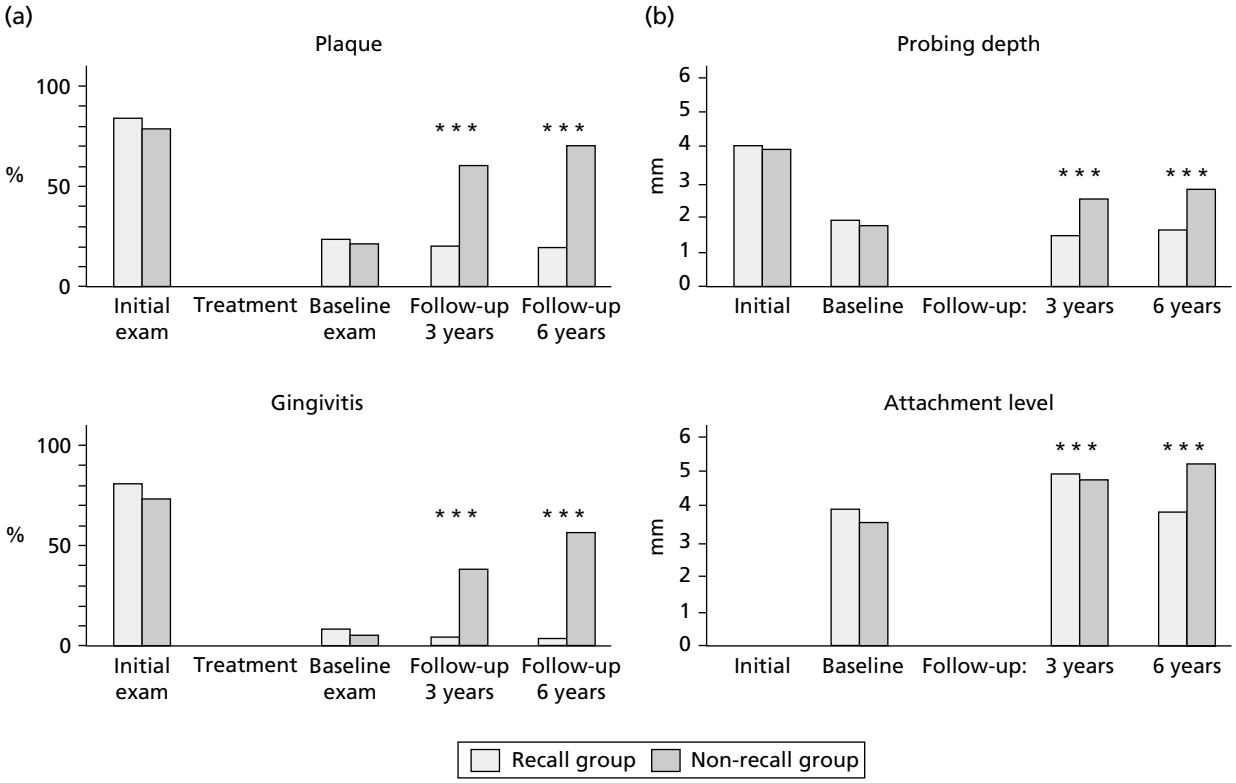

Fig. 48-2 Histograms showing (a) average percentages of tooth surfaces harboring visible biofilm (above) and inflamed gingival units (bleeding on probing) (below), and (b) average probing depth (above) and probing attachment levels (below), at initial, baseline, and follow-up examinations. (Source: Data from Axelsson & Lindhe 1981b. Reproduced with permission from John Wiley & Sons.)

Table 48-2 Percentage of various probing depths in supportive periodontal therapy (SPT) and non-SPT patients at the initial examination, 2 months after active periodontal treatment, and at 3- and 6-year follow-up visits.

Examinations	Percentage of pockets of various depths					
	≤3 mm		4–6 mm		≥7 mm	
	SPT	Non-SPT	SPT	Non-SPT	SPT	Non-SPT
Initial	35	50	58	38	8	12
Baseline	99	99	1	1	0	0
3 years	99	91	1	9	0	0
6 years	99	80	1	19	0	1

(Source: Adapted from Axelsson & Lindhe 1981b. Reproduced with permission from John Wiley & Sons.)

to this risk category by virtue of their past history, an adequate maintenance care program is of utmost importance for a beneficial long-term treatment outcome. SPT has to be aimed at the regular removal of the subgingival microbiota and must be supplemented by the patient's efforts for optimal supragingival biofilm control.

Supportive periodontal therapy for patients with gingivitis

Several studies, predominantly in children, have documented that periodic professional prophylactic visits in conjunction with reinforcement of personal oral hygiene are effective in controlling gingivitis (Badersten *et al*. 1975; Poulsen *et al*. 1976; Axelsson & Lindhe 1981a, b; Bellini *et al*. 1981). This, however, does not imply that maintenance visits in childhood preclude the development of more severe disease later in life. It is obvious, therefore, that SPT must be a lifelong commitment of both patients and oral health professionals.

Adults whose effective oral hygiene was combined with periodic professional prophylaxis were clearly healthier periodontally than patients who did not participate in such programs (Lövdal *et al*. 1961; Suomi *et al*. 1971). One particular study of historical significance was performed on 1428 adults from an industrial company in Oslo, Norway (Lövdal *et al*. 1961). Over a 5-year observation period, the subjects were recalled two to four times per year for instruction in oral hygiene and supragingival and subgingival scaling. Gingival conditions improved by approximately 60% and tooth loss was reduced by about 50% of what would be expected without these efforts.

In another study (Suomi *et al*. 1971), loss of periodontal tissue support in young individuals with gingivitis or only loss of small amounts of attachment was followed over 3 years. An experimental group receiving scaling and instruction in oral hygiene every 3 months yielded significantly less biofilm and gingival inflammation than the control group in which no special efforts had been made. The mean loss of probing attachment was only 0.08 mm per surface in the experimental as opposed to 0.3 mm in the control group.

When adult patients with gingivitis were treated with scaling and root planing, but did not improve their oral hygiene procedures, the gingival condition did not improve compared with individuals receiving prophylaxis at 6-month intervals (Listgarten & Schifter 1982).

Summary: The available information indicates that the prevention of gingival inflammation and early loss of attachment in patients with gingivitis depends primarily on the level of personal biofilm control, but also on further measures to reduce the accumulation of supragingival and subgingival biofilm.

Supportive periodontal therapy for patients with periodontitis

As mentioned previously, a series of longitudinal studies on periodontal therapeutic modalities has been performed, first at the University of Michigan, USA, later at the University of Gothenburg, Sweden, and also at the Universities of Minnesota, Nebraska, and Loma Linda, USA. These studies always enrolled patients into a well-organized maintenance care system with SPT visits at regular intervals (generally 3–4 months). Although the patients performed biofilm control with various degrees of efficacy, the SPT resulted in excellent maintenance of postoperative attachment levels in most patients (Knowles 1973; Ramfjord *et al*. 1982).

On average, excellent treatment results with maintained reduced PPD and maintained gains of probing attachment were documented for most of the patients in the longitudinal studies irrespective of the treatment modality chosen (Ramfjord *et al*. 1975; Lindhe & Nyman 1975; Rosling *et al*. 1976; Nyman *et al*. 1977; Knowles *et al*. 1979, 1980; Badersten *et al*. 1981; Hill *et al*. 1981; Lindhe *et al*. 1982a; Pihlström *et al*. 1983; Westfelt *et al*. 1983a, b, 1985; Isidor & Karring 1986; Badersten *et al*. 1987).

In a study on 75 patients with extremely advanced periodontitis, who had been successfully treated for the disease with cause-related therapy and modified Widman flap procedures (Lindhe & Nyman 1984), recurrent infection occurred in only very few sites during a 14-year period of effective SPT. However,

it has to be realized that recurrent periodontitis was noted at completely unpredictable time intervals but was concentrated in about 25% of the patient population (15 of 61). This suggests that, in a periodontitis-susceptible risk population, the majority of patients can be "cured" provided an optimally organized SPT is performed, while a relatively small proportion of patients (20–25%) will suffer from occasional episodes of recurrent periodontal re-infection. It is obviously a challenge for the therapist to identify such patients with very high disease susceptibility and to monitor the dentitions for recurrent periodontitis on a long-term basis.

Two decades later, the effect of a 30-year biofilm control-based maintenance program in a private dental office on tooth mortality, caries, and periodontal disease progression was presented (Axelsson *et al*. 2004). This prospective controlled cohort study initially included 375 test and 180 control patients who received traditional maintenance care (by the referring dentist once or twice a year). After 6 years, the control group was discontinued. The test group was subjected to prophylactic visits every second month for the first 2 years and every 3–12 months (according to their individual needs) over 3–30 years. The prophylactic visits to the dental hygienist included biofilm disclosure and professional mechanical tooth cleaning, including the use of a fluoride-containing dentifrice. During the 30 years of maintenance, very few teeth were lost (0.4–1.8), and rare teeth loss was predominately the result of root fractures. Over the 30 years of maintenance, 1.2–2.1 new carious lesions (>80% secondary caries) were found. During this period, only 2–4% of all sites exhibited periodontal attachment loss of ≥2 mm. This unique study clearly demonstrated that SPT based on biofilm control tailored to the individual needs of the patient will result in very low tooth mortality, minimal recurrent caries, and almost complete periodontal stability.

Summary: SPT is an absolute prerequisite to guarantee beneficial treatment outcomes with maintained levels of clinical attachment over long periods of time. For the majority of patients, the maintenance of treatment results has been documented for up to 14 years, and in a private practice situation even up to 30 years, but it has to be realized that a small proportion of patients will experience recurrent infections with progression of periodontal lesions in a few sites in a completely unpredictable mode. The continuous risk assessment at subject, tooth, and tooth-site levels, therefore, represents a challenge for the SPT concept.

Continuous multilevel risk assessment

As opposed to an initial periodontal diagnosis which considers the sequelae of the disease process, in other words documents the net loss of periodontal attachment, the concomitant formation of periodontal pockets, and the existence of inflammation, clinical diagnosis during SPT has to be based on the variations of the health status following successful active periodontal treatment. This, in turn, means that a new baseline has to be established once the treatment goals of active periodontal therapy (i.e. phases 1–3) are reached and periodontal health is restored (Claffey 1991). This baseline includes the level of clinical attachment achieved while the inflammatory parameters are supposed to be under control. Under optimal circumstances, SPT would maintain the clinical attachment levels obtained after active therapy for many years. However, if re-infection occurs, the loss of clinical attachment will progress. The relevant question is, therefore, which clinical parameters serve as early indicators for a new onset or recurrence of the periodontal disease process, that is re-infection and progression of periodontal breakdown of a previously treated periodontal site? It is also very important to achieve consistency in the definition of a "progressive" case in order to be able to interpret the results of clinical studies evaluating risk factors/indicators for the disease progression. Such a definition was proposed during the 5th European Workshop in Periodontology (Tonetti & Claffey 2005): presence of two or more teeth with longitudinal loss of proximal attachment of ≥3 mm. Where serial proximal attachment level measurements are not available, longitudinal radiographic bone loss of ≥2 mm at two or more teeth may be used as a substitute.

From a clinical point of view, the stability of periodontal conditions reflects a dynamic equilibrium between bacterial aggression and effective host response. As such, this homeostasis is prone to sudden changes whenever one of the two factors prevails. Hence, it is evident that the diagnostic process must be based on continuous monitoring of the multilevel risk profile. The intervals between diagnostic assessments must also be chosen based on the overall risk profile and the expected benefit. To schedule patients for SPT on the basis of an individual risk evaluation for recurrence of disease has been demonstrated to be cost-effective (Axelsson & Lindhe 1981a, b; Axelsson *et al*. 1991).

Subject periodontal risk assessment

The patient's risk for recurrence of periodontitis may be evaluated on the basis of a number of clinical conditions whereby no single parameter displays a paramount role. The entire spectrum of risk factors and risk indicators should be evaluated simultaneously. For this purpose, a functional diagram has been constructed (Fig. 48-3) (Lang & Tonetti 2003) including the following aspects:

- Patient-level percentage of bleeding on probing (BoP)
- Prevalence (number) of residual pockets ≥4 mm following active periodontal therapy
- Loss of teeth from a total of 28 teeth

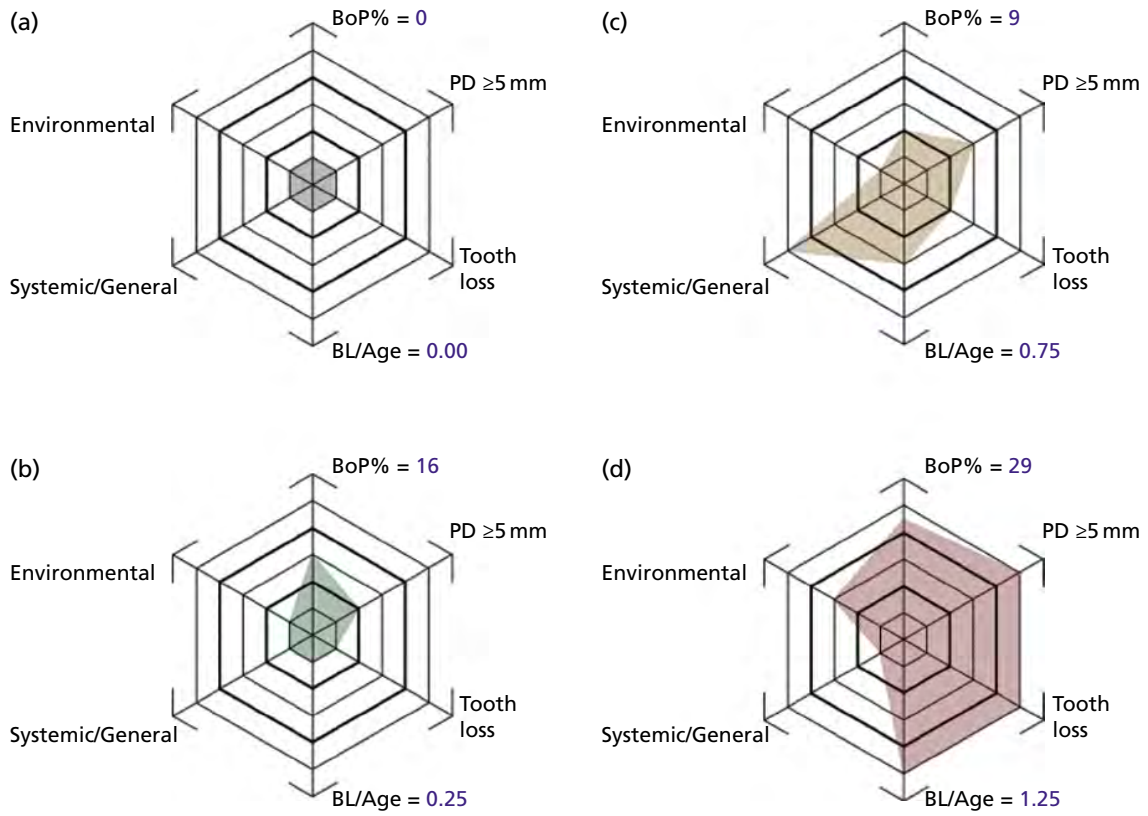

Fig. 48-3 (a) Functional diagram to evaluate the patient's risk for recurrence of periodontitis. Each vector represents one risk factor or indicator with an area of relatively low risk, an area of medium risk, and an area of high risk for disease progression. All factors have to be evaluated together and hence, the area of relatively low risk is found within the center circle of the polygon, while the area of high risk is found outside the periphery of the second polygon in bold. Between the two rings in bold, there is the area of moderate risk. Source: From: www.perio-tools.com/pra. (b) Functional diagram of a low-risk maintenance patient. Bleeding on probing (BoP) is 15%, four residual pockets of ≥5 mm are diagnosed, two teeth have been lost, the bone factor in relation to the patient's age is 0.25, no systemic factor is known, and the patient is a non-smoker. (c) Functional diagram of a medium-risk maintenance patient. BoP is 9%, six residual pockets of ≥5 mm are diagnosed, four teeth have been lost, the bone factor in relation to the patient's age is 0.75, the patient has type I diabetes, but is a non-smoker. (d) Functional diagram of a high-risk maintenance patient. BoP is 32%, 10 residual pockets of ≥5 mm are diagnosed, 10 teeth have been lost, the bone factor in relation to the patient's age is 1.25, no systemic factors are known, and the patient is an occasional smoker. BL, bone loss; PPD, probing pocket depth. (Source: Lang & Tonetti 2003. Reproduced with permission from John Wiley & Sons.)

- Loss of periodontal support in relation to the patient's age
- Systemic and genetic conditions
- Environmental factors such as cigarette smoking.

Each parameter has its own scale for low, medium, and high-risk profiles. A comprehensive evaluation of these factors after active periodontal therapy will provide an individualized total risk profile and help in determining the frequency and complexity of SPT visits. Modifications may be made to the functional diagram if additional factors become important in the future. The validity of the periodontal risk assessment (PRA) in identifying various patient-based risk levels for disease progression following active periodontal treatment has been tested in several cohort studies around the world (Lang *et al*. 2015).

The assessment of the risk parameters for the subject-based risk assessment may be repeated after a number of years, preferably 5 years. In the meantime, more detailed assessment of the residual periodontal pocket profiles and BoP may be additionally helpful to decide on the specific interval of 3 to a maximum of 12 months (see Determination of personalized supportive periodontal therapy intervals).

The PRA tool may easily be used online at www.perio-tools.com/pra.

Compliance with the SPT system

Several investigations have indicated that only a minority of periodontal patients comply with the prescribed SPT (Wilson *et al*. 1984; Mendoza *et al*. 1991; Checchi *et al*. 1994; Demetriou *et al*. 1995). In a more recent study it was confirmed that approximately 25% of patients no longer returned for SPT despite a recommendation being made (Ramseier *et al*. 2014). Because it has been clearly established that treated periodontal patients who comply with regular periodontal maintenance appointments have a better prognosis than patients who do not comply (Axelsson & Lindhe 1981a; Becker *et al*. 1984; Cortellini *et al*. 1994, 1996), non-compliant or poorly compliant patients should be considered at higher risk for periodontal

disease progression. A report that investigated the personality differences of patients participating in a regular SPT program following periodontal therapy as compared with patients who did not, revealed that the latter patients had higher incidences of stressful life events and less stable personal relationships (Becker *et al*. 1988). Moreover, it is convincingly demonstrated that smokers yielded a significantly lower compliance rate than did non-smokers or former smokers (Ramseier *et al*. 2014).

Oral hygiene

Since bacterial biofilms are by far the most important etiologic agent for the occurrence of periodontal diseases (for review see Kornman & Löe 1993), it is evident that full-mouth assessment of the bacterial load must have a pivotal role in the determination of the risk for disease recurrence. It has to be realized, however, that regular interference with the microbial ecosystem during periodontal maintenance will eventually obscure such obvious associations. In patients treated with various surgical and non-surgical modalities, it has been clearly established that biofilm-infected dentitions will yield recurrence of periodontal disease in multiple locations, while dentitions under biofilm control and regular SPT maintain periodontal stability for many years (Rosling *et al*. 1976; Axelsson & Lindhe 1981a, b). Studies have thus far not identified a level of biofilm infection compatible with maintenance of periodontal health. However, in a clinical set-up, a biofilm control record of at most 20% will be tolerated in most patients. It is important to realize that the full-mouth biofilm score has to be related to the host response of the patient, in other words compared with inflammatory parameters.

Percentage of sites with bleeding on probing

Bleeding on gentle probing represents an objective inflammatory parameter which has been incorporated into index systems for the evaluation of periodontal conditions (Löe & Silness 1963; Mühlemann & Son 1971) and is also used as a parameter alone (Lang *et al*. 1986, 1991). In a patient's risk assessment for recurrence of periodontitis, BoP reflects, at least in part, the patient's compliance and standards of oral hygiene performance. No acceptable level of prevalence of BoP in the dentition above which there is a higher risk for disease recurrence has been established. However, a BoP prevalence of 20% was the cut-off point between patients with maintained periodontal stability for 5 years and patients with recurrent disease in the same timeframe in a retrospective study (Ramseier *et al*. 2015) (Fig. 48-4). Further evidence of BoP percentages between 20% and 30% determining a higher risk for disease progression originates from studies by Claffey *et al*. (1990), Badersten *et al*. (1990), and Joss *et al*. (1994).

In assessing the patient's risk for disease progression, BoP percentages reflect a summary of the patient's ability to perform proper biofilm control, his/her host response to the bacterial challenge, and his/her compliance. The percentage of BoP, therefore, is used as the first risk factor in the functional diagram of risk assessment (see Fig. 48-3). The scale runs in a quadratic mode with 4, 9, 16, 25, 36, and >49% being the divisions on the vector.

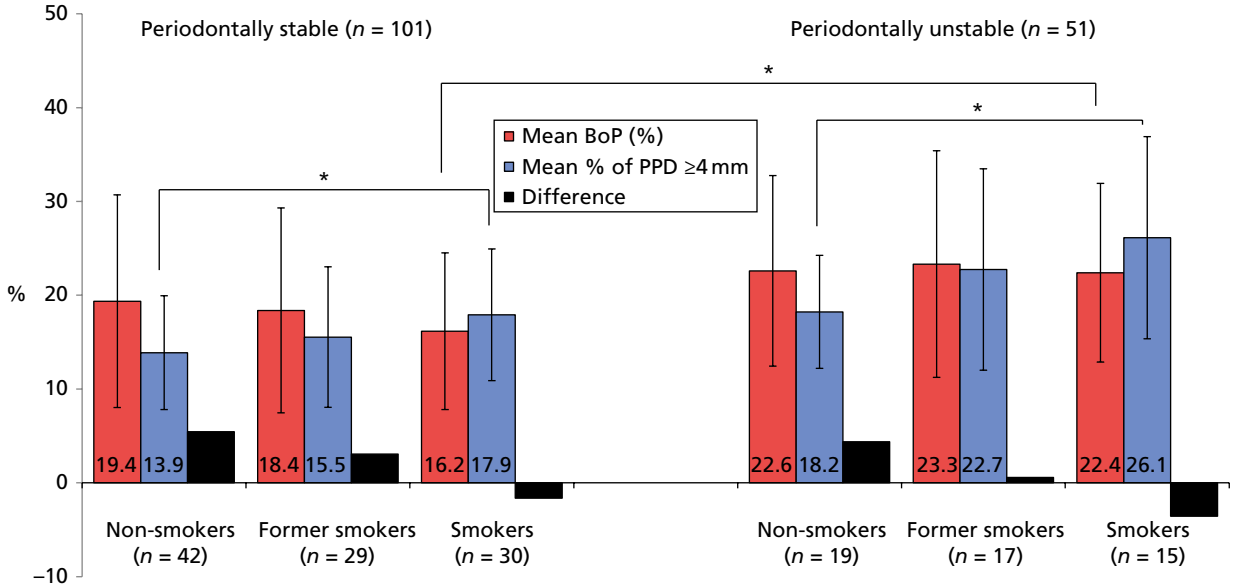

Fig. 48-4 Mean bleeding on probing (BoP), mean percentage of periodontal probing depths (PPD) ≥4 mm and calculated difference per smoking status over 5 years of supportive periodontal therapy in 101 periodontally stable and 51 periodontally unstable patients initially categorized with periodontitis stage III. Error indicators specify the standard deviation (SD). Calculated negative differences in both periodontally stable and unstable smokers represent a higher mean percentage of PPD ≥4 mm compared with a lower mean BoP. *Statistically significant difference at $P < 0.05$. (Source: Data from Ramseier *et al*. 2015. Reproduced with permission from John Wiley & Sons.)

Individuals with low mean BoP percentages (<10% of the surfaces) may be regarded as patients with a low risk for recurrent disease (Lang *et al*. 1990), whereas patients with mean BoP percentages of >25% should be considered to be at high risk for re-infection.

Prevalence of residual pockets of ≥5 mm

The enumeration of the residual pockets with a PPD of ≥5 mm represents, to a certain extent, the degree of success of the periodontal treatment rendered. Although this depth *per se* does not make much sense when considered as a sole parameter, the evaluation in conjunction with other parameters, such as BoP and/or suppuration, will reflect existing ecologic niches from and in which re-infection might occur. It is, therefore, conceivable that periodontal stability in a dentition is reflected by a minimal number of residual pockets. At a site level, the presence of deep residual pockets after initial periodontal therapy and deepening of pockets during SPT has been associated with high risk for disease progression (Badersten *et al*. 1990; Claffey *et al*. 1990; Matuliene et al. 2008). At the patient level, however, this evidence is evolving. In one study of 16 patients suffering from advanced periodontitis (Claffey & Egelberg 1995), the presence of high proportions of residual PPD of ≥6 mm after initial periodontal therapy indicated patient susceptibility for further attachment loss over a 42-month period. In a retrospective study of mean duration of 11.3 years, SPT was provided for 172 patients treated for periodontitis (Matuliene *et al*. 2008). Analysis of the data at the patient level demonstrated that, besides heavy smoking (≥20 cigarettes/day), SPT duration exceeding 10 years, initial diagnosis of periodontitis stage III and IV (Tonetti & Claffey 2005), and the presence of at least one site with PPD of ≥6 mm or nine or more sites with PPD of ≥5 mm contribute significantly to the risk of periodontitis progression (Matuliene *et al*. 2008).

On the other hand, it has to be realized that an increased number of residual pockets does not necessarily imply an increased risk for re-infection or disease progression, because a number of longitudinal studies have established that, depending on the individual SPT provided, even deeper pockets may be stable without further disease progression for years (e.g. Knowles *et al*. 1979; Lindhe & Nyman 1984; Ramseier *et al*. 2019).

Nevertheless, in assessing the patient's risk for disease progression, the number of residual pockets with a PPD of ≥5 mm is assessed as the second risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 48-3). The scale runs in a linear mode with 2, 4, 6, 8, 10, and ≥12% being the divisions on the vector. Individuals with up to four residual pockets may be regarded as at a relatively low risk, while patients with more than eight residual pockets may be regarded as at high risk for recurrent disease.

Loss of teeth from a total of 28 teeth

Although the reason for tooth loss may not be known, the number of remaining teeth in a dentition reflects the functionality of the dentition. Mandibular stability and individual optimal function may be assured even with a shortened dental arch of premolar to premolar occlusion, that is 20 teeth. The shortened dental arch does not seem to predispose the individual to mandibular dysfunction (Witter *et al*. 1990, 1994). However, if more than eight teeth from a total of 28 teeth are lost, oral function is usually impaired (Käyser 1981, 1994, 1996). Since tooth loss also represents a true end-point outcome variable reflecting the patient's history of oral diseases and trauma, it is logical to incorporate this risk indicator as the third parameter in the functional diagram of risk assessment (see Fig. 48-3). The number of teeth lost from the dentition without the third molars (28 teeth) is counted, irrespective of their replacement being pontics or implants. The scale runs also in a linear mode with 2, 4, 6, 8, 10, and ≥12% being the divisions on the vector.

Individuals with up to four teeth lost may be regarded as patients at low risk, while patients with more than eight teeth lost may be considered as being at high risk.

Loss of periodontal support in relation to the patient's age

The extent and prevalence of periodontal attachment loss (i.e. previous disease experience and susceptibility), as evaluated by the height of the alveolar bone on radiographs, may represent the most obvious indicator of subject risk when related to the patient's age. In light of the present understanding of periodontal disease progression, and the evidence that both onset and rate of progression of periodontitis might vary among individuals and over different timeframes (van der Velden 1991; Ramseier *et al*. 2017), it has to be realized that previous attachment loss in relation to the patient's age does not rule out the possibility of rapidly progressing lesions. Therefore, the actual risk for further disease progression in a given individual may occasionally be underestimated. Hopefully, the rate of progression of disease has been positively affected by the treatment rendered and, hence, previous attachment loss in relation to the patient's age may be a more accurate indicator during SPT than before active periodontal treatment. Given the hypothesis that a dentition may be functional for the most likely life expectancy of the subject in the presence of a reduced height of periodontal support (i.e. 25–50% of the root length), the risk assessment in treated periodontal patients may represent a reliable prognostic indicator for the stability of the overall treatment goal of keeping a functional dentition for a lifetime (Papapanou *et al*. 1988).

The estimation of the loss of alveolar bone is performed in the posterior region on either periapical

radiographs, in which the worst site affected is estimated grossly as a percentage of the root length, or on bitewing radiographs in which the worst site affected is estimated in millimeters. One millimeter equates to 10% bone loss. The percentage is then divided by the patient's age. This results in a factor. As an example, a 40-year-old patient with 20% bone loss (BL) at the worst posterior site affected would be scored BL/Age = 0.5. Another 40-year-old patient with 50% BL at the worst posterior site scores BL/Age = 1.25.

In assessing the patient's risk for disease progression, the extent of alveolar bone loss in relation to his/her age is estimated as the fourth risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 48-3). The scale runs in increments of 0.25 of the factor BL/Age, with 0.5 being the division between low and moderate risk, and 1.0 being the division between moderate and high risk for disease progression. This, in turn, means that a patient who has lost a higher percentage of posterior alveolar bone than expected for his/her own age is at high risk regarding this vector in a multifactorial assessment of risk.

Systemic conditions

The most substantiated evidence for modification of disease susceptibility and/or progression of periodontal disease arises from studies on type I and type II (insulin-dependent and non-insulin-dependent) diabetes mellitus populations (Gusberti *et al*. 1983; Emrich *et al*. 1991; Genco & Löe 1993).

It has to be realized that the impact of diabetes on periodontal diseases has been documented in patients with untreated periodontal disease. It is reasonable to assume that the influence of systemic conditions may also affect recurrence of disease.

In recent years, genetic markers have become available to determine various genotypes of patients regarding their susceptibility for periodontal diseases. Initial research on the interleukin-1 (IL-1) polymorphisms has indicated that *IL-1* genotype-positive patients show more advanced periodontitis lesions than *IL-1* genotype-negative patients of the same age group (Kornman *et al*. 1997). Also, there is a trend to higher tooth loss in the *IL-1* genotype-positive subjects (McGuire & Nunn 1999). In a retrospective analysis of over 300 well-maintained periodontal patients, the *IL-1* genotype-positive patients showed significantly higher BoP percentages, and a higher proportion of these patients yielded higher BoP percentages during a 1-year SPT period than the *IL-1* genotype-negative control patients (Lang *et al*. 2000). Also, the latter group had twice as many patients with improved BoP percentages during the same maintenance period, indicating that *IL-1* genotype-positive subjects do indeed represent a group of hyperreactive subjects even if they are regularly maintained by effective SPT (Lang *et al*. 2000). In a prospective study over 5 years on Australian white and blue collar workers at a university campus, the *IL-1* genotype-positive group aged above 50 years showed significantly deeper PPD than their *IL-1* genotype-negative counterparts, especially when they were non-smokers (Cullinan *et al*. 2001). Moreover, tooth loss was assessed in 5117 adults categorized as either low or high risk as determined by the quantitative presence of risk factors such as cigarette smoking, diabetes, and *IL-1* genotype, respectively. Specifically, in adults at high risk, two annual dental visits were positively associated with reduced tooth loss when compared with high-risk individuals attending fewer annual dental visits (Giannobile *et al*. 2013).

In assessing the patient's risk for disease progression, systemic factors are only considered, if known, as the fifth risk indicator for recurrent disease in the functional diagram of risk assessment (see Fig. 48-3). In this case, the area of high risk is marked for this vector. If not known or absent, systemic factors are not taken into account in the overall evaluation of risk.

Research on the association and/or modifying influence on susceptibility and progression of periodontitis of physical or psychological stress is sparse (Cohen-Cole *et al*. 1981; Green *et al*. 1986; Freeman & Goss 1993). The hormonal changes associated with this condition, however, are well documented (Selye 1950).

Cigarette smoking

Consumption of tobacco, predominantly in the form of smoking or chewing, affects the susceptibility and the treatment outcome of patients with adult periodontitis. Classic explanations for these observations have included the association between smoking habits and poor oral hygiene, as well as lack of awareness of general health issues (Pindborg 1949; Rivera-Hidalgo 1986). More recent evidence, however, has established that smoking *per se* represents a true risk factor for periodontitis (Ismail *et al*. 1983; Bergström 1989; Bergström *et al*. 1991; Haber *et al*. 1993). In a young population (19–30 years of age), 51–56% of periodontitis was associated with cigarette smoking (Haber *et al*. 1993). The association of smoking and periodontitis has been shown to be dose-dependent (Haber *et al*. 1993). It has also been shown that smoking affects the treatment outcome after scaling and root planing (Preber & Bergström 1985), modified Widman flap surgery (Preber & Bergström 1990), and regenerative periodontal therapy (Tonetti *et al*. 1995). Furthermore, a high proportion of so-called refractory patients have been identified as smokers (Bergström & Blomlöf 1992). The impact of cigarette smoking on the long-term effects of periodontal therapy in a population undergoing SPT has been reported. Smokers displayed less favorable healing responses both at re-evaluation and during a 6-year period of SPT (Baumert-Ah *et al*. 1994). This was confirmed in another study in which higher percentages

of heavy smokers experienced more multiple (≥9) residual pockets (≥5 mm) than non-smokers both after active periodontal therapy (31.2% versus 7.3%, respectively) and after 11 years of SPT (52.4% versus 14.8%, respectively) (Matuliene *et al*. 2008). In this study, heavy smoking was found to be a significant risk factor for periodontitis progression. Moreover, smoking was the main statistically significant risk factor for the recurrence of periodontitis after 10.5 years of SPT in the 84 patients with periodontitis stage IV, grade C. More than half of the current smokers in this study showed a recurrence of disease at re-examination and had a ten-fold increased risk for a relapse compared with non-smokers (Bäumer *et al*. 2011). In a systematic review of 13 observational studies of long-term periodontal maintenance, smoking was found to be associated with tooth loss, which could be interpreted as the end-point event of periodontitis progression (Chambrone *et al*. 2010).

In conclusion, today there is enough evidence relating cigarette smoking to impaired outcomes during SPT. Therefore, it seems reasonable to include heavy smokers (>20 cigarettes/day) in a higher risk group during SPT.

In assessing the patient's risk for disease progression, environmental factors such as smoking must be considered as the sixth risk factor for recurrent disease in the functional diagram of risk assessment (see Fig. 48-3). While non-smokers (NS) and former smokers (FS) (>5 years since cessation) have a relatively low risk for recurrence of periodontitis, heavy smokers (HS), as defined by smoking more than one pack per day, are definitely at high risk. Occasional (OS; <10 cigarettes/day) and moderate smokers (MS; 11–19 cigarettes/day) may be considered at moderate risk for disease progression.

Conducting the patient's individual periodontal risk assessment

Based on the six parameters specified above, a multifunctional diagram is constructed for the PRA. In this diagram, the vectors have been constructed on the basis of the scientific evidence available. It is obvious that ongoing validation may result in slight modifications.

- *Low periodontal risk (PR) patient*: all parameters within the low-risk categories or at the most one parameter in the moderate-risk category (Fig. 48-3b)
- *Moderate PR patient*: at least two parameters in the moderate category, but at most only one parameter in the high-risk category (Fig. 48-3c)
- *High PR patient*: at least two parameters in the high-risk category (Fig. 48-3d).

The application of the multifunctional diagram for the subject-based PRA was validated in several studies. A 4-year prospective cohort study (Persson *et al*. 2003) yielded complete periodontal stability after individually tailored SPT intervals for all patients with a negative *IL-1* gene polymorphism. For the *IL-1* genotype-positive patients, however, the PRA resulted only in periodontal stability for 90% of the patients. On the other hand, two recently published studies of 100 and 160 patients evaluating the results of SPT of mean duration of >10 years demonstrated that patients with a high-risk profile after active periodontal therapy were more prone to recurrence of periodontitis (Matuliene *et al*. 2010) and to tooth loss (Eickholz *et al*. 2008; Matuliene *et al*. 2010) than the patients with a moderate- or a low-risk profile.

Summary: The subject risk assessment may estimate the risk for susceptibility to progression of periodontal disease. It consists of an assessment of the level of infection (full-mouth BoP), the prevalence of residual periodontal pockets, tooth loss, an estimation of the loss of periodontal support in relation to the patient's age, an evaluation of the systemic conditions of the patient, and finally, an evaluation of environmental and behavioral factors such as smoking and stress. All these factors should be contemplated and evaluated together. A functional diagram (see Fig. 48-3) may help the clinician in determining the risk for disease progression at the subject level. A tool to compute patient-level periodontal risk profile is found online at www.perio-tools.com/pra. This may be useful in customizing the frequency and content of SPT visits.

Tooth risk assessment

It has to be realized that the subject-based risk assessment may be supplemented by the individual tooth risk assessment which encompasses an estimation of the residual periodontal support, an evaluation of tooth positioning, furcation involvements, presence of iatrogenic factors, and a determination of tooth mobility to evaluate functional stability. A risk assessment at tooth level may be useful in evaluating the prognosis and function of an individual tooth and may indicate the need for specific therapeutic measures during SPT visits.

Site risk assessment

It is suggested that patients are evaluated at *three different levels*. At the *patient-level*, loss of support in relation to patient age, full-mouth biofilm and/or BoP scores, and prevalence of residual pockets are evaluated, together with the presence of systemic conditions or environmental factors, such as smoking, which can influence the prognosis. The clinical utility of this first level of risk assessment influences primarily the determination of the SPT frequency and time requirements of maintenance. It should also provide a perspective for the evaluation of the risk assessment conducted at the tooth and tooth-site levels.

At the *tooth- and tooth-site levels*, residual periodontal support, inflammatory parameters and their persistence, presence of difficult to access ecologic niches, such as furcations, and presence of iatrogenic factors have to be put into perspective with the patient's overall risk profile. The clinical utility of tooth and tooth-site risk assessment relates to the rational allocation of the time available for therapeutic intervention to the sites with higher risk, and possibly to the selection of different forms of therapeutic intervention.

Objectives for supportive periodontal therapy

The objective of maintenance care must be the continued preservation of gingival and periodontal health, obtained as a result of the active periodontal treatment. Irrespective of whether or not additional treatment such as prosthetic reconstructions or placement of implants has been rendered, the regular and adequate removal of supragingival biofilm by the patient is, therefore, a prerequisite for a good long-term prognosis. In order to achieve these goals, regular clinical re-evaluations with appropriate interceptive treatment, continued psychological support and encouragement of the patient, and a lifelong commitment by the therapists are required.

General rules regarding frequency of maintenance care visits are difficult to define. However, there are a few aspects to consider in this respect: the patient's individual oral hygiene standard, the prevalence of sites exhibiting BoP, and the pretherapeutic attachment level and alveolar bone height. This in turn means that patients with suboptimal biofilm control and/or concomitant high prevalence of bleeding sites should be recalled more frequently than patients exhibiting excellent biofilm control and healthy gingival tissues. Nevertheless, patients with healthy gingival conditions, but with a severely reduced height of periodontal support, should also be recalled at short time intervals (not exceeding 3–4 months) in order to exclude or at least reduce the risk of additional tooth loss. In most of the longitudinal studies referred to above, positive treatment results were maintained with regular maintenance care provided at 3–6-month intervals. It seems reasonable to commence post-therapeutic maintenance with SPT visits once every 3–4 months and then shorten or prolong these intervals in accordance with the aspects discussed above.

Since clinical attachment levels are usually stable 6 months following active periodontal therapy, it has been suggested that the first 6 months after completion of therapy be considered a healing phase (Westfelt *et al*. 1983b) during which frequent professional tooth cleaning has been recommended. Following this healing phase, it is generally agreed to recall SPT patients treated for periodontal disease at intervals of 3–4 months in a well-organized system of SPT. It has to be realized that tissue contours may be subjected to remodeling processes despite stable clinical attachment levels and, hence, morphologic changes may still improve the accessibility of all tooth surfaces to oral hygiene practices for months and even years. Proper oral hygiene practices appear to be the most important patient factor that can guarantee long-term stability of treatment results (Knowles *et al*. 1979; Ramfjord *et al*. 1982; Lindhe & Nyman 1984; Ramfjord *et al*. 1987). This, in turn, necessitates optimization of the patient's skills and continuous motivation and reinforcement to perform adequate mechanical oral hygiene practices. It is obvious that regular visits for SPT should be scheduled soon after completion of cause-related therapy, even if periodontal surgical procedures are still to be performed following a careful re-evaluation of the tissue response. To postpone the organization of a maintenance care program until corrective procedures such as surgery, endodontic, implant, operative or reconstructive therapy have been performed may reinforce a possible misconception by the patient that the professional visits to a therapist or hygienist guarantee positive treatment outcomes and optimal long-term prognosis rather than the patient's own regular performance of individually optimal and adequate oral hygiene practices.

Determination of personalized supportive periodontal therapy intervals

As the PRA is applied after periodontal therapy and then at intervals of approximately 5–10 years, it is desirable to develop an algorithm for fine-tuning the interval between SPT visits to be applied at every visit. The basis for such an effort comes from a recently published study (Ramseier *et al*. 2019). In this study, a total of 445 patients were followed over a period of at least 5 years resulting in a total 8741 SPT visits evaluated. Special attention had been given to the profile of residual pockets of various depths and the longitudinal performance of the patients depending on their SPT interval. An algorithm was constructed in which the interval between SPT visits was tailored to the residual pocket profile of a given patient. Generally, the pocket probing depths tended to decrease with shorter intervals, whereas, with longer SPT intervals, the number of residual pockets increased between two subsequent visits. The intersection of the numbers of residual pockets that were increasing or decreasing, respectively, resulted in a number of thresholds determining the interval which maintained periodontal stability (Fig. 48-5).

In Fig. 48-5 it is evident that, for example, a patient, following an SPT interval of 3 months, may yield periodontal stability with 30% of 4 mm or more, 20% of at least 5 mm, and even 4% of 6 mm PPD. However, if the SPT interval is higher (4 months) the respective percentages for residual pockets tolerated for periodontal stability are 20% for ≥4 mm, 10% for

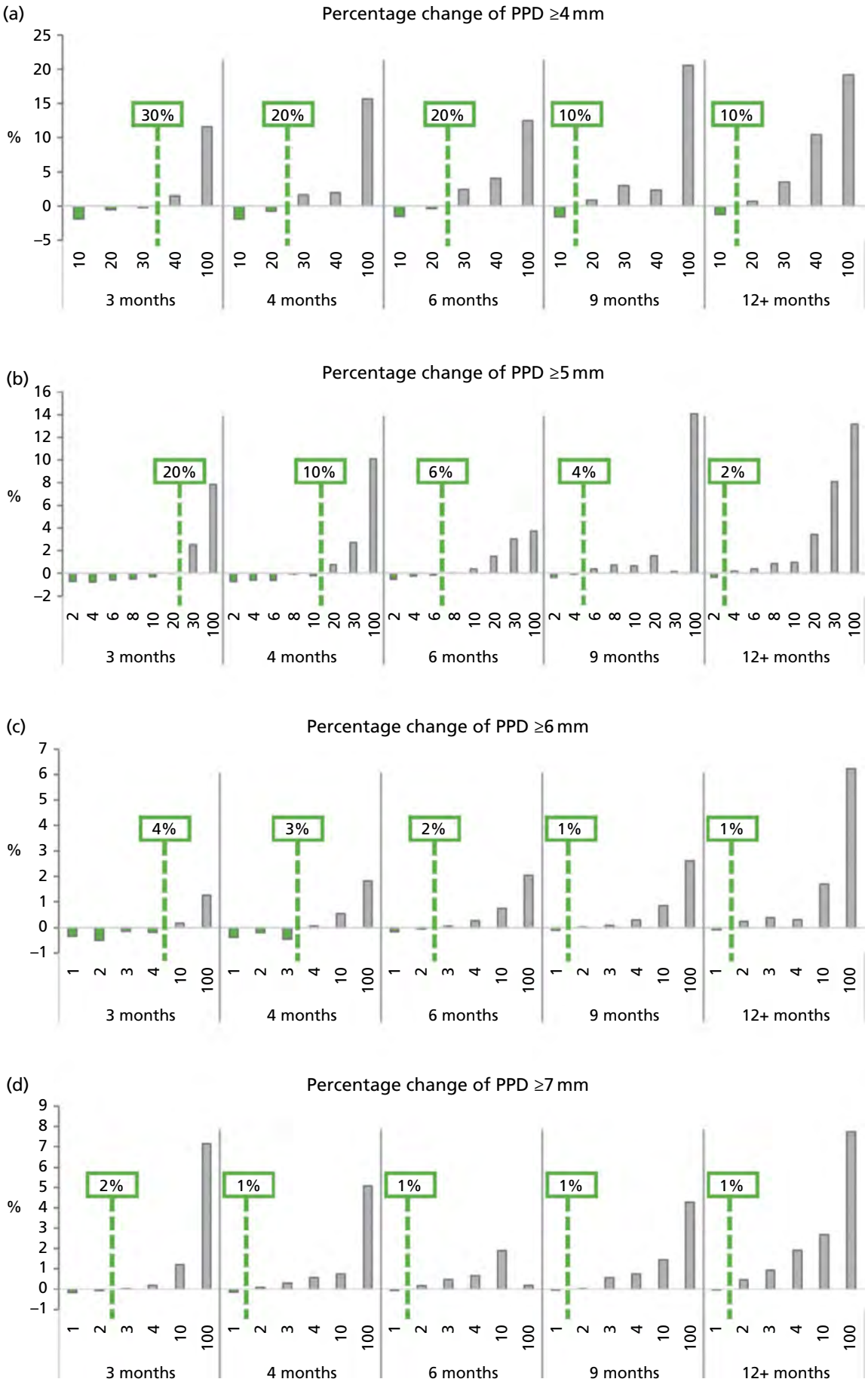

Fig. 48-5 Percentage change increase (+) and decrease (-) of residual periodontal probing depths (PPD) from 11 842 supportive periodontal therapy (SPT) visits and 883 patients in relation to the length of SPT intervals (3, 4, 6, 9, and 12+ months) and the category of residual PPD recorded at the previous SPT visit. Empirically determined thresholds of no change of PPD are labelled and indicated by dashed lines in (a) for PPD% ≥4 mm (-5–25%), (b) for PPD% ≥5 mm (-2–16%), (c) for PPD% ≥6 mm (-1–7%), and (d) for PPD% ≥7 mm (-1–9%). (Source: Data from Ramseier *et al*. 2019. Reproduced with permission from John Wiley & Sons.)

≥5 mm, and 3% for ≥6 mm. Moreover, if the SPT interval was 6 months, periodontal stability was achieved with <20% of 4 mm pockets, 6% of 5 mm, and 2% of 6 mm pockets. This clearly indicates that only very few residual pockets are compatible with periodontal stability.

Such an analysis of the profile of residual pockets may be calculated on www.perio-tools.com/spt.

Supportive periodontal therapy in daily practice

The SPT visit should be planned to meet the patient's individual needs. It basically consists of four different sections which may require various amounts of time during a regularly scheduled visit:

- Examination, re-evaluation, and diagnosis (ERD)
- Motivation, re-instruction, and instrumentation (MRI)
- Treatment of re-infected sites (TRS)
- Polishing of the entire dentition, application of fluorides, and determination of future SPT (PFD).

The SPT visit (Fig. 48-6) generally consists of 10–15 minutes of diagnostic procedures (ERD) followed by 30–40 minutes of motivation, re-instruction, and instrumentation (MRI), with the instrumentation concentrated on the sites diagnosed with persistent inflammation. Treatment of re-infected sites (TRS) may include small surgical corrections, applications of local drug delivery devices or just intensive instrumentation under local anesthesia. Such procedures, if judged necessary, may require an additional appointment. The SPT visit is normally concluded with polishing of the entire dentition, application of fluorides, and another assessment of the situation, including the determination of future SPT visits (PFD). Approximately 5–10 minutes must be reserved for this section.

Examination, re-evaluation, and diagnosis

Since patients on SPT may experience significant changes in their health status and the use of medications, an update of the information on general health issues is appropriate. Changes in health status and medications should be noted. In middle-aged to elderly patients especially, these aspects might influence the future management of the patient. An extraoral and intraoral soft tissue examination should be performed at any SPT visit to detect any abnormalities and to act as a screening for oral cancer. The lateral borders of the tongue and the floor of the mouth should be inspected in particular. An evaluation of the patient's risk factors will also influence the choice of future SPT and the determination of the SPT interval at the end of the maintenance visit. Following the assessment of the subject's risk factors, the tooth site-related risk factors are evaluated.

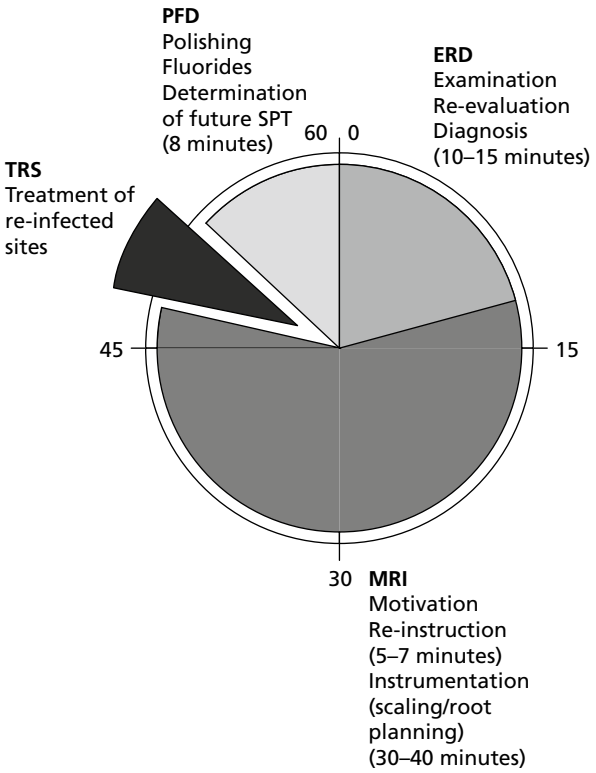

Fig. 48-6 An supportive periodontal therapy (SPT) visit is divided into four sections. (1) Examination, re-evaluation, and diagnosis (ERD) providing information on stable and inflamed sites. This segment uses 10–15 minutes. (2) Motivation, re-instruction of oral hygiene where indicated, and instrumentation (MRI) use the bulk of the visit (30–40 minutes). Sites diagnosed as not stable are instrumented. (3) Treatment of re-infected sites (TRS) may require a second appointment. (4) Polishing all tooth surfaces, application of fluorides, and determination of the future SPT interval (PFD) conclude the visit (5–10 minutes).

As indicated above, the diagnostic procedure usually includes an assessment of the following:

- Oral hygiene
- Determination of sites with BoP, indicating persistent inflammation
- Scoring of clinical probing depths and clinical attachment levels. The latter is quite time-consuming and requires the assessment of the location of the cementoenamel junction as a reference mark on all (six) sites of each root. Therefore, an SPT evaluation usually only includes scoring of clinical probing depths
- Inspection of re-infected sites with pus formation
- Evaluation of existing reconstructions, including vitality checks for abutment teeth
- Exploration for carious lesions.

All these evaluations are performed for both teeth and oral implants. Occasionally, conventional dental radiographs should be obtained at SPT visits. Especially for devitalized teeth, abutment teeth, and oral implants, single periapical films exposed with a parallel and preferably standardized technique are

of great value. Bitewing radiographs are of special interest for caries diagnostic purposes. They also reveal biofilm-retentive areas such as overhanging fillings and ill-fitting crown margins. Since only approximately 10–15 minutes are available for this section, these assessments have to be performed in a well-organized fashion. It is preferable to have a dental assistant available to note all the results of the diagnostic tests unless a voice-activated computer-assisted recording system is used.

Motivation, re-instruction, and instrumentation

This aspect uses most of the available time of the SPT visit. When informed about the results of the diagnostic procedures, for example the total percentage BoP score or the number of pockets exceeding 4 mm, the patient may be motivated either in a confirmatory way in the case of low scores or in a challenging fashion in the case of high scores. Since encouragement usually has a greater impact on future positive developments than negative criticism, every effort should be made to acknowledge the patient's performance.

Patients who have experienced a relapse in their adequate oral hygiene practices need to be further motivated. Positive encouragement is especially appropriate if a patient's personal life situation has influenced his/her performance. Standard "lecturing" should be replaced by an individual approach.

Occasionally, patients present with hard tissue lesions (wedge-shaped dental defects) which suggest overzealous and/or faulty mechanical tooth cleaning (Fig. 48-7). Such habits should be broken, and the patient re-instructed in toothbrushing techniques which emphasize vibratory rather than scrubbing movements.

Because it appears impossible to instrument 168 tooth sites in a complete dentition in the time allocated, only those sites which exhibit signs of inflammation and/or active disease progression will be re-instrumented during SPT visits. Trauma from repeated instrumentation of healthy sites will inevitably result in continued loss of attachment (Lindhe *et al*. 1982a). In contrast, residual pockets of ≥6 mm may lead to periodontitis progression and tooth loss (Badersten *et al*. 1990; Claffey *et al*. 1990, Matuliene *et al*. 2008). Interestingly, the association of the residual PPD with tooth loss over a mean of 11.3 years of maintenance was calculated at the site and at the tooth level (Table 48-3). Starting from a residual PPD of 4 mm, the increase of the PPD by 1 mm was highly statistically significantly associated with tooth loss (Matuliene *et al*. 2008). Hence, all the BoP-positive sites and all pockets with a PPD exceeding 4 mm are carefully rescaled and root planed as instrumenting healthy sites repeatedly will inevitably result in mechanically induced loss of attachment (Lindhe *et al*. 1982a).

Similar observations were made in clinical studies by Claffey *et al*. (1988): loss of clinical attachment levels immediately following instrumentation was

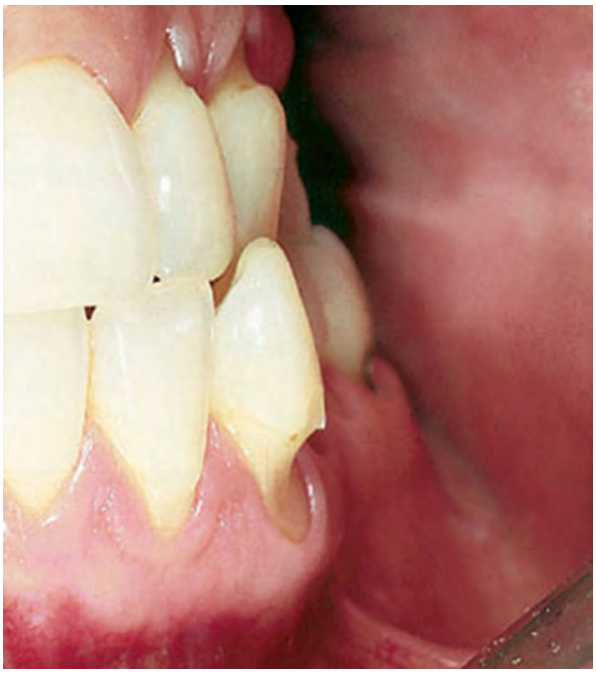

Fig. 48-7 Wedge-shaped defects apical to the cementoenamel junction following recession of the gingival tissues resulting from overzealous or faulty toothbrushing.

Table 48-3 Results from multilevel logistic regression models for the association of site probing pocket depth (PPD) and deepest PPD of a tooth at the end of therapy with tooth loss during supportive periodontal therapy of mean duration of 11.3 years (not accounting for bleeding on probing).

PPD (mm)	Site level			Tooth level		
	OR	95% CI	*P* value	OR	95% CI	*P* value
≤3	1.0					
4	2.6	2.2–3.1	<0.0001	2.5	1.8–3.6	<0.0001
5	5.8	4.3–7.9	<0.0001	7.7	4.8–12.3	<0.0001
6	9.3	6.2–13.9	<0.0001	11.0	6.1–20.1	<0.0001
≥7	37.9	17.9–80.2	<0.0001	64.2	24.9–165.1	<0.0001

OR, odds ratio; CI, confidence interval.(Source: Adapted from Matuliene *et al*. 2010. Reproduced with permission from John Wiley & Sons.)

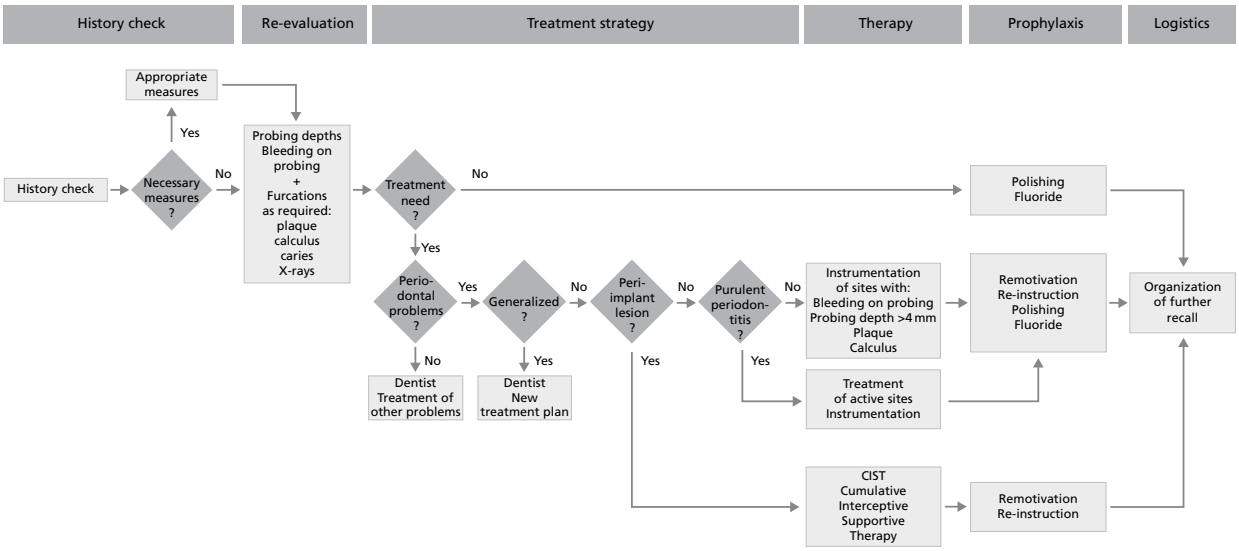

Fig. 48-8 Flow diagram of supportive periodontal therapy (SPT) with strategic decision tree for the SPT visit.

observed in 24% of the sites. It is also known from regression analyses of several longitudinal studies (e.g. Lindhe *et al*. 1982b) that probing attachment may be lost following instrumentation of pockets below a "critical probing depth" of approximately 2.9 mm. Instrumentation of shallow sulci is, therefore, not recommended. As it has been shown in several studies that sites that do not bleed on probing represent stable sites (Lang *et al*. 1986, 1990; Joss *et al*. 1994), it appears reasonable to leave non-bleeding sites for polishing only and to concentrate on periodontal sites with a positive BoP test or PPD of >5 mm. To protect the hard tissues, root planing should be performed with great caution. The deliberate removal of "contaminated" cementum during SPT is no longer justified (Nyman *et al*. 1986, 1988; Mombelli *et al*. 1995). During SPT visits, root surface instrumentation should be aimed especially at the removal of subgingival biofilm rather than "diseased" cementum. This may require a more differentiated approach than hitherto recommended. In this respect, the use of ultrasonics may have to be re-evaluated.

Treatment of re-infected sites

Single sites, especially furcation sites or sites that are difficult to access, may occasionally be re-infected and demonstrate suppuration. Such sites require a thorough instrumentation under anesthesia, the local application of antibiotics in controlled-release devices, or even open debridement with surgical access. It is evident that such therapeutic procedures may be too time-consuming to be performed during the routine SPT visit, and hence, it may be necessary to reschedule the patient for another appointment. Omission of thorough retreatment of such sites or only performing incomplete root instrumentation during SPT may result in continued loss of probing attachment (Kaldahl *et al*. 1988; Kalkwarf *et al*. 1989).

Treatment choices for re-infected sites should be based on an analysis of the most likely causes for the re-infection. Generalized re-infections are usually the result of inadequate SPT. Although not all sites positive for BoP may further progress and lose attachment, high BoP percentages call for more intensive care and more frequent SPT visits. Sometimes, a second visit 2–3 weeks after the SPT visit may be indicated to check the patient's performance in oral home care. It is particularly important to supervise patients closely for advanced periodontitis if they have a high subject risk assessment (Westfelt *et al*. 1983b; Ramfjord 1987). Local re-infections may either be the result of inadequate biofilm control in a local area or the formation of ecologic niches conducive to periodontal pathogens. The risk assessment at the tooth level may identify such niches which are inaccessible for regular oral hygiene practices. Furcation involvements often represent special periodontal risk factors which may require additional therapy to be performed following diagnosis in the regular SPT visit.

Polishing, fluorides, and determination of supportive periodontal therapy interval

The SPT visit is concluded with polishing the entire dentition to remove all remaining soft deposits and stains. This may give the patient a feeling of freshness and facilitates the diagnosis of early carious lesions. Following polishing, fluorides should be applied in high concentration in order to replace the fluorides which may have been removed by instrumentation from the superficial layers of the teeth. Fluoride or chlorhexidine varnishes may also be applied to prevent root surface caries, especially in areas with gingival recession. The determination of future SPT visits must be based on the patient's risk assessment.

Summary: Figure 48-8 provides a flowchart for SPT. The SPT visit is divided into four sections. Whereas the first 10–15 minutes are reserved for examination, re-evaluation, and diagnosis, the second and most time-consuming section of 30–40 minutes is devoted to re-instruction and instrumentation of sites identified to be at risk in the diagnostic process. Some re-infected sites may require further treatment, and hence, the patient may have to be rescheduled for an additional appointment. The SPT visit is concluded by polishing the dentition, applying fluorides, and determining the frequency of future SPT visits.

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Lindhe's Clinical Periodontology and Implant Dentistry, Seventh Edition. Edited by Tord Berglundh, William V. Giannobile, Niklaus P. Lang, and Mariano Sanz.

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