Periodontal Disease and Overall Health: A Clinician’s Guide
Second Edition

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ISBN-10: 0-9662849-0-9

Published by…

Professional Audience Communications, Inc.
PO Box 243
Yardley, Pennsylvania 19067 USA

Editorial Quality Control: Teri S. Siegel
Copyediting/Proofreading: Alison T. Kelley
Layout and Design: Horizons Advertising & Graphic Design
Cover Design: Horizons Advertising & Graphic Design
Indexing: Allegheny Writing & Publishing Services, LLC
Publisher: Stephen M. Siegel

Printed in the United States of America

Last digit is the print number: 6 5 4 3 2 1
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From the Editors

Dear Colleagues:

We are very pleased to have had the privilege of assembling and editing the 2nd Edition of the textbook, *Periodontal Disease and Overall Health: A Clinician's Guide*.

The relationship of oral disease to overall disease is certainly not a new concept. For centuries, the role of oral infection and inflammation in contributing to diseases elsewhere in the body has been studied and reported. Going back to ancient times in Greece, we learn that Hippocrates treated two patients suffering from joint pain by removal of teeth. Clearly, this was an early example of oral disease being associated with afflictions elsewhere in the body. Then, moving forward in time from 1912 to around 1950, the era of “focal infection” dominated our thinking. Reports by individuals such as WD Miller, William Hunter, and Frank Billings noted that in their opinion many of the diseases of humans could be traced to infections elsewhere in the body, such as the teeth and gums, the tonsils, or the sinuses. While these observations were not supported by sound scientific evidence, and in fact led to largely incorrect practices, they nonetheless brought attention to the effect of the mouth on the rest of the body.

Then in 1989, with a series of intriguing reports from Finland, the current interest in the role of oral health and disease on contributing to general health and systemic conditions was launched. Kimmo Mattila and his coworkers reported that individuals presenting to the emergency room with a myocardial infarction were overwhelmingly likely to have periodontal disease. Might periodontal disease be a risk factor for cardiovascular disease? Since then, a phenomenal body of work has been directed at understanding how periodontal disease might affect distant sites and organs, and thus have an effect on overall health.

Recent studies of the human microbiome using DNA sequencing technologies have revealed new insights into the possible mechanisms that help explain how oral infections can occur in distinct sites such as atheromas, the colon, and reproductive tissues. These findings, pointing to a “mobile microbiome,” and other new research findings are included in this revision.

Renowned clinicians and scientists worldwide have studied the relationship of periodontal disease to overall health and disease, and along the way several conferences and workshops have been convened to examine the evidence to date for the relationship between periodontal disease and the risk for systemic conditions. At one of those conferences, in January 2008, we discussed the need for a textbook that would summarize and put into context the current information on periodontal disease and systemic disease together for students of dentistry and medicine. Happily for us, Foti Panagakos and his team at the Colgate-Palmolive Company agreed to support, through an educational grant to the publisher, the undertaking of this textbook. We were fortunate to have assembled a group of respected and scholarly clinicians and scientists who, in 18 chapters, provide a current and thoughtful perspective on the relationship of periodontal disease to systemic conditions.

It is a pleasure to present the second edition of this textbook. We hope you find it useful and that you enjoy it.

Sincerely,

Robert J. Genco, DDS, PhD

Ray C. Williams, DMD
Dear Reader:

I am delighted to be presenting the Second Edition of the textbook *Periodontal Disease and Overall Health: A Clinician's Guide*. And how appropriate that we launch this new edition at a time when we commemorate the 100th anniversary of the American Academy of Periodontology, an organization dedicated to improving the overall health of patients.

The dynamic nature of the science behind the oral-systemic relationship demanded an update based on new learnings since the textbook was first published in 2010. It is noteworthy that nearly all of our contributing authors in the first edition concurred with this assessment and are on board for the second edition.

This edition is the result of a 15-month updating process based on the most contemporary thinking behind what the dental and medical literature suggest is an association between oral and systemic diseases. As before, the book delves into the sciences behind diabetes mellitus, atherosclerosis, adverse pregnancy events, respiratory diseases, osteoporosis, rheumatoid arthritis, and cancer; looks at risk factors in common with periodontal disease, such as inflammatory processes; then, logically, follows with a discussion of the steps needed for comprehensive comanagement of the diseases by both dental and medical caregivers.

This Second Edition of *Periodontal Disease and Overall Health: A Clinician's Guide* has been developed to serve as a resource for dental students, dental hygiene students, medical students, faculty members of dental schools, dental hygiene programs, and medical schools, and for practicing dental and medical professionals. As alliances between the dental and medical professions grow, we believe this textbook will provide important information to facilitate a more effective collaboration relative to the patients they treat.

We would like to again express our deep appreciation to the book’s Editors, Dr. Robert J. Genco and Dr. Ray C. Williams. It was through their knowledge of this vitally important subject, their professional relationships with the key opinion leaders doing research in this field, their backgrounds as highly regarded researchers and educators in dentistry, and their encouragement to publish an update to our 2010 edition that we are able to bring you this significant work.

Since the launch of its first toothpaste in 1873, the Colgate-Palmolive Company has been a world leader in oral care, both through cutting-edge therapeutics, as well as important educational services to the dental professions. The Second Edition of *Periodontal Disease and Overall Health: A Clinician's Guide*, which has been produced and distributed through an educational grant from the company (by which the company provided funding to the publisher), is a prime example of our continuing commitment to ensuring the dental professions’ education.

Sincerely,

Fotinos S. Panagakos, DMD, PhD
Global Director, Scientific Affairs

The views expressed in this textbook are those of the authors, not necessarily those of the Colgate-Palmolive Company.
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“A person can’t have good general health without good oral health.”

—Former U.S. Surgeon General C. Everett Koop
INTRODUCTION
We welcome you to the Second Edition of Periodontal Disease and Overall Health: A Clinician’s Guide. Research into the relationship between periodontal disease and general health continues to emerge at a rapid pace. Thus, an update to our 2010 edition seems appropriate and necessary.

Periodontal disease is one of the most common diseases of man and is responsible for most of the tooth loss in adults. This oral disease has received considerable attention in the last several decades, and a new understanding of it is emerging. The microbial causes of periodontal disease, the mechanisms through which periodontal tissues are destroyed, the effect of the host on periodontal disease expression, and the impact periodontal disease has on overall health have been subjects of intense study. Understanding the complex interaction between chronic infections such as periodontal disease and systemic conditions such as cardiovascular disease has led to a new way of thinking about the importance of periodontal disease in overall health.

Periodontal Disease as an Integral Link to Systemic Disease
According to the National Center for Health Statistics of the Centers for Disease Control and Prevention, the seven leading causes of death in the United States in 2010 were heart disease (597,689), cancer (574,743), chronic lower respiratory disease (130,080), stroke/cerebrovascular diseases (129,476), unintentional accidental injuries (120,859), Alzheimer’s disease (83,494), and diabetes (69,071). Five of these, including heart disease, cancer, respiratory disease, stroke, and diabetes, are chronic diseases related to periodontal disease.1 By successfully meeting the challenge to improve oral health through the management of periodontal disease, general health will also be advanced through shared approaches targeting common risk factors. To best address the common risk factors and interactions between oral and systemic disease, it is important to understand the extent to which periodontal disease is related to certain systemic diseases, the historical foundations of current therapeutic approaches, the role of inflammation, and the possibilities for intervention.

THREE HISTORICAL ERAS OF PERIODONTAL DISEASE
In the last 50 years, considerable progress has been made in understanding the etiology and pathogenesis of periodontal disease and its interactions with the host. The studies and concepts can be described as having occurred in three phases or eras: the etiopathologic (or host-parasite) era, the risk factor era, and, most recently, the periodontal disease-systemic disease era.

Etiopathologic Era
The etiopathologic era included landmark investigations into the microbial etiology and pathogenesis of periodontal disease. The role of bacteria as a cause of periodontal disease was demonstrated by a series of seminal studies conducted from the 1960s to the
1980s. Classic studies by Löe and colleagues\textsuperscript{3} clearly demonstrated that microbial plaque buildup on the teeth was associated with the onset of gingivitis and that the removal of microbial plaque resulted in the resolution of gingivitis. These studies provided unarguable evidence that microbial dental plaque buildup, rather than other suspected agents such as calculus, was responsible for gingivitis.

In the 1970s and 1980s, Socransky and coworkers\textsuperscript{4} conducted studies showing that specific organisms were associated with periodontal disease (for review see Socransky and Haéfle, 2005). These studies identified several categories of organisms, ranging from early colonizers, which are commensal and relatively nonviral to, moderately virulent organisms, which bridged the early colonizers and interconnected them to specific pathogens such as Porphyromonas gingivalis, Tannerella forsythensis and Treponema denticola. Research from many investigators found that the specific pathogens, in combination with the early colonizers and moderately virulent organisms, form a complex microflora that exists as a biofilm within the periodontal pocket. More recent studies using 16S rRNA sequencing techniques, which reveal most if not all of the organisms at a site (i.e., the microbiome), have revealed a set of new potential pathogens.\textsuperscript{5} These new studies support the shift from a gram-positive community in health to a gram-negative–dominated community in periodontal disease. Several new genera and species—some not able to be cultivated and others newly described—emerge as potential periodontal pathogens.

Microbiome analysis by 16S rRNA sequencing has opened a new and fruitful approach to studying the migration of organisms from the oral community to distant sites, a phenomenon that may help explain the many associations of periodontal disease with systemic diseases such as heart disease, colon cancer, and fatal prenatal septicemia.\textsuperscript{6}

Other investigators began to explain the pathogenesis of periodontal disease, describing how the host in fact was responsible for tissue destruction. We came to understand that the initial response to the bacteria on the tooth and subgingivally is a series of immunopathologic actions. Antibodies to these bacteria are formed, which in combination with neutrophils, provide important protection.\textsuperscript{7,8} It was seen that when neutrophils are suppressed, more severe periodontal disease occurs. Soon thereafter, the role of the macrophage was understood. This important cell invades the gingival tissue and, on triggering by bacterial products such as endotoxin, produces proinflammatory cytokines and matrix metalloproteinases that destroy the connective tissues of the periodontium. Inflammatory mediators such as prostaglandin E\textsubscript{2} and interleukin 1 induce alveolar bone resorption. As the role of the host becomes more understood, inflammation and the inflammatory response can explain much of the tissue destruction caused by periodontal disease.\textsuperscript{9,10}

**Risk Factor Era**

The second era of discovery brought the identification of risk factors that influence or modulate the expression of periodontal disease. Epidemiologic studies reported that the risk factors in and of themselves were not etiologic, but rather modified or exaggerated the etiopathologic processes set into motion by the causative bacteria. The following risk factors were identified in the late 1980s and early 1990s: genetic elements, behaviors such as smoking, and acquired disorders such as diabetes mellitus.\textsuperscript{11–13} The concept of modifying risk factors as part of the management of periodontal disease is now well established.

**Periodontal Disease-Systemic Disease Era**

The understanding of periodontal disease is currently focused on the relation of peri-
odontal disease as a risk for certain systemic diseases. Robust studies have shown that periodontal disease is independently associated with certain systemic diseases such as cardiovascular disease, diabetes and complications of diabetes, adverse pregnancy outcomes, and respiratory infections.

Evidence supporting the association of periodontal disease with systemic disease was reviewed by a panel of experts from the United States and throughout Europe. The authors concluded that scientific evidence shows a strong association between periodontal disease and several systemic disorders. Periodontal disease likely contributes to the bacterial burden that causes a destructive systemic inflammatory response, thus contributing to these diseases. Treatment of periodontal disease reduces this burden. It is clear that periodontal disease, especially severe periodontitis, may also initiate general health issues.

The periodontal disease-systemic disease concept has amassed enough evidence and support that it is now believed that findings about this interrelationship should be incorporated into the curriculum in schools for health professionals and should also be made available to enhance the knowledge base of practicing healthcare professionals.

The association of periodontal disease with several systemic conditions, such as diabetes and cardiovascular disease, is likely related to the inflammatory response associated with periodontal disease. C-reactive protein is an important marker of the inflammatory response and is elevated in subjects with periodontal disease; its levels in peripheral blood are reduced when periodontal disease is treated. Another indication of the systemic inflammatory response associated with periodontal disease is the presence of cytokines, including tumor necrosis factor alpha and interleukins 1 and 6, often found in the circulation of patients with periodontal disease. Other conditions also contribute to a systemic inflammatory response such as rheumatoid arthritis, psoriasis, and obesity. This chronic systemic inflammatory response in turn increases the risk for cardiovascular disease, diabetes and complications of diabetes, adverse pregnancy outcomes, and possibly some cancers. The research supporting these associations is discussed in detail in the following chapters.

THE ROLE OF DENTISTRY IN RISK FACTOR MODIFICATION

Common Risk Factors
A theme throughout this text is that periodontal disease and several diseases associated with periodontal disease are chronic diseases, often associated with aging. Those individuals with cardiovascular disease, diabetes, and cancer often share common risk factors with those with periodontal disease, such as smoking and obesity. These common risk factors may account for some of the associations. But at least for cardiovascular disease, diabetes, respiratory diseases, and some forms of cancer associated with periodontal disease, they are not entirely accounted for because periodontal disease is also an independent risk factor for these diseases in nonsmokers. Aside from the issue of causation; the clinical implication is that management of these common risk factors will likely reduce the risk for periodontal disease as well as for cardiovascular disease, diabetes, cancer, and respiratory diseases. This is a compelling argument for proactive common risk factor management by dental professionals, since it can result in better general health as well as in better oral health.

GOALS FOR THIS TEXTBOOK
Much research is focused on understanding how periodontal disease increases the risk for systemic diseases. It is not yet clear what impact the biofilm in the oral cavity might have on distant sites and organs; likewise the
role of the inflammatory response is not fully understood. Some chapters review the biologic plausibility of periodontal disease as a risk for systemic conditions. Mechanisms through which periodontal disease can confer this risk are also presented.

The overall goal of this second edition of the textbook is to present the latest emerging and compelling evidence that periodontal disease is a risk for several systemic conditions and to look at the role of oral health in contributing to overall health. As before, this book also seeks to provide the reader with a guide to patient management in which dentistry and medicine work together.

Textbook Organization
The chapters in this book are organized in a manner that is consistent with the first edition.

The initial chapters outline the basics of understanding periodontal disease and its interrelationship with systemic disease: Chapter 2 discusses the causes and pathogenesis of periodontal disease; the role of infection and inflammation in periodontal disease is examined in Chapter 3; and the history of the oral disease-systemic disease relationship is explained in Chapter 4.

An overview of diabetes (Chapter 5) and atherosclerotic diseases (Chapter 7) are followed by chapters that describe the relation of periodontal disease to these conditions (Chapters 6 and 8, respectively).

The next chapters examine the evidence for periodontal disease being a risk for adverse pregnancy outcomes (Chapter 9), respiratory diseases (Chapter 10), osteoporosis (Chapter 11), rheumatoid arthritis (Chapter 12), and cancer (Chapter 13).

The last section discusses the comangement of periodontal disease in diabetes (Chapter 14), cardiovascular disease (Chapter 15), pregnancy (Chapter 16), and other conditions associated with periodontal disease (Chapter 17). Finally, Chapter 18 describes the role of dental professionals in the education of the public and other health professionals about the oral health-general health interrelationship.

Our Hope for This Textbook
The hope of the authors and editors is that this textbook will provide an up-to-date understanding of the information that details the relation of periodontal disease to systemic disease, with each chapter outlining a state-of-the-art understanding of the optimal management of patients. This textbook has been prepared as a resource for dental students, dental hygiene students, faculty members of dental educational institutions, and dental professionals in general. We also believe this resource will prove valuable to students as well as practicing members of other health professionals in the medical community. The integration of medicine and dentistry grows daily, and a common resource such as this textbook can serve as a constructive tool to help the two disciplines work collaboratively.

The editors would like to thank the authors and coauthors of this textbook for their role in preparing and updating information in a complete, yet concise and readable manner in this revision. We are hopeful that this textbook will find broad readership and will be useful to the dental and medical communities and—most important—that it will result in better general health as well as oral health.

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CHAPTER 2
Periodontal Diseases: Classification, Epidemiology, Pathogenesis, and Management

Ying Gu, Maria Emanuel Ryan, Bruno G. Loos

INTRODUCTION
Periodontal diseases are serious chronic infections that involve destruction of the tooth-supporting apparatus, including the gingiva, periodontal ligament, and alveolar bone. These diseases are initiated by a local accumulation of bacteria (dental plaque) adjacent to the tooth in susceptible persons. Periodontal diseases, including gingivitis and periodontitis, can affect one tooth or many teeth and, if left untreated, can lead to tooth loss, particularly in adults. It is the most common dental condition in adults and also one of the most common chronic inflammatory diseases, possibly affecting a majority of the population in the world. Moreover, it has been indicated as a contributing factor to other systemic diseases such as diabetes and cardiovascular diseases. Although plaque is essential for the initiation of periodontal diseases, most destructive processes associated with these diseases are due to an excessive host response to the bacterial challenge. Therefore, periodontal disease is a multifactorial, complex disease. The purpose of this chapter is to provide a general overview of the types of periodontal disease, the risk factors associated with the disease, and the etiology, pathogenesis, and management of periodontal diseases.

TYPES OF PERIODONTAL DISEASE
For many years, periodontal diseases have been described as being divided into two general categories based on whether there is loss of connective tissue attachment and alveolar bone loss: gingivitis and periodontitis. Gingivitis is considered a reversible form of the disease and generally involves inflammation of the gingival tissues without loss of connective tissue attachment.\(^1\) Periodontitis has been defined as gingival inflammation at sites of pathologic detachment of collagen fibers from cementum, apical migration of the junctional epithelium, and radiographic evidence of alveolar bone loss. The inflammatory events associated with connective tissue attachment loss lead to the resorption of tooth-supporting alveolar bone.\(^2\) The concept of periodontal disease is continually changing as new research evidence emerges. Therefore, the classification of periodontal disease has changed since the system was developed at the 1989 World Workshop in Clinical Periodontics. The classification from the most recent 1999 International Workshop organized by the American Academy of Periodontology (AAP) is presented in this chapter.

The classification of periodontal diseases \textit{now} includes eight general types\(^3\):

1. Gingivitis
2. Chronic periodontitis
3. Aggressive periodontitis
4. Periodontitis as a manifestation of systemic diseases
5. Necrotizing periodontal diseases
6. Abscesses of the periodontium
7. Periodontitis associated with endodontic lesions
8. Developmental or acquired deformities and conditions

The overall classification system is presented in Table 1.\(^3\) In addition, this classification is different from that of case types pr-
viously developed by the AAP. The current case types for periodontal diseases are:
- Gingivitis (Case Type I)
- Mild periodontitis (Case Type II)
- Moderate periodontitis (Case Type III)
- Advanced periodontitis (Case Type IV)
- Refractory periodontitis (Case Type V)

Each of the eight general types of periodontal disease are discussed briefly in the following text.

**Table 1. Periodontal Diseases**

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**Gingival Diseases**

Gingival disease is further characterized into plaque-induced and non-plaque-induced categories.

**Plaque-Induced Gingival Diseases**

Gingivitis is gingival inflammation associated with dental plaque and calculus accumulation. It is the most common form of gingival disease. Gingivitis may or may not progress to periodontitis, in which clinical attachment and alveolar bone loss will develop. Gingivitis can occur on teeth with no attachment loss and also occurs in the gingiva of the teeth previously treated for periodontitis with no further attachment loss.

**Dental Plaque Only:** Gingivitis is initiated by local accumulation of bacteria (i.e., dental plaque organized in a biofilm) adjacent to the tooth. The bacterial antigens and their metabolic products (e.g., endotoxin) stimulate epithelial and connective tissue cells to produce inflammatory mediators that result in a localized inflammatory response recruiting polymorphonuclear leukocytes (PMNs or neutrophils) to the site. An antibody response to bacterial antigens is also mounted. Inflammatory cells and their products, such as cytokines and enzymes, are present at the site of inflammation. Thus, a host immunoinflammatory response is established in the gingival tissues, and the clinical signs of gingivitis develop, including redness, swelling, and bleeding. The plaque-host interaction can be altered by the effects of local factors, systemic factors, or both.

**Systemic Factors:** Systemic hormonal change associated with puberty, menstrual cycle, and pregnancy, as well as chronic diseases such as diabetes, can alter the host response to dental plaque. Hormonal changes and certain diseases can upregulate systemic cellular and immunologic function, resulting in local severe gingival inflammation even in the presence of minimal plaque. Significant gingivitis is commonly seen in pregnant women who have not had adequate oral hygiene before becoming pregnant. Blood dyscrasias such as leukemia may also alter immune function by decreasing normal immunologic function. Patients usually present with gingival enlargement and bleeding, which is associated with edematous and erythematous gingival tissues.

**Medications:** Medications such as anticonvulsant drugs (e.g., dilantin), immunosuppressive
drugs (e.g., cyclosporin A), and calcium channel blockers (e.g., diltiazem) can cause severe gingival enlargement and pseudo-periodontal pocketing (i.e., increased probing depths with no associated attachment or bone loss). Medication-associated gingival conditions are often reversed after discontinuation of the offending medications.

**Malnutrition:** The host immune system can be diminished when malnutrition develops, resulting in excessive gingival inflammation. Severe ascorbic acid (vitamin C) deficiencies (scurvy) can produce bright red, swollen, and bleeding gingival tissues. In vitamin C deficiency, gingivitis is associated with a suppressed synthesis of both connective tissue collagens (e.g., types I and III) and basement membrane collagen (type IV), because vitamin C is one of the elements required for collagen synthesis. Improved dietary intake and/or vitamin C supplements can reverse this condition.

**Non-Plaque-Induced Gingival Lesions**
Non-plaque-induced gingival lesions usually are rare and are mainly due to systemic conditions. In addition, bacteria, viruses, and fungi that are not normally part of the dental biofilm can cause these types of gingival lesions. Sexually transmitted diseases such as gonorrhea (*Neisseria gonorrhoeae*) and syphilis (*Treponema pallidum*) can cause lesions in the tissues of the periodontium. In addition, primary streptococcal gingivitis is an acute inflammation of the oral mucosa associated with pain, fever, edematous and erythematous gingival tissues, with bleeding or abscess formation. These lesions can be managed with routine periodontal scaling and root planing and targeted antibiotic therapy. Herpes simplex virus type I is a common virus that can cause gingival lesions. In children and young adults, herpes infections can be primary and usually without symptoms, but in some cases pain and fever are reported. In these cases, the gingival tissues appear red and swollen, followed by the formation of small blisters, which eventually break down to form shallow, painful ulcers. These lesions are usually self-limiting and heal within 1 to 2 weeks. After a primary infection, the herpes virus becomes latent and is preserved in the ganglion of the trigeminal nerve. The virus may be reactivated later in life by reduced immune function or stress, resulting in recurrent herpes labialis, gingivitis, and stomatitis.

Gingival lesions of fungal origin usually occur in people with diabetes or other immunocompromised states. A shift in the normal oral flora related to the long-term use of systemically administered antibiotics can also lead to lesions of fungal origin. The most common fungal infection is candidiasis, caused by *Candida albicans*, often seen in patients wearing removable prosthetic devices such as dentures, and in patients with dry mouth due to multiple medications or salivary gland dysfunction. Clinical manifestations include white patches on the gingiva, tongue, or oral mucous membranes, which can be removed with a cotton swab or with gauze, leaving behind a bright red, bleeding surface. Treatment with antifungal agents is often necessary to resolve these conditions.

Gingival lesions can also be caused by genetic, systemic mucocutaneous disorders, allergic reactions, trauma, and foreign body reactions. One of the most common genetic conditions associated with gingival lesions is autosomal dominant, hereditary gingival fibromatosis—a benign condition affecting both dental arches. In this condition, the gingival tissues are enlarged and asymptomatic. This may be an isolated finding or associated with other syndromes. Treatment is gingivectomy; recurrence is possible. Systemic conditions, such as pemphigoid, pemphigus vulgaris, erythema multiforme, and lupus erythematosus, can cause desquamative lesions and ulceration. Gingival changes due to allergic reactions to certain restorative materi-
als, toothpastes, or mouth rinses are rare, but have been observed.\textsuperscript{10} Traumatic lesions are usually produced unintentionally.\textsuperscript{10} Aggressive tooth brushing and flossing can cause gingival damage. Traumatic lesions can also be iatrogenically induced by healthcare professionals during oral examinations or dental care. Eating crunchy foods or foods with small particles that can be lodged in the interproximal areas and directly into the gingival tissues can cause these types of lesions as well. Hot foods and drinks can cause minor burns of the gingival tissues. Localized inflammation can also develop when gingival tissue is exposed to foreign materials. The most common example is the amalgam remaining in gingival tissues during restorations or surgical procedures, eventually producing amalgam tattoos.\textsuperscript{10}

**PERIODONTITIS**

Periodontitis is a chronic inflammatory disease of the supporting tissues around the teeth that results in irreversible periodontal attachment loss, alveolar bone destruction, and ultimately, if left untreated, tooth loss.\textsuperscript{14} The current concept of the cause of periodontitis is that it is a complex disease in which multiple causal factors \textit{simultaneously} play a role.\textsuperscript{15} There are three main causal risk factors: microbiology (subgingival bacterial biofilm), genetics, and lifestyle (Figure 1). Subgingival bacteria in the biofilm and their metabolic products (e.g., endotoxin) as well as other antigens, initiate the periodontal inflammatory reactions, which lead to the recruitment of neutrophils and other inflammatory cells into the gingival tissues. Subsequently, the recruited immune cells, particularly neutrophils, release proinflammatory mediators, including cytokines, prostanooids, and enzymes. The type and severity of the periodontal inflammatory reaction to the dental biofilm is determined by genetic risk factors and lifestyle risk factors such as smoking, stress, and micronutrients. The periodontal inflammation results in the degradation of the gingival connective tissues.

**Figure 1.**

Periodontitis is a complex disease; multiple causal risk factors act \textit{simultaneously} in its onset and progression. Three main causal risk factors always play a role: microbiologic, genetic, and lifestyle. When the patient has a systemic disease, such as diabetes, which could affect the onset and/or progression of periodontitis, another overlapping circle needs to be added. Note that the relative contribution of each of the causal factors may vary from patient to patient (see Figure 2).

Notably, the junctional epithelium proliferates and also produces cytokines and other immune mediators and tissue-destructive proteinases. These participate in the degradation of the basement membrane and allow for the apical migration of the junctional epithelium along the root surface, contributing to the deepening of the gingival crevice and producing periodontal pockets and associated attachment loss—the hallmark of periodontitis. Osteoclasts are then stimulated to resorb the underlying alveolar bone. Some of the clinical signs include bleeding on probing, deep pockets, attachment loss and recession, radiographic evidence of alveolar bone loss, and tooth mobility. Often, this destructive process is silent and painless and continues for years without being identified. Eventually, teeth can become loose and may be lost on their own or deemed hopeless and require extraction. There are many forms of periodontitis.
Chronic Periodontitis
Chronic periodontitis is the most common form of periodontitis and is characterized by pockets with associated attachment and bone loss and/or recession of the gingival tissues. It is common in adults, but can occur at any age. Progression of attachment loss usually occurs slowly, but periods of rapid progression or periods of remission can occur. Several studies have addressed the “episodic” nature of periodontitis. The rate of disease progression may be influenced by local or systemic conditions; the latter can alter the immune response to the biofilm. Local factors such as large accumulations of dental plaque and calculus due to poor oral hygiene and lack of preventive measures (lifestyle factors) or, less commonly, to subgingivally placed fillings or crowns, can promote gingival inflammation and clinical attachment loss. Other lifestyle risk factors such as smoking, lack of proper micronutrients and vitamins, and stress, reduce in general the host resistance to the dental biofilm. Genetic factors play a less important role in chronic periodontitis than in aggressive periodontitis (Figure 2). Systemic factors such as diabetes and HIV infection can decrease host defenses to bacterial infection. Lifestyle risk factors such as smoking and stress can also decrease host immune function, resulting in increased susceptibility to disease. Chronic periodontitis can occur as a localized form, in which less than 30% of sites are involved, or as a more generalized form, in which more than 30% of existing sites demonstrate increased pocket depth, attachment, and bone loss. As previously mentioned, the severity of disease can be described as slight, moderate, or severe, based on the level of destruction.

Aggressive Periodontitis
Aggressive periodontitis was previously categorized as early-onset periodontitis, as in juvenile periodontitis. Common features are rapid attachment loss and bone destruction in the absence of large accumulations of plaque and calculus. These forms of periodontitis usually affect young persons (juveniles, adolescents, post-adolescents), often during puberty from 10 years to 30 years of age, with a strong genetic predisposition (see Figure 2). The microbiologic risk factor most often associated with aggressive periodontitis is Aggregati-

Figure 2. Genetic and Microbiologic Risk Factors Associated with Periodontitis

| Case 1: aggressive periodontitis (11 years old) | Case 2: aggressive periodontitis (16 years old) | Case 3: aggressive periodontitis (35 years old) | Case 4: chronic periodontitis (54 years old) |

Genetics contribute more in relatively younger patients with aggressive periodontitis than in adults with chronic periodontitis. Conversely, in relatively older patients, the microbiologic risk factors and lifestyle factors contribute the most to onset and/or progression, whereas genetics plays a smaller role.
bacter actinomycetemcomitans (previously Actinobacillus actinomycetemcomitans). Individuals present with hyperactive inflamma-
tory cells producing high levels of cytokines and enzymes causing rapid, aggressive destruction of periodontal tissues. Aggressive periodontitis can be further characterized as localized or generalized. The localized form usually affects first molars and incisors. The generalized form usually involves at least three teeth other than first molars and incisors.

Periodontitis as a Manifestation of Systemic Diseases
Systemic conditions such as diabetes are associated with this form of periodontitis.\(^9\) Diabetes, and any other chronic condition that lowers the host resistance to bacterial infections, increases the susceptibility and progression of periodontitis. Several hematologic and genetic disorders have also been associated with the development of periodontitis, such as acquired, familial, and cyclic neutropenias; constitutive neutropenia (Kostman syndrome [case 1 in Figure 2]); leukemias; Down syndrome; certain types of Ehlers-Danlos syndrome, such as types IV and VIII; Papillon-Lefèvre syndrome; Cohen syndrome; and hypophosphatasia. The mechanisms by which all these disorders affect the health of the periodontium are not fully understood and continue to be investigated by many basic and clinical researchers. However, the strong genetic component is clear for most of these syndromes. Genetic mutations affect host defense mechanisms in various ways and cause hypo- or hyperinflammatory responses, resulting in fast progressive and aggressive periodontal destruction.

Necrotizing Periodontal Diseases
Necrotizing lesions are most commonly observed in persons with a poor state of health and systemic condition and strongly associated with smoking, stress, and poor nutrition. Certain systemic conditions, such as HIV infection, but also immunosuppres-
sion can increase the risk. Necrotizing periodontal diseases are further divided into two forms: necrotizing ulcerative gingivitis (NUG) and necrotizing ulcerative periodontitis (NUP). These two diseases have the same etiology and clinical signs, except that NUP involves clinical attachment and alveolar bone loss.\(^3\)

Abscesses of the Periodontium
Periodontal abscess is a localized purulent infection of the periodontal tissues.\(^2\) Iatrogenic abscess formation can be precipitated after inadequate scaling and root planing, leading to a tightening of the coronal epithelial cuff with continued subgingival calculus driving inflammation. Abscesses can also occur in healthy periodontal tissues owing to the presence of foreign objects lodged in the gingival crevice such as a toothbrush bristle or a popcorn kernel being tightly packed into the interproximal spaces or between the tooth and the tissues.

A pericoronal abscess is an infection of the gingiva around a partially erupted tooth, leading to pericoronitis. A small flap of tissue may cover a partially erupted tooth surface, serving as a nidus for food and debris to accumulate and become trapped beneath the tissue flap. Patients usually find it very difficult to keep these areas clean and can develop inflammation and infection. In addition, trauma due to constant contact between the tissue flap and a tooth in the opposing arch can also lead to a pericoronal abscess. The areas most commonly affected are associated with mandibular third molars. Pain, swelling, redness, and suppuration are associated with periodontal abscesses. Treatment may include incision and drainage, use of antibiotics, and removal of the offending source.

EPIDEMIOLOGY AND RISK FACTORS
Epidemiology of Gingivitis
Gingivitis can occur in early childhood, becomes more prevalent during teenage
years, and decreases in older persons. In 1986–1987, the National Institute of Dental Research (NIDR) conducted a national survey of oral health in US school children and reported that approximately 60% of children 14–17 years of age were found to have gingivitis. A 2005 AAP position paper reported that over 50% of adults had gingivitis on an average of three to four teeth, whereas 63% of 13- to 17-year-old teenagers had gingival bleeding according to the National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994. Both surveys assessed gingival bleeding by a gingival sweep method.

**Epidemiology of Periodontitis**

Basic clinical measurements for periodontitis are gingival bleeding on probing (BOP), clinical attachment loss (CAL), and pocket depths accompanied by radiographic bone loss. These types of clinical measurements may be somewhat subjective. As our knowledge of the pathogenesis of periodontitis improves, new diagnostic markers for periodontitis may emerge to better screen for, diagnose, and manage periodontitis. Inflammatory cytokines, enzymes, and bone breakdown products released into the gingival crevicular fluid reflect the host response to the bacterial challenge. These biochemical markers may be good candidates for new diagnostic or prognostic markers of disease. A number of cytokines have been associated with active disease, including prostaglandin E2 (PGE2), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and others. Enzymes such as matrix metalloproteinases (MMPs) and breakdown products, such as the collagen telopeptide (ICTP), have been studied as well.

To date, these biochemical markers in gingival crevicular fluid are still being investigated. It will be helpful to both clinicians and researchers if one or more of these markers can be developed as a more objective tool to measure active periodontitis. The development of these markers will also help to facilitate screening for periodontal diseases by medical professionals or even help patients in self-assessment of oral inflammation, prompting referrals to the dental office for clinical assessment. Monitoring levels of these markers may also help in assessing patient response to various periodontal therapeutic options.

The national data suggest that the milder forms of periodontitis are close to universal. The more severe forms are less prevalent. According to a review of the literature by Brown and Löe focused on a number of epidemiologic studies resulting from a 1981 national probability survey, the prevalence of chronic periodontitis was about 36% for the adult US population as assessed by pocket depth measurements. The prevalence of periodontitis increased with age; 29% in those age 19 to 44 years of age had chronic periodontitis, which increased to 50% for people 45 years or older. In general, moderate periodontitis occurred in 28% of all people, and 8% had advanced disease. However, the prevalence of moderate and severe periodontitis increased to 44% in the population greater than 45 years of age. Based on the presence of periodontal pockets ≥ 4 mm, it was determined that 30% of the population had periodontitis on an average of three to four teeth. Severe pockets of ≥ 6 mm were found in less than 5% of the population. The prevalence of aggressive periodontitis was low with less than 1% in this 1991 survey.

Following this report, the NHANES III reported the prevalence of periodontitis for adults ages 30 to 90 years old. Attachment loss and probing depths were assessed at two sites per tooth. Attachment loss of ≥ 3 mm was found in 53% of the population. The prevalence of attachment loss increased with age, from approximately 35% for the 30-year-old participants to 89% for the 80-year-old...
old participants. Probing depths of \( \geq 3 \text{ mm} \) were found in approximately 64% of the population. The prevalence of periodontitis increases with age and was found to be more prevalent in males than females, and in African and Mexican Americans than Caucasians. Most recently, it was reported that periodontal disease may have significantly decreased between NHANES III and NHANES 1999–2004.\(^{31}\) However, on further evaluation, it was recognized that partial-mouth periodontal examination protocols used in NHANES underestimated the prevalence of periodontitis by approximately 50% when compared with a full-mouth “gold standard” periodontal examination in a convenience sample of 454 adults \( \geq 35 \) years of age.\(^{32}\) These findings prompted a full-mouth assessment of pocket depth and clinical attachment loss in NHANES 2009–2010 revealing periodontitis in over 47% of the population aged 30 years and older, with 8.7% mild, 30% moderate, and 8.5% severe.\(^{33}\)

**Risk Factors**

As previously explained, periodontitis is a complex disease, with three main causal factors simultaneously playing a role—microbiologic, genetic, and lifestyle (see Figure 1). Within these clusters, various risk factors have been identified.\(^{34-39}\) Estimating and/or determining risk is helpful in developing recommendations for prevention and in determining strategies for the overall management of periodontitis. It has been recognized that the severity and progression of periodontal disease varies from individual to individual. Within the microbiologic cluster of risk factors, the known periodontal pathogens and other still unknown bacteria are essential for the initiation of the disease. However, it is the host response to the bacterial challenge that determines the severity and progression of the disease. The original concept of host susceptibility by Page and Schroeder in 1976\(^{40}\) has recently led to a new paradigm shift in our understanding of the etiology of periodontal disease: namely, that periodontal destruction is not caused by dental plaque in a biofilm per se, but rather by the host’s inflammatory response.\(^{41}\) Both hyper- and hyporesponsiveness of the immune system toward the microbial challenge in periodontitis has been described.\(^{42}\) Host susceptibility is essentially the aggregate of unfavorable genetic and lifestyle factors, which in turn determines disease expression and/or progression of an existing disease.\(^{1,43}\)

The complexity of these interrelated factors explains the variation in phenotypes between individuals and among populations.

Summarized below are risk factors within the three main clusters of causal factors for periodontitis.

The microbiologic cluster is the subgingival biofilm containing the known and as-yet unknown periodontal pathogenic bacteria. The risk bacteria include *A. actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Tannerella forsythia*, and *Treponema denticola*. The cluster of lifestyle risk factors for periodontitis includes smoking, stress, and shortage of micronutrients such as vitamin C.\(^{44}\) The level of oral hygiene, motivation for oral health, and regular check-ups by a dental professional also are considered part of lifestyle factors.

The specific genetic risk factors for periodontitis are largely unknown. The initial candidate gene studies that examined the association of genetic polymorphisms with periodontitis focused on genes that are involved in the innate and adaptive immunity and thus have the potential to determine disease susceptibility and severity, e.g., genes of the interleukin [IL] and Toll-like receptor families, MMPs, or various metabolic pathways.\(^{15}\) Recently, 23 genes, which were repeatedly proposed to be associated with increased disease risk in white populations, were replicated in a comprehensive associa-
tion study using a large population of northern European patients with aggressive periodontitis. The potential relevance of the observed association was subsequently tested in chronic periodontitis subjects. It was concluded that all analyzed putative susceptibility genes, except for IL-10, do not carry common risk variants and that previous positive reports were probably caused by false-positive results (type 1 errors). For complex diseases, large case-control populations are the indispensable prerequisite for any association study to overcome the inherent heterogeneity within populations. It is currently believed that in complex diseases, common markers or causative genetic variants usually do not exceed an odds ratio (OR) of 1.3, with many having even much smaller ORs. To identify such a variant in the population (OR 1.3 and with a variant allele frequency of 20%, for example), a minimum of 1,000 well-defined cases is necessary to reach the required statistical power of 0.8, and at least the same amount of healthy controls. None of the early candidate gene studies reached this sample size and were underpowered. Hence, most associations of the past seem arbitrary and suffer from a lack of successful replication, the gold standard of any association study.

In addition to power and sample size issues, another important limitation of candidate gene studies in the field of periodontitis is that initial studies did not capture the complete genetic information of a particular region of interest. In almost all studies, only one or a few variants rather than the complete set of all haplotypes of a gene were genotyped. However, information about the complete haplotypes must be assessed to ensure that all potentially relevant polymorphisms are analyzed. Further limitations of most previous studies on genetics in periodontitis often include inadequate phenotype classification for disease and control subjects, as well as that of failing to take into account lifestyle effects such as smoking, age, and the presence of other diseases.

Within the cluster of specific genetic risk factors, the IL-1 composite genotype ad modum, Kornman and colleagues deserve special attention because of the large number of studies that have been carried out on the relation between this composite genotype and the two main forms of periodontitis in a variety of ethnic populations. The IL-1 genes, comprising IL-1A, IL-1B, and IL-1RN, are located in close proximity to each other on the long arm of chromosome 2. IL-1A −889 (rs1800587, in linkage with +4845), IL-1B −511 (in linkage with −31), IL-1B +3954 (rs1143634, also mentioned in the literature as +3953) and IL-1RN VNTR (in linkage with +2018 [rs419598]) have been studied extensively in relation to chronic periodontitis. Kornman and colleagues were the first to report that the combined presence of the minor allele of the IL-1A gene at position −889 and the minor allele of the IL-1B gene at position +3954 was associated with severity of chronic periodontitis, in particular in nonsmoking whites; these authors proposed this combination to be the “IL-1 composite genotype.” Carriage rates of the IL-1 composite genotype vary across populations; for example, a low minor allele frequency ([MAF] < 5%) was seen in Asian populations compared with white populations. The IL-1 composite genotype and the other IL-1 candidate single-nucleotide polymorphisms (SNPs) are not associated with European patients with aggressive periodontitis. A recent systematic review on IL-1 gene polymorphisms in chronic periodontitis patients and controls in whites suggested evidence for the minor alleles in IL-1A, in IL-1B and the composite genotype to be risk factors. However, the latter results also demonstrated significant heterogeneity among the included studies, indicating that some of the included studies may suffer from a type 1 error. In that respect, a recent...
letter is useful for the evaluation of systematic reviews on genetic risk factors.54

Taking into consideration the limitations just mentioned, the following genes are currently considered to carry validated susceptibility variants for periodontitis; these genes were successfully replicated in a large sample population:

- **GLT6D1**: In 2010, in the first genome-wide association study on periodontitis, **GLT6D1** was found to be associated with AgP.55 **GLT6D1** encodes a protein belonging to a family of proteins that is characterized by a glycosyltransferase domain-1. It was shown that the rare allele of SNP rs1537415 resulted in impaired binding of the transcription factor GATA-3.

- **ANRIL**: This gene was identified as the first genetic risk factor of coronary artery disease.56-59 In 2009, **ANRIL** was identified to be a shared genetic risk factor of coronary artery disease and aggressive periodontitis.60 This association was further replicated in several independent aggressive and chronic periodontitis case-control samples of Northern European descent,61 a combined group of aggressive periodontitis patients in a German and Northern Irish population,62 and in a Turkish aggressive periodontitis case-control population.45 Functional characterization of the molecular function of **ANRIL** showed, apart from others, a long-distance regulatory effect on the activity of the CAMTA1/VAMP3 region.63 This region was previously shown to be associated with increased periodontal pathogen colonization.

- **COX-2**: Associations of **COX-2** with periodontitis were first identified in Taiwanese and Chinese case-control populations and subsequently validated in a Northwest-European population.54-66 **COX-2** converts arachidonic acid into prostaglandin H2, which is the precursor of PGE2. PGE2, which mediates proinflammatory and anti-inflammatory reactions in many tissues, is also partly responsible for the resorption of the alveolar bone during the pathogenesis of periodontitis.

- **DEFB1**: Genetic markers within **DEFB1** coding for beta defensin B1 were also validated for periodontitis.67 In a fine mapping approach, SNP rs1047031 was best associated with both aggressive and chronic periodontitis, and the rare allele was predicted to impair a microRNA binding site at the 3'-untranslated region (UTR) of **DEFB1**. The antimicrobial peptide that is encoded by **DEFB1** was suggested to be responsible for maintaining a healthy status in the mucosal epithelia prior to infection with pathogenic bacteria.68

To conclude this section on genetic risk factors for periodontitis, note that common genetic risk variants for complex diseases are generally not located within the protein coding sequences of the classic candidate genes, but rather lie within the regulatory elements of unforeseen genes and chromosomal regions.69 Most common human genomic variants that are genome-wide associated with over 400 complex diseases and traits are located within regulatory and intronic regions and not within coding regions. This was also demonstrated for the risk variants for periodontitis, which are located within introns (**ANRIL** and **GLT6D1**), 5' to the promoter region (**COX-2**) and within the 3'-UTR (**DEFB1**).

Certain risk factors (Table 2) and risk reduction strategies (Table 3) should be considered when assessing each patient.70 Some risk factors can be modified to reduce a patient’s susceptibility. Lifestyle factors such as tobacco use and stress can be managed with smoking cessation and stress management; for acquired factors such as systemic
Table 2. Risk Assessment for Periodontitis

1. Estimate the relative contribution of genetic factors by the age of the patient and by family history

2. Smoking, including frequency, current use, and history

3. Hormonal variations such as those seen in:
   a. Pregnancy, in which increased levels of estradiol and progesterone may change the environment and permit the virulent organisms to become more destructive
   b. Menopause, in which the reduction in estrogen levels leads to osteopenia and eventually osteoporosis

4. Systemic diseases such as:
   a. Diabetes (duration and level of control are important)
   b. Osteoporosis
   c. Immune system disorders such as HIV
   d. Hematologic disorders such as neutropenias
   e. Connective tissue disorders such as Marfan’s and Ehlers-Danlos syndromes
   f. Metabolic syndrome and obesity

5. Stress as reported by the patient

6. Nutritional deficiencies that may require a dietary analysis

7. Medications such as
   a. Calcium channel blockers
   b. Immunomodulatory agents
   c. Anticonvulsants
   d. Those known to cause dry mouth or xerostomia

8. Faulty dentistry such as overhangs and subgingival margins

9. Poor oral hygiene resulting in excessive plaque and calculus

10. History of periodontal disease


diseases, medications usually prescribed by the physician help in the management and control of these chronic disorders and should therefore reduce susceptibility to infectious processes such as periodontitis (see Table 3). Chemotherapeutic agents specifically designed to improve upon the clinical outcomes of mechanical treatments for periodontal diseases may be particularly useful in the management of those with single or multiple risk factors. Risk assessment can help the practitioner to establish an accurate diagnosis, provide an optimal treatment plan, and determine appropriate maintenance programs. In patients with multiple risk factors, the practitioner may aggressively use pharmacologic adjuncts such as antimicrobials and host modulatory therapy in addition to mechanical therapy. It is also important to update and assess risk factors for each patient on a regular basis because some of these factors are subject to change throughout life.

ETIOLOGY AND PATHOGENESIS OF PERIODONTAL DISEASE

Initially, periodontal disease was thought to be related to aging and was therefore uniformly distributed in the population, with disease severity being directly correlated with plaque levels. Now, as a result of extensive research, it has been shown that periodontal disease is initiated by the microorganisms in the subgingival biofilm (dental plaque), but the severity and progression of the disease are determined by the host response (aggregate of genetic risk factors and lifestyle risk factors) to the bacterial biofilm. Thus, some
**Table 3. Risk Reduction Strategies**

1. More frequent visits for those with a high estimated genetic predisposition; use of pharmacotherapeutics for the management of periodontitis
2. Smoking cessation, using one or more of the six approved regimens; these regimens rarely are successful as sole therapies (multiple forms of therapy often are used in combination with counseling to achieve success)
3. Hormonal variations such as those seen in:
   a. Pregnancy, which requires good oral care before pregnancy to prevent complications during pregnancy; treatment of women during pregnancy may be necessary to prevent adverse pregnancy outcomes
   b. Menopause, which may require hormonal supplements, calcium, and other medications and supplements prescribed by the physician to prevent osteopenia
4. Systemic diseases that require consultation with the physician and pharmacotherapeutics include:
   a. Diabetes (for improved glycemic control)
   b. Osteoporosis (requiring calcium supplements, bisphosphonates)
   c. Immune system and hematologic disorders
   d. Connective tissue disorders
   e. Weight loss for obesity and metabolic syndrome
5. Stress management; possible referral to a psychologist or psychiatrist
6. Nutritional supplementation; referral to a nutritionist
7. Medications can be changed in consultation with the physician
8. Corrective dentistry
9. Occlusal adjustments
10. Improved oral hygiene


People with severe plaque and calculus accumulation may have gingivitis, but not necessarily periodontitis. On the other hand, certain individuals, despite maintaining adequate oral hygiene, find themselves susceptible to aggressive forms of periodontitis, with deep pockets, tooth mobility, and early tooth loss.

To better treat and manage periodontal diseases, we need a more detailed understanding of periodontal pathogenesis (Figure 3). The bacteria and their metabolic products (e.g., endotoxin) stimulate the junctional epithelium to proliferate and to produce tissue-destructive proteinases. This infection also increases the permeability of the junctional epithelium, which allows microbes and their products to gain access to the subepithelial connective tissue. Epithelial and connective tissue cells are thus stimulated to produce inflammatory mediators that result in an inflammatory response in the tissues. Microbial products also chemotactically attract a constant flux of proinflammatory cells migrating from the circulation to the gingival crevice. Neutrophils, or PMNs, are predominant in the early stages of gingival inflammation. Thus, an immune response is generated in the periodontal tissues, and proinflammatory cytokines such as IL-1β, TNF-α, and MMPs are produced by inflammatory cells recruited to the lesion site. The functions of PMNs include phagocytosis and destruction of bacteria. Initially, the clinical signs of gingivitis are evident. This response is essentially protective in nature to control the bacterial infection. In persons who are not susceptible to periodontitis, the primary defense mechanisms control the infection, and chronic inflammation (i.e., chronic gingivitis) may persist. However, in persons susceptible to periodontitis, the latter inflammatory process persists and eventually extends apically and laterally to involve deeper connective tissues and alveolar
bone, recruiting monocytes and lymphocytes to the site of infection at later stages. These monocytes and macrophages are activated by the bacterial endotoxins such as LPS, leading to the production of high levels of prostaglandins (e.g., PGE₂), interleukins (e.g., IL-1α, IL-1β, IL-6), TNF-α, and MMPs by the host cells. The MMPs break down collagen fibers, disrupting the normal anatomy of the gingival tissues, resulting in destruction of the periodontal apparatus. If left untreated, the inflammation continues to extend apically, and osteoclasts are stimulated to resorb alveolar bone triggered by the high levels of prostaglandins, interleukins, and TNF-α in the tissues. The elevated levels of proinflammatory mediators and MMPs are counterbalanced by a protective response in the host with elevations in anti-inflammatory mediators such as the cytokines IL-4 and IL-10, as well as other mediators such as IL-1ra (receptor antagonist) and tissue inhibitors of matrix metalloproteinases (TIMPs) (Figure 4).  

Under normal healthy conditions, the anti-inflammatory mediators are balanced with inflammatory mediators, thereby controlling tissue destruction. If an imbalance occurs, with excessive levels of the proinflammatory mediators, upregulated MMP expression, and insufficient levels of protective anti-inflammatory mediators, the loss of periodontal connective tissue and bone will occur.

Thus, plaque bacteria initiate the disease, followed by an inflammatory response mounted by the host producing excessive levels of proinflammatory mediators (prostaglandins, interleukins) and enzymes (MMPs) and resulting in the destruction of periodontal tissue. If this inflammation continues and extends farther apically, more bone is resorbed, and more periodontal tissue is broken down. This leads to deeper and deeper pockets and associated attachment and bone loss revealed as the clinical and radiographic signs of periodontitis. In people with periodontitis, these inflammatory mediators (e.g.,
prostanoids and cytokines) and local oral bacteria eventually enter into the circulation, stimulating the liver to produce acute-phase proteins (notably C-reactive protein [CRP]), but also fibrinogen, haptoglobin, etc.), which are biomarkers of a systemic inflammatory response. Emerging evidence supports the fact that this chronic systemic inflammatory response driven by the chronic infection and inflammation associated with periodontitis eventually increases a person’s risk for developing a number of systemic diseases, including cardiovascular diseases, adverse pregnancy outcomes, and diabetic complications. In a recent workshop jointly held by the European Federation of Periodontology and the American Academy of Periodontology, potential mechanisms linking periodontitis to systemic conditions were discussed. Metastatic infections, innate inflammatory responses, and adaptive immunity were proposed as three basic mechanisms for this association.  

Although the causative relation between periodontitis and systemic diseases cannot be established, current studies have identified shared common risk factors and plausible mechanistic pathways. Despite our gap in research, it is clear that periodontitis can be considered a contributing factor to many systemic conditions and diseases. The details are presented in other chapters of this book.

**MANAGEMENT OF PERIODONTAL DISEASES**

Periodontal management includes a complete assessment of each patient. Medical and dental history, clinical and radiographic examination, and assessment of risk factors all are important in making an accurate diagnosis and prognosis and in developing an optimal treatment plan. Many treatment options are available for the management of periodontal diseases, and review of treatment outcomes or re-evaluation is key to successful management and long-term maintenance.

In the past, treatments that focused on reduction of the microbial load were basically the sole consideration for all periodontal therapy. Currently, because of increased knowledge of the host response, host modu-
lution therapies have been used as adjunctive approaches to both nonsurgical and surgical treatments to aid in reducing probing depths, increasing clinical attachment levels, and regenerating the lost attachment apparatus. In the future, more effective therapeutic approaches are likely to include multiple synergistic host modulation therapies combined with treatments that target the microbial etiology.

In addition to reducing the bacterial challenge and modulating the host response, reduction of risk is also a key treatment strategy when managing periodontitis. For example, it is known that smoking can contribute to periodontal disease and can make the management of the disease more difficult. Therefore, smoking cessation would benefit all patients with periodontitis. Smoking cessation can be undertaken in the dental office (if the staff is appropriately trained) or in a medical setting. A variety of medications aid in smoking cessation, counseling is important, and alternative medicine such as acupuncture may be used. When poorly controlled, systemic diseases such as diabetes increase a patient’s risk for periodontitis. When treating people with diabetes, knowing the patient’s level of diabetic control is important in assessing risk. Collaboration with medical colleagues to improve control of diabetes is essential to ensure successful periodontal treatment. Periodontitis is also prevalent in patients with cardiovascular disease. Periodontal therapy may have a positive impact on the overall health status of these individuals.

The treatment of patients with periodontitis can therefore involve the following complementary treatment strategies:

- Patient education, including oral hygiene instruction and explanation of the rationale for any adjunctive treatments
- Risk factor modification and risk reduction strategies
- Reduction of the bacterial burden by traditional scaling and root planing
- Intensive periodontal treatment with local antimicrobial administration or general antimicrobial therapy with oral administration of antibiotics
- Host modulation therapy
- Periodontal surgery

It is the responsibility of the dentist to provide appropriate treatments on an individual basis. A combination of treatment approaches for each patient provides optimal periodontal treatment and results in a better prognosis (Figure 5).7

Figure 5. Complementary Treatment Strategies in Periodontitis

Adapted from: Carranza’s Clinical Periodontology, 10th ed. WB Saunders Company; 2006:275–82.

The Antimicrobial Approach

Traditional periodontal therapy based on the antimicrobial approach consists of mechanical nonsurgical and surgical therapies, which may or may not be supplemented by local antisepsics and/or local or systemic antibiotics.

Mechanical Therapy

Preventive and maintenance strategies for the patient include adequate home care. Brushing and flossing make up the most basic approach to microbial reduction and control for the patient. Good oral hygiene can effectively reduce bacterial loads to prevent gingivitis and aid in the treatment and management of periodontitis. This simple approach
relies on an individual’s knowledge of the correct techniques and compliance with home care instructions. The Bass technique of brushing for 2 minutes twice daily, along with flossing once daily, is the current recommendation. The use of end tuft and proxy-brushes as well as powered toothbrushes can improve home care in certain patients.

Routine scaling of teeth every 6 months by the dental care provider is also a key component in treating and preventing gingivitis. Scaling and root planing is the traditional nonsurgical treatment of periodontitis, with many clinical studies demonstrating that it effectively reduces the microbial load and leads to reductions in bleeding on probing, reduces probing depths, and allows for gains in clinical attachment. However, this procedure can be very time-consuming and is operator-dependent. Surgical procedures can be used to visualize remaining subgingival calculus, and through resective or regenerative procedures will also lead to decreased probing depths that are more manageable for long-term maintenance of patients with periodontitis. Although nonsurgical and surgical procedures aimed at reducing the bacterial load, reducing probing depths, and restoring the attachment apparatus continue to be the most widely used methods of treating periodontitis, these strategies alone may be insufficient at reducing the bacterial load adequately. It has been recognized that significant numbers of microorganisms may be left behind, requiring additional therapeutic approaches. Many putative pathogens remain within the oral cavity at distant sites, allowing for repopulation in the future. Therefore, the need for the development of chemotherapeutic agents as adjuncts to mechanical debridement was deemed necessary.

Antiseptics and Toothpastes

Antiseptic Mouthrinses

Unfortunately, many patients are not compliant with brushing and flossing. They lose motivation and do not spend a sufficient amount of time brushing or flossing on a daily basis. For this reason, oral antiseptic rinses have been developed. Antiseptic mouthrinses have been found to improve on plaque reduction as well as reductions in gingival inflammation seen with brushing and flossing alone. Therefore, antiseptic rinses have been accepted as adjuncts to the mechanical approach of brushing and flossing. Two clinically proven American Dental Association (ADA)-accepted antiseptic mouthrinses are Peridex® (chlorhexidine gluconate) and the four essential oils in Listerine®. An association between oral conditions such as periodontal disease and several respiratory conditions such as pneumonia and chronic obstructive pulmonary disease has been noted. The plaque surrounding the teeth is an excellent harbor for respiratory pathogens. Studies have shown that using a chlorhexidine oral rinse can reduce the risk of pneumonia in institutionalized patients with poor oral hygiene.

Locally Applied Antiseptics

Periochip® contains the active ingredient of chlorhexidine gluconate (2.5 mg) that is released into the pocket over a period of 7 to 10 days. It has been found to suppress the bacteria in the pocket for up to 11 weeks after application. Periochip is the only ADA-approved locally applied antiseptic used as an adjunct to scaling and root planing procedures to aid in the reduction of pocket depths.

Dentifrices

Major improvements in the oral health of populations in developed countries have been seen over the last 50 years. Most of this has resulted from reduction in the caries rate of about 50%. The principle reason for this is thought to be the addition of fluoride to dentifrices. Modern commercial dentifrices, in addition to providing the anticaries effects
of fluoride, also contribute to reduction of plaque, gingivitis, calculus formation, and tooth stain. They reduce halitosis and result in a clean, fresh mouth feel. Two dentifrices available in the United States that are approved by the ADA for their effects on the reduction of gingivitis include a stannous fluoride/sodium hexametaphosphate dentifrice and a sodium fluoride/triclosan/copolymer dentifrice.

There is a large amount of literature on the latter dentifrices and other dentifrices containing chlorhexidine and other agents in the control of gingivitis. A review of the role of triclosan/copolymer toothpaste in the management of periodontal disease was carried out by Blinkhorn and colleagues. They found approximately 200 articles dating from 1998 to 2008 relating to triclosan/copolymer dentifrice and concluded that twice daily use of this dentifrice will result in clinically significant improvements in plaque control and gingivitis with slowed progression of periodontal disease. Further long-term studies extending over several years with these dentifrices are needed to establish whether the short-term effects will be sustained over the long term and indeed result in preventing the initiation of periodontitis and slowing the progression of already existing periodontitis.

Furthermore, the Cochrane Oral Health Group has recently published a review of 30 clinical trials that included 14,835 participants and examined the effect of triclosan/copolymer as compared to an ordinary fluoride toothpaste on various endpoints and concluded that there was “moderate-quality evidence” supporting the fact that toothpaste containing triclosan/copolymer reduced plaque and gingivitis, including gingival inflammation and gingival bleeding, as compared to a regular fluoride toothpaste.

It should be noted that the antiplaque and antigingivitis effects of dentifrices during a tooth brushing regimen are mainly on the occlusal and smooth surfaces of the teeth and that interproximal plaque and gingivitis control is not optimally achieved with tooth brushing alone with or without a dentifrice. Interproximal aids such as flossing, interproximal brushing, and, to some extent, flushing with effective mouth rinses, are often needed for full plaque control on interproximal surfaces of the teeth. Since periodontal disease is often initiated and progresses more rapidly in interproximal spaces, it is clear that interproximal cleansing is an important adjunct to tooth brushing with dentifrices.

Antibiotics
Locally Applied Antimicrobials
Atridox: An FDA-approved locally delivered tetracycline system, Atridox® is a 10% formulation of doxycycline in a bioabsorbable, “flowable” poly(DL-lactide) and N-methyl-2-pyrrolidone mixture delivery system that allows for controlled release over 7 days. This system is applied subgingivally to the base of the pocket through a cannula. Atridox is a resorbable, site-specific, locally applied antibiotic proven to promote clinical attachment gains and reduce pocket depths, bleeding on probing, and levels of pathogenic bacteria for up to 6 months after placement. Periodontal disease has been linked to systemic diseases such as diabetes. Research has shown that periodontal treatment with topically delivered doxycycline (10 mg) in periodontal pockets produces favorable clinical results in diabetic patients.

Arestin: An FDA-approved minocycline microsphere system, Arestin® is bioadhesive and biore sorbable, allowing for sustained release of 1 mg of minocycline. Arestin can be used as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. Arestin is delivered to sites of 5 mm or greater. Periodontitis has been associated
with increased systemic inflammation, which is directly linked to diabetes and cardiovascular diseases. Recent research has shown that periodontal therapy with local Arestin administration resulted in decreased HbA1c levels in diabetic subjects and significant reductions in systemic inflammatory biomarkers, which are risk factors for cardiovascular disease.8788

**Systemic Antimicrobials**

Systemic antimicrobial therapy is usually reserved for advanced cases of periodontitis (1) for patients with sites that have not responded to treatment, as so-called “refractory periodontitis,” and (2) for patients demonstrating progressive periodontal destruction.70 Systemic antibiotics can be used as adjuncts to conventional mechanical therapy, but strong evidence for their use as a monotherapy has not been developed. For these special situations, randomized double-blind clinical trials and longitudinal assessments of patients indicate that systemic antimicrobials may be useful in slowing disease progression.89 Metronidazole can be used to cure acute necrotizing ulcerative gingivitis,90 and metronidazole amoxicillin combination therapy can be used to treat aggressive adolescent periodontitis associated with *A. actinomycetemcomitans*.91

Systemic antibiotic therapy has the advantage of simple, easy administration of drugs to multiple periodontal sites. However, patient compliance needs to be considered, inability to achieve adequate concentrations at the site of infection, adverse drug reactions, and the development of antibiotic resistance are possible issues.92 Common antibiotic therapies for the treatment of periodontitis are metronidazole, clindamycin, doxycycline or minocycline, ciprofloxacin, azithromycin, metronidazole and amoxicillin, and metronidazole and ciprofloxacin.93 For adult patients with acute periodontal abscesses, amoxicillin is used as an adjunct to incision and drainage. For patients with allergies to beta-lactam drugs, azithromycin or clindamycin would be the drug of choice.

Researchers have shown that periodontal treatment can improve on systemic diseases known to be associated with periodontitis, such as diabetes. Periodontal therapy, including the use of antibiotics and extraction of hopeless teeth, reduced the number of insulin injections required daily in young patients with diabetes.94 Grossi and colleagues reported that diabetic patients undergoing scaling and root planing with systemic doxycycline showed significant reductions in mean HbA1c.95 Effective treatment of periodontal infection and reduction of periodontal inflammation are associated with a reduction in levels of glycated hemoglobin.

**Host Modulation Therapy**

Bacteria and the host response are two essential components in the development of periodontitis. Reduction of bacterial loads is the conventional approach for the management of periodontal diseases. More recently, periodontal treatment strategies have included host modulatory therapy as an adjunctive treatment option. It addresses the host response to either reduce the excess production of cytokines and destructive enzymes so that there is less damage to the periodontal tissues or to stimulate the regenerative process, allowing for the restoration of connective tissue attachment and bone formation.

Host modulation was first introduced to dentistry by Williams96 and Golub and colleagues.97 Williams stated: “There are compelling data from studies in animals and human trials indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing the progression of periodontitis.”96 Golub and colleagues discussed “host mod-
ulation with tetracyclines and their chemically modified analogues. A variety of drug classes have been evaluated as host modulation agents, including the nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, tetracyclines (Figure 6), enamel matrix proteins, growth factors, and bone morphogenetic proteins.

**Systemically Administered Agents**

**Subantimicrobial-Dose Doxycycline**

Subantimicrobial-dose doxycycline (SDD) is the only FDA-approved MMP inhibitor and systemic host modulatory therapy for the management of periodontitis. SDD is a 20-mg dose of doxycycline (Periostat®) taken twice daily for at least 3 months, and used in multicenter clinical trials for up to 24 months of continuous dosing. SDD is used as an adjunct to scaling and root planing in the treatment of chronic periodontitis. Its host modulatory effects include enzyme inhibition, cytokine reductions, and effects on osteoclast function. Since periodontitis is associated with many systemic diseases, such as osteoporosis, diabetes, and cardiovascular disease, researchers have investigated the effect of SDD on these systemic conditions. Studies have shown that SDD

1. Can effectively reduce the levels of localized and systemic inflammatory mediators (hsCRP) in osteopenic patients in addition to improving on the clinical measurements of periodontitis.

2. Has been shown to reduce systemic inflammatory biomarkers (hsCRP) in patients with cardiovascular disease.

3. Decreases HbA1c in patients who are taking normally prescribed hypoglycemic agents.

The impact of SDD therapy has been shown in many studies to go beyond the clinical benefits to periodontitis.

**Locally Administered Agents**

**Enamel Matrix Proteins, Growth Factors, and Bone Morphogenetic Proteins**

A number of local host modulation agents have been investigated for potential use as adjuncts to surgical procedures to improve periodontal health. These have included...
enamel matrix proteins (Emdogain®), bone morphogenetic proteins (BMP-2), and growth factors (PDGF). The initial local host modulatory agent approved by the FDA for adjunctive use during surgery to assist with clinical attachment gain and wound healing was Emdogain. PDGF combined with a resorbable synthetic bone matrix (GEM 21S) was developed as an adjunct to surgical regenerative procedures for periodontitis rhBMP-2 (INFUSE®) soaked onto an absorbable collagen sponge was developed to assist with ridge and sinus augmentation for implant placement. The technology behind GEM 21S also has been marketed for use in wound healing, particularly in people with diabetes. INFUSE has been used for quite some time for spinal surgery and impaired healing of fractures within the orthopedic community.

CONCLUSION

The findings discussed with regard to the use of host modulation therapy as an adjunct to better manage chronic periodontal disease may have applications in better management of other chronic systemic diseases such as arthritis, diabetes, osteoporosis, and cardiovascular disease. The use of adjuncts in addition to mechanical therapies has often been referred to as intensive periodontal therapy. Studies using locally applied antimicrobials as part of an intensive periodontal therapy regimen have shown very promising results in patients with diabetes and cardiovascular diseases. Future studies may demonstrate that in addition to our current standard therapies, intensive periodontal therapy with adjunctive antibiotics and/or host modulation for the management of periodontal disease may have profound positive effects on the overall health status of high-risk patients. The proper management of local infection and inflammation (periodontitis) will have a significant impact on the general overall health of the population.

Acknowledgments

The authors would like to acknowledge Dr. Hsi-ming Lee, Rene Martin, and Laura Bertolotti for their assistance in the organization of this manuscript.

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INTRODUCTION

Periodontal diseases (gingivitis and periodontitis) are destructive inflammatory diseases of the gingiva and the supporting structures of the teeth induced by a microbial biofilm commonly called dental plaque. The fundamental principle of the bacterial etiology of gingivitis was first established in a landmark study by Löe et al. in 1965. Using a novel—and now classic—experimental design, it was demonstrated that when students with healthy gingiva abstained from oral hygiene practices for 10 to 21 days, marginal inflammation of the gingiva (gingivitis) developed as a result of plaque accumulation. When oral hygiene was reinstated, gingival health returned. Today, in vitro and in vivo experiments, along with histologic assessments of inflamed and healthy gingiva, have provided a clearer understanding of the nature of the interactions between bacteria and host cells. However, current understanding of the etiology and pathogenesis of the periodontal diseases is far from complete.

Periodontal bacteria possess a plethora of virulence factors that, upon interaction with host cells, induce production of inflammatory mediators at the gingival level. These mediators are thought to be important for the initiation and progression of an inflammatory response, which though intended to eliminate the bacterial challenge, inevitably results in tissue damage when the bacterial challenge persists. It is also important to note that inflammation is not confined solely to periodontal tissues. Bacteria and inflammatory mediators may enter blood circulation to induce systemic inflammation. Evidence is increasing that cardiovascular disease (CVD), adverse pregnancy outcomes, diabetes mellitus, and possibly cancer are associated with oral organisms entering the circulation and elevated systemic inflammation. The coexpression of inflammatory periodontitis with other inflammatory diseases suggests a common pathway in pathogenesis.

Depending on the effectiveness of the innate immune response, bacterial infection may persist and lead to perpetuation of inflammation, which may become chronic with the development of acquired immunity. However, if the infection is cleared, then resolution of inflammation occurs with the return of tissue homeostasis without permanent damage. Recent discoveries have altered our understanding of inflammation resolution and return of tissue homeostasis. We now understand that resolution of inflammation is an active process, not the passive decay of proinflammatory signals as once thought. The ability to manipulate these processes may provide a new treatment paradigm for both local and systemic inflammatory diseases.

Chapter Goals

This chapter is structured to (1) provide background information regarding the initiation and orchestration of inflammation at the gingival level after the interaction of the biofilm with host cells; (2) examine the evidence for periodontal disease influencing systemic inflammation and describe the possible biologic pathways, as well as the cellular and molecular events that may occur; (3) explore the idea that systemic inflammation may be the link that associates periodontal disease with other systemic diseases, focusing on the potential mechanisms of action; and (4) address the role of resolution of inflammation in the pathogenesis.
of inflammatory diseases; and (5) introduce new strategies directed at mechanisms of inflammation resolution that may be used in treating inflammatory diseases.

**PART I: INFLAMMATION AT THE GINGIVAL LEVEL**

Periodontal disease is an inflammatory disorder of the supporting tissues of the teeth in a susceptible host. Bacteria in the oral cavity colonize the teeth, the gingival sulcus, and eventually the periodontal pocket, forming an organized biofilm. Depending on the stage of maturation, the biofilm may consist of several hundred bacterial species, many of which have yet to be identified. Some of these species are associated with health, whereas others are associated with pathology. However, the identity of the organisms that actually initiate disease remains unknown.

**Bacterial Components**

The formation of organized biofilms enhances the ability of bacteria to survive. Bacteria have also evolved a variety of virulence factors to further enhance their survival, such as toxins, proteases, and glycosidases. Virulence factors are presumably intended to hide the bacteria from host detection as well as to provide essential molecules for nourishment. Conversely, the host has evolved mechanisms for detection of bacteria through the recognition of structural components of the bacterial surface, such as lipopolysaccharide (LPS), peptidoglycan (PGN), and other cell surface components such as fimbriae, which perform essential physiologic functions for the bacteria. Variations of these bacterial components may be seen among various species, or even among different strains of the same species. Despite their structural heterogeneity, most of these molecules have conserved motifs known as pathogen-associated molecular patterns (PAMPs), which are recognized by host cell receptors called pattern recognition receptors (PRRs). These highly conserved innate immune receptors evolved for detection of invading bacteria. Binding of PAMPs by PRRs activates specific signaling pathways in host cells that are important for the initiation of an inflammatory response. Although this response is intended to eliminate the microbial challenge, the inflammatory mediators that are secreted may lead to further tissue damage if bacterial clearance is not achieved. Today, the most studied bacterial factors are LPS, PGN, lipoteichoic acids (LTAs), fimbriae, proteases, heat-shock proteins (HSPs), formyl-methionyl peptides, and toxins. Host PRRs include the Toll-like receptors (TLRs) and other G-protein-coupled receptors (GPCRs). Table 1 presents a summary of the results by actions of various bacterial factors after interaction with specific host cells.

**Bacteria and Gastrointestinal Equilibrium**

The oral cavity, as part of the gastrointestinal tract, is naturally colonized by a wide variety of bacteria. This physiologic situation does not always result in pathology. The tooth-gingival interface is the site of a variety of natural, innate host defense mechanisms, including the regular shedding of epithelial cells, the washing effect of the saliva and the gingival crevicular fluid (GCF), and, most important, the phagocytic action of neutrophils that migrate continuously through the junctional epithelium into the gingival sulcus. These mechanisms preserve an equilibrium in the number of bacteria around the teeth. However, excess inflammation may disturb this equilibrium and pathogenic bacteria may overgrow, initiating the pathogenesis of gingivitis and possibly periodontitis.

Current understanding of the steps leading to periodontal disease includes periodontal bacteria attaching to epithelial cells using their fimbriae and PRR recognition of PAMPs, inducing epithelial cell secretion of
Table 1. Summary of Main Effects of Bacterial Virulence Factors on Host Cells

<table>
<thead>
<tr>
<th>Bacterial Factor</th>
<th>Epithelial Cells</th>
<th>Monocytes/ Macrophages</th>
<th>Endothelial Cells</th>
<th>Fibroblast Cells</th>
<th>Mast Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS</td>
<td>IL-8</td>
<td>IL-1β, TNF-α, IFN-γ, IL-6, IL-12, IP-10, MCP-5, MIP-1α, MIP-2, PGE₂, NO L-selectin, CD11α/CD18, CD11β/CD18</td>
<td>E-, P-selectin, MCP-1</td>
<td>MCP-1, IL-1β, IL-6, IL-8, ICAM-1</td>
<td>IL-1β, TNF-α, IFN-γ, IL-6, IL-12, IP-10</td>
</tr>
<tr>
<td>PGN</td>
<td>IL-8</td>
<td>IL-1β, TNF-α, IL-6, IL-8, MIP-1α, NO</td>
<td>ICAM-1, IL-8</td>
<td>IL-8</td>
<td>Histamine, TNF-α, Prostaglandins, IL-4, IL-5, IL-10</td>
</tr>
<tr>
<td>LTA</td>
<td>IL-8</td>
<td>IL-1β, TNF-α, IFN-γ, IL-6, IL-8, IL-10, NO</td>
<td>IL-6, IL-8, E-selectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fimbriae</td>
<td>IL-1β, TNF-α, IL-6, IL-8</td>
<td>IL-1β, TNF-α, IL-6, NO</td>
<td>MCP-1, IL-8, ICAM-1, VCAM-1, P⁺, E-selectin</td>
<td>IL-1β, TNF-α, IL-6</td>
<td></td>
</tr>
<tr>
<td>Proteases</td>
<td>IL-6, β-defensins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP</td>
<td>IL-6</td>
<td></td>
<td></td>
<td>IL-6, IL-8</td>
<td></td>
</tr>
<tr>
<td>fMLP</td>
<td></td>
<td>TNF-α, CD11α/CD18, CD11β/CD18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxins</td>
<td>IL-1β, IFN-γ, IL-6, IL-8, IL-10</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

proinflammatory cytokines (TNF-α, IL-1β, IL-6), and the chemokine IL-8 in the connective tissue. Normally, the intact sulcular and junctional epithelium serves as an effective natural barrier that keeps the bacteria from entering host tissues. However, several periodontopathogens (e.g., Porphyromonas gingivalis, Aggregatibacter [formerly Actinobacillus] actinomycetemcomitans) have been shown to invade and transverse epithelial cells to gain access to the connective tissue. Moreover, bacterial components (e.g., LPS, PGN) and products (e.g., proteases, toxins) that are either shed or secreted can also diffuse through the epithelial junctions to the connective tissue.11

**Bacteria in Connective Tissue**

Bacteria and/or their virulence factors found in the periodontal pocket epithelium and the connective tissue directly stimulate host cells residing in this area, such as leukocytes, fibroblasts, mast cells, endothelial cells, dendritic cells, and lymphocytes. Neutrophils, macrophages, fibroblasts, and mast cells release more proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12), chemoattractants (IL-8, MIP-1-α, MIP-2, MCP-1, MCP-5), and prostaglandin E2 (PGE2) in the connective tissue. In addition, degranulation of mast cells results in the secretion of histamine and leukotrienes, further amplifying the inflammatory cascade.12,13

Mediators that are secreted from activated host cells (e.g., IL-1β, TNF-α, PGE2, and histamine) further assist bacterial virulence factors in the activation of endothelial cells. This leads to secretion of more chemokines (IL-8, MCP-1) and expression of adhesion molecules on the surface of endothelial cells, which are important for leukocyte extravasation (P- and E-selectins as well as intercellular adhesion molecule 1 [ICAM-1] and ICAM-2).14 Specifically, P- and E-selectins interact with glycoproteins on leukocytes, allowing the cells to adhere reversibly to the vessel wall and causing circulating leukocytes to appear to “roll” along the activated endothelium. Then, IL-8 and other chemokines, bound to proteoglycans on the surface of leukocytes, trigger a conformational change of integrins (LFA-1, CD11b; CD18). As a result, adhesive properties increase dramatically, and leukocytes attach firmly to ICAM-1 expressed on endothelial cells. Tumor necrosis factor-α (TNF-α), PGE2, and histamine increase vascular permeability, allowing leukocytes to squeeze between the endothelial cells, thereby entering the connective tissue in a process known as diapedesis. Finally, chemokines, such as IL-8, which are produced at the site of infection and bind to proteoglycans of the extracellular matrix, and along with bacterial chemoattractants (IMLP, fimbriae), form a concentration gradient that guides the leukocytes to migrate to the focus of infection.

**The Inflammatory Cascade**

Neutrophils are the first leukocytes to arrive, followed by mononuclear phagocytes, which subsequently differentiate into macrophages. The interaction of these cells with bacterial virulence factors induces further activation, which enhances their phagocytic activity by increasing the production of nitric oxide (NO) and the expression of complement receptors (CR3). If the innate immune response is successful, the bacteria are eliminated, and resolution of inflammation follows. However, persistence of bacteria leads to a chronic response characterized by extracellular release of neutrophil granule contents, including degradative enzymes and reactive oxygen species that spill into the extracellular milieu, leading to local tissue damage and amplification of acute inflammatory signals.15

Proinflammatory cytokines (TNF-α, IL-1β, IL-6) from the site of inflammation enter the circulation and reach the liver, where they activate hepatocytes. This leads,
among other events, to the synthesis of plasma proteins known as acute-phase proteins, including LPS-binding protein (LBP) and CD14, which are important for the recognition of bacterial virulence factors. Complement proteins and C-reactive protein (CRP) contribute by opsonizing bacteria, thereby aiding in recognition for phagocytosis. These products enter the circulation and, because of increased vascular permeability, diffuse into the inflamed gingival tissues. Figure 1 illustrates the initiation of inflammation at the gingiva.

**Figure 1. Initiation of Inflammation at the Gingival Level**

Neutrophils in the gingival crevicular fluid (GCF) and epithelial cells comprise the first line of defense to prevent bacteria from invading the host. The interaction of the bacterial biofilm with epithelial cells leads to activation and secretion of proinflammatory cytokines (green). Bacteria and their virulence factors (red) may penetrate the epithelial lining and enter the connective tissue. In this compartment, they may interact with host cells, such as macrophages, fibroblasts, and mast cells to stimulate these cells to release more proinflammatory mediators such as TNF-α, IL-1β, IL-8, LTB-4, and histamine. These mediators, along with bacteria/virulence factors, may activate endothelial cells to attract circulating leukocytes in the connective tissues. In this compartment, phagocytic cells take up bacteria and their antigenic molecules. This process, if further enhanced by acute-phase response proteins, such as CRP, which are produced from activated hepatocytes, enter the connective tissue via circulation as a result of increased vascular permeability. If the noxious agents are eliminated, resolution of inflammation follows. However, if the bacterial challenge persists, the more efficient adaptive immune response takes over.


**The Immune Response**

If the infection persists, the acquired immune response is initiated, and the established lesion is created, as described by Page and Schroeder.16 Briefly, dendritic cells within the epithelium take up bacterial antigens and migrate to the peripheral lymph nodes. The antigens are processed into a form that is recognizable by the immune system; that is, the antigenic peptide binds to a class II major histocompatibility complex (MHC) receptor that consequently “presents” the antigen. As a result, antigen-specific effector
T cells and antibody-secreting B cells are generated by clonal expansion and differentiation over the course of several days, during which time the induced responses of innate immunity continue to function. Eventually, antigen-specific T cells, and then antibodies, are released into the blood to target the infection site.¹⁷ Macrophages that engulf bacteria at the site of infection express costimulatory molecules (MHC II) and present bacterial antigens on their surface. Antigen-specific T cells see the antigens and activate the macrophages, enabling them to destroy intracellular bacteria more efficiently.

In addition, secreted antibodies protect the host from infection by (1) inhibiting the toxic effects or infectivity of pathogens by binding (neutralization); (2) opsonizing the pathogens and promoting phagocytosis; and (3) activating the complement system. Failure to clear the infection at this point leads to further tissue damage. Activated macrophages produce oxygen radicals, NO, and proteases in the gingival tissues, which are toxic to the host cells. Moreover, recent work on a mouse model revealed that the induction of an adaptive immune response to colonizing pathogens results in receptor activator of nuclear factor-kappaB ligand-dependent periodontal bone loss.¹⁸

**Summary of Part I**
The trigger that causes the shift from tissue homeostasis to pathology remains unclear. The logical extension of Löe’s observation is that this is caused by specific bacteria, and indeed, a large body of evidence suggests that certain bacteria are associated with progressive disease. However, studies of the microbiota of the periodontal lesion are cross-sectional, and definitive cause-effect relationships have not been demonstrated.

A longitudinal study of periodontal disease progression failed to implicate any single organism or group of organisms in the initiation of periodontal attachment loss.¹⁹ In addition, recent animal studies suggest that the level of host inflammation has a major impact on the composition of the biofilm. It is interesting that inflammation is a stronger predictor of periodontal attachment loss than the composition or quantity of the oral biofilm.²⁰ Clearly, the etiology and pathogenesis of periodontitis require further study. It is also apparent that traditional periodontal pathogens (Socransky’s red complex) contribute to and accelerate disease when they overgrow in the periodontal environment. However, the role of inflammation and the host immune response has taken on a new perspective, potentially determining susceptibility and providing a novel therapeutic target.

**PART II: SYSTEMIC INFLAMMATION DUE TO PERIODONTAL INFECTION**
Despite the localized nature of periodontal disease, infection of the sulcus/periodontal pocket with periodontopathogens may be responsible for inflammatory responses that develop beyond the periodontium. To date, several biologic pathways have been recognized that present reasonable hypotheses for periodontal disease induction of systemic inflammation.

**Inflammatory Pathways**
In health, the sulcular epithelium, along with innate immune molecules, acts as a natural barrier system that prevents bacterial penetration. Hence, only a small number of bacteria, mostly facultative anaerobes, manage to enter the gingival tissues and the bloodstream. However, in cases of periodontal disease, the inflamed and ulcerated pocket epithelium is vulnerable to bacterial penetration and forms an easy port of entry for the bacteria. This leads to an increase in the number of periodontopathogens, mainly anaerobic gram-negative, in the gingival tissues and consequently in the circulation. Bacteremia can be further aggravated after mechanical irritation of the inflamed gingiva
during tooth brushing, chewing, oral examination, and scaling and root planing. The microorganisms that gain access to the blood are usually eliminated by the reticuloendothelial system within minutes (transient bacteremia) and usually without any other clinical symptoms except possibly a slight increase in body temperature. However, if the disseminated bacteria find favorable conditions, they may colonize distant sites and form ectopic foci of infection.

Similarly, bacterial virulence factors that are secreted or shed in the gingival tissues may also disseminate via the circulation and stimulate remote tissues. Bacteria and bacterial antigens that are systemically dispersed can trigger significant systemic inflammation. Leukocytes as well as endothelial cells and hepatocytes respond to bacteria/virulence factors, producing proinflammatory immune mediators. Moreover, soluble antigens may react with circulating specific antibodies, forming macromolecular complexes that may further amplify inflammatory reactions at sites of deposition.

### Proinflammatory Mediators

A different biologic pathway that may explain the systemic inflammation induced by periodontal disease involves proinflammatory mediators, such as IL-1β, IL-6, TNF-α, and PGE₂, which are produced by host cells in the inflamed gingival tissues. These mediators are secreted locally in response to bacterial challenge, but may spill into the circulation and exert distant or systemic effects.

Specifically, cytokines may reach distant sites and further activate endothelial cells, leading in some cases to endothelial dysfunction. Moreover, the circulating mediators, because of the increased vascular permeability at the sites of inflammation, may enter inflamed tissues and exacerbate the inflammatory processes. However, the most important impact of these circulating mediators is systemic. Proinflammatory cytokines may induce leukocytosis, which is characterized by an increase in circulating neutrophils. Moreover, IL-1β, TNF-α, and especially IL-6 may reach the liver and activate hepatocytes to produce acute-phase proteins. The most important acute-phase reactants are CRP, serum amyloid A (SAA) protein, fibrinogen, plasminogen activator inhibitor 1 (PAI-1), complement proteins, LBP, and soluble CD14. These proteins are released in the plasma and possess a wide variety of functions, such as proinflammatory activities and stimulation of tissue repair mechanisms. The production of these proteins is part of an acute-phase response that is characterized by fever, increased vascular permeability, and a general elevation of metabolic processes. An acute-phase response starts within hours or days of most forms of acute tissue damage or inflammation and, despite its name, persists with chronic inflammation. As acute-phase reactants enter the circulation, they may return to the inflamed gingival tissues. However, since they circulate throughout the body, they can affect ectopic sites, causing inflammation or exacerbation of existing inflammatory processes. This concept takes on new meaning in light of the recent implication of CRP in the pathogenesis of CVD.

Because no consensus exists to date on the mechanisms that induce systemic inflammation from periodontal disease, any of the above pathways (bacteremia, systemic spilling of cytokines, and activation of the acute-phase response) must be considered a candidate for the generation of systemic inflammation. It is also possible that, depending on the severity of periodontal disease, any of these mechanisms may occur alone or in combination, leading to variations of induced systemic inflammation.

### Acute-Phase Proteins

CRP is produced mainly by the liver, but it
may also be synthesized locally at sites of inflammation. CRP opsonizes different bacteria by binding to phosphorylcholine found on the surface, thereby assisting in bacterial uptake by phagocytes.26 Opsonization and phagocytosis are further enhanced by activation of the complement system by CRP. Other proinflammatory activities of CRP include the upregulation of the expression of adhesion molecules, such as ICAM-1 and E-selectin on endothelial cells and the induction of IL-6, IL-1β, and TNF-α, and of the chemokines IL-8 and MCP-1. Other properties of CRP that may not be of obvious importance in periodontal disease but may significantly affect other systemic inflammatory diseases (e.g., atherosclerotic lesions) include thrombosis due to the procoagulant activity and reduction of fibrinolysis by inducing an increase in the expression of PAI-1, the main inhibitor of fibrinolysis.27

Finally, CRP mediates proliferation and activation of smooth muscle cells and decreases the expression of endothelial nitric oxide synthase (eNOS). CRP may also have anti-inflammatory properties, and hence its primary role is likely to be the regulation of acute inflammation.

**Serum Amyloid A**
SAA proteins are a family of apolipoproteins associated with high-density lipoprotein in plasma. They have several proinflammatory functions, such as the recruitment of immune cells to inflammatory sites and the induction of enzymes that degrade extracellular matrix. Also, SAA proteins transport cholesterol to the liver for secretion into the bile.

**Fibrinogen**
Fibrinogen is a soluble plasma glycoprotein. Processes in the coagulation cascade activate prothrombin to thrombin, which is responsible for converting fibrinogen into fibrin. Fibrin is then cross-linked by factor XIII to form a clot. Thus, fibrinogen is involved in blood coagulation and platelet activation.

**Plasminogen Activator Inhibitor 1**
PAI-1 is produced by the liver and endothelial cells. It inhibits the serine proteases tPA and uPA/urokinase, and therefore is an inhibitor of fibrinolysis, the physiologic process that degrades blood clots.

**Complement Proteins**
Complement proteins take part in a triggered enzyme cascade that activates the complement system. There are three ways by which complement is involved in inflammatory processes. First, activated complement proteins may bind covalently to pathogens as opsonins for engulfment by phagocytes bearing receptors for complement. Second, the small fragments of some complement proteins act as chemoattractants to recruit more leukocytes to the site of complement activation. Third, terminal complement components damage certain bacteria by creating pores in the bacterial membrane.28

**LPS-Binding Protein and Soluble CD14**
The proteins LBP and soluble CD14 play an important role in transferring LPS and PGN to the TLRs. Hence, their presence is critical for initiating and organizing an inflammatory immune response after bacterial challenge.

**Systemic Cellular and Molecular Markers of Inflammation**
Periodontal infection may induce an inflammatory response that is not limited to the tissues surrounding the teeth, but is also extended systemically. The main cellular and molecular markers of systemic inflammation induced by periodontal disease include the increased number of peripheral leukocytes, the higher concentrations of serum antibodies against periodontopathogens, and the ele-
vated levels of circulating proinflammatory cytokines and acute-phase proteins.

With the exception of serum antibodies against periodontopathogens, these markers are not specific for periodontal disease, but can be shared with distant inflammatory processes that have systemic effects. As such, these markers can be affected by other inflammatory diseases that can occur concomitantly. The following systemic markers have been associated with the presence of periodontal disease and are usually affected by the severity of inflammation in the gingiva.

**Peripheral Blood Leukocytes**

In patients with periodontitis, leukocyte counts have been shown to be slightly elevated compared with the counts of healthy subjects, though not always significantly. The elevated level of circulating leukocytes depends largely on the extent and severity of periodontal disease. Periodontal therapy may lead to a reduction in the number of peripheral leukocytes. Polymorphonuclear leukocytes are the main leukocytes that are increased; these cells are possibly recruited at higher levels during episodes of bacteremia and leakage of bacterial virulence factors during periodontal disease.

**Serum Antibodies Against Periodontopathogens**

In chronic periodontal disease, in which the adaptive immune response has been activated, local and systemic exposure to periodontopathogens leads to an increase in the levels of circulating antibodies against the pathogenic antigens. Treatment of disease is followed by a reduction in antibody levels.

**Serum Proinflammatory Cytokines**

In healthy subjects, the levels of circulating proinflammatory cytokines are very low or nondetectable. However, in patients with periodontitis, several proinflammatory cytokines may spill into the bloodstream and increase their concentration in the plasma. Of the proinflammatory mediators studied, only IL-6 levels have been consistently shown to be elevated in the serum. This increase is related to the extent and severity of inflammation in periodontal tissues. However, controversial reports have been published on the impact of periodontal therapy on IL-6 levels, suggesting the need for further research on the topic. Finally, most of the studies looking at the levels of serum IL-1 and TNF-α among healthy and periodontitis patients failed to report any differences, and in most cases cytokine levels were not measurable.

**Acute-Phase Proteins**

The levels of several acute-phase reactants, such as CRP, fibrinogen, LBP, and soluble CD14 have been studied and have been shown to be elevated in patients with periodontal disease. However, the acute-phase proteins that have received the most attention and are consistent markers of systemic inflammation in periodontal disease are CRP and fibrinogen. A large number of studies, both in animal models and in humans, have revealed a positive association between periodontal disease and circulating CRP levels, whereas a recent meta-analysis limited to human studies has confirmed that plasma CRP is elevated in patients with periodontitis compared with CRP in healthy persons. Moreover, this increase was proportional to the extent and severity of the disease. Several studies report a decrease of plasma CRP after periodontal intervention, but there is modest evidence that periodontal therapy lowers the levels of this protein. Finally, in several studies, the levels of fibrinogen have also been found to be elevated in patients with periodontitis compared with fibrinogen levels in healthy individuals. However, no available evidence exists to support that theory that periodontal therapy actually reduces the amount of circulating fibrinogen.
CHAPTER 3 Infection and Inflammation

Possible Role of Systemic Inflammation in Various Disorders

During the late nineteenth and early twentieth centuries, the focal infection theory dominated the medical world. This theory held that foci of sepsis were responsible for the initiation and progression of a variety of inflammatory diseases, such as arthritis, peptic ulcers, and appendicitis. As a result, therapeutic full-mouth extractions became a common dental practice. However, many teeth were extracted without evidence of infection. When it was finally realized that there was no therapeutic benefit, the theory was discredited and the practice abandoned. During the final two decades of the twentieth century—as our knowledge concerning the inflammatory component of systemic diseases was enriched and our understanding of the relation of periodontal disease to systemic inflammation increased—the idea that periodontal infection may affect the progression of systemic disorders such as CVD, adverse pregnancy complications, diabetes mellitus, and other diseases re-emerged.

Hence, to date, a large volume of data has been gathered evaluating the possible association of periodontal disease with systemic diseases. Observational studies have primarily used several clinical parameters such as probing pocket depth, clinical attachment loss, and bleeding on probing to assess the severity of periodontal disease and consequently the risk for systemic exposure. However, the results of these studies are not always consistent, indicating that these parameters separately may not be able to reflect the inflammatory burden at the gingival level. Thus recently, Nesse et al. introduced a new index that incorporates the latter parameters. This index calculates the surface area of the inflamed periodontal tissues (periodontal inflamed surface area, PISA), which may reflect, in a way, the magnitude of systemic inflammatory exposure posed by periodontal disease. This may be important because increasing evidence suggests that elevated levels of the markers of systemic inflammation are associated with an increased risk for systemic diseases.

Cardiovascular Disease

There is now abundant clinical evidence demonstrating that many biomarkers of inflammation are elevated years in advance of first-ever myocardial infarction (MI) or thrombotic stroke, and that these same biomarkers are highly predictive of recurrent MI, recurrent stroke, and death due to CVD. Moreover, studies demonstrate that serum IL-6 levels were significantly elevated in subjects who subsequently experienced an MI compared with IL-6 levels of age-matched controls. Similarly, plasma levels of soluble P-selectin, soluble CD40L, and macrophage-inhibitory cytokine-1 all were significantly increased in healthy subjects who subsequently developed CVD events compared with those of matched controls. Elevated plasma concentrations of TNF-α have also been associated with CVD, and specifically with recurrent nonfatal MI or other CVD events. Moreover, TNF-α levels were persistently higher among post-MI patients at increased risk for recurrent coronary events.

Besides these proinflammatory cytokines, several acute-phase reactants have also been associated with CVD. One of the factors with the strongest evidence as a biomarker for predicting CVD events is CRP (specifically, high-sensitivity CRP, hsCRP). When measured in the blood, hsCRP proved to be a strong, independent predictor of future MI and stroke among apparently healthy asymptomatic men. Also, the relative risk for first MI and ischemic stroke increased significantly with each increasing quartile of baseline concentrations of CRP. As described already, CRP may contribute to the initiation and development of atherothrombotic lesions not only by upreg-
ulating the expression of proinflammatory cytokines, but also by mediating proliferation and activation of smooth muscle cells and by activating the procoagulant system. This last property may be further enhanced by another acute-phase protein, fibrinogen, which is often found to be elevated in patients with CVD.

**Adverse Pregnancy Outcomes**

Systemic inflammation has also been implicated in adverse pregnancy outcomes, since elevated concentrations of CRP in early pregnancy are associated with an increased risk of preterm birth and very-preterm birth.

**Diabetes Mellitus**

Finally, systemic inflammation has been associated with both type 1 and type 2 diabetes mellitus. Recent studies suggest that in type 1 diabetes, the levels of systemic markers of inflammation, such as CRP, do not differ between healthy persons and persons for which type 1 diabetes has been just diagnosed. However, the levels of circulating CRP are significantly higher in those with long-term diabetes. It is also believed that inflammatory processes may have a more pronounced effect on the development of complications of type 1 diabetes. Thus, elevated levels of plasma CRP and of the proinflammatory soluble adhesion molecule, vascular cell adhesion molecule-1 (VCAM-1) have been found in patients with microvascular disease compared with those without microvascular disease.

In those with type 2 diabetes, inflammatory processes are more strongly associated with the development of the disease. Systemic markers of inflammation are found to be increased in healthy persons who develop type 2 diabetes later in life. Among Pima Indians, a population in whom type 2 diabetes is highly prevalent, subjects with white blood cell counts within the highest tertile were more likely to develop type 2 diabetes over a period of 20 years compared with those in the lowest tertile. Moreover, in two other studies, healthy persons demonstrating serum levels of CRP and IL-6 within the highest quartiles were more likely to develop type 2 diabetes in the next 4 to 7 years compared with those in the lowest quartile. Similar results were found with increased levels of PAI-1, another acute-phase protein. Insulin resistance, which is associated with type 2 diabetes and usually precedes the development of frank diabetes, may also be affected by preexisting systemic inflammation, since several proinflammatory and acute-phase proteins, such as TNF-α, IL-6, MCP-1, PAI-1, and SAA, are associated with the induction of insulin resistance.

**Summary of Part II**

Based on available evidence, systemic inflammation may actually be the link that associates periodontal disease with other systemic diseases. Details of the plausible biologic mechanisms that may associate periodontal disease with various systemic diseases are further analyzed in other chapters of this book.

**PART III: RESOLUTION OF INFLAMMATION IN PERIODONTITIS AND OTHER SYSTEMIC DISEASES**

Inflammation is thought to play a central role in the progression of periodontal disease and a number of systemic diseases. Experiments in animal models and in man have demonstrated that periodontal destruction is mediated primarily by the inflammatory response, although periodontal pathogens are a necessary etiologic factor. Genetic polymorphisms and other factors may also be responsible for a hyperinflammatory phenotype, which may further affect the susceptibility of the host to periodontal disease and tissue destruction. Currently, it is believed that in chronic periodontal disease, destruc-
tion does not follow a linear pattern with time, but occurs in random bursts with periods of remission and exacerbation. However, the reasons behind this random progression are not fully understood. Disease progression becomes even more enigmatic considering that it is not always clear why a chronic inflammation of the gingiva remains as gingivitis in some patients and progresses to periodontitis in others. Regardless of the nature of periodontal disease progression, the perpetuation of the inflammatory process in the gingiva may lead to a chronic low-grade systemic inflammatory response, which in turn potentially contributes to the progression of systemic diseases.

Process of Inflammatory Resolution
The landmark events during inflammation include the accumulation of leukocytes in the infected area and phagocytosis of the bacteria and/or their virulence factors. As part of the inflammatory process, activation of neutrophil lysosomal phospholipase releases free arachidonic acid from membrane phospholipids. Once free arachidonic acid is available, two separate pathways can be initiated: (1) the cyclooxygenase (COX) pathway, which leads to the production of prostaglandins (e.g., PGE₂, prostacyclins, and thromboxanes), and (2) the lipooxygenase (LO) pathways, which lead to the production of a series of hydroxyl acids characterized by the 5-LO products, the leukotrienes (e.g., LTB4). There are three cell type-specific LOs: the 5-LO from myeloid cells, the 12-LO from platelets, and the 15-LO of epithelial and endothelial cells. PGE₂ is a potent activator of osteoclast-mediated bone resorption, and with other eicosanoids mediates inflammation and periodontal tissue destruction. LTB4 attracts neutrophils, stimulates the release of granule associated enzymes from neutrophils, and contributes to proinflammatory processes and to further tissue damage.

Returning to Homeostasis
After inflammation reaches its peak, resolution of inflammation occurs with the reduction or removal of leukocytes and debris from inflamed sites with a return to homeostasis. Until recently, resolution of inflammation was considered to be a passive process in which the lack of bacterial stimuli decreased the production of inflammatory mediators, which in turn reduced the inflammatory response, thereby returning to normal function. New data suggest that resolution of inflammation is an active biochemical and metabolic process initiated by a newly identified class of receptor agonists that emerge temporally as the inflammatory lesion matures. Although prostaglandins and leukotrienes secreted by neutrophils have proinflammatory properties, as inflammation proceeds, the same prostaglandins (PGE₂ and PGD₂) may promote expression of the 15-LO gene. This leads to a switch in the expression of biosynthetic enzymes by infiltrating neutrophils (Figure 2). Binding of lipoxin A₄ to neutrophils leads to a phenotypic change, stopping all proinflammatory activity of neutrophils and leading to apoptosis. As a result, they stop secreting the chemoattractant LTB4, and several cellular pathways are activated, producing, at a local level, other dual-acting anti-inflammatory and proresolution lipid mediators, including resolvins and protectins.

Mechanisms of Inflammation Resolution
Resolvins and protectins provide potent signals that orchestrate and accelerate mechanisms that promote resolution of inflammation and homeostasis. Specifically, as depicted in Figure 3, proresolution mediators stop neutrophil infiltration and drive neutrophils to apoptosis, while at the same time attracting monocytes to the lesion. Lipoxin-stimulated monocytes/macrophages obtain a non-phlogistic phenotype, which results in phagocytosis of apoptotic neutrophils and
**Figure 2.** Biosynthesis of Proresolving Lipid Mediators

Chemical mediators involved in the initiation of acute inflammation, such as prostaglandins and leukotrienes, induce "class switching" toward proresolving lipid mediators. The proresolving mediators include arachidonic acid-derived lipoxins (LXs), aspirin-Triggered LXs (ATLs), eicosapentaenoic acid (EPA)-derived resolvins Es (RvEs), docosahexaenoic acid (DHA)-derived resolvins Ds (RvDs), and protectins (PDs) (or neuroprotectins in neural tissues).

**Figure 3.** Dual Anti-inflammatory and Proresolution Actions of Specific Lipoxins, Resolvins, and Protectins

enhanced mucosal clearance of bacteria without concomitant secretion of proinflammatory mediators that could contribute to tissue damage. Moreover, proresolution lipid molecules increase the exit of phagocytes from the inflamed site through the lymphatics. Finally, some of these molecules may also stimulate the uptake and clearance of local cytokines by apoptotic neutrophils. After neutrophils and debris are removed, homeostasis returns and repair mechanisms are initiated; lipoxins are antifibrotic and allow for complete tissue healing without scarring.

Hence, it can be argued that the persistence of an inflammatory disease, such as periodontal disease, may be caused by too much proinflammatory signal or not enough proresolution signal. In other words, a hyperinflammatory phenotype due to a particular genetic background of the host may result in oversecretion of inflammatory mediators in response to bacterial stimuli, which in turn contributes to periodontal disease susceptibility, or a failure of resolution pathways. As high levels of inflammatory cytokines are maintained, tissue destruction continues and inflammation persists. If proresolution signals are weak, neutrophils are not removed and monocytes/macrophages maintain a phlogistic phenotype. This results in further production of inflammatory cytokines and perpetuation of the inflamed state.

**New Treatment Paradigms**

It is reasonable to suggest that the understanding and ability to manipulate resolution of inflammation may provide a new treatment paradigm for inflammatory diseases, local and systemic. Although human data are not yet available, a growing and promising literature from in vitro work and animal models supports the beneficial actions of resolution agonists on both periodontal disease and other systemic diseases.  

**Role of Proresolution Mediators**

Examples of the actions of therapeutic proresolution mediators in periodontal disease include overexpression of lipoxin A₄ in transgenic rabbits, protecting against periodontitis and atherosclerosis. In another study, topical treatment with resolvins (omega 3 fatty acid-derived resolution agonists, *vice versa*) prevented more than 95% of alveolar bone destruction in rabbits. Moreover, histologic analysis revealed few, if any, neutrophils in the tissue and little tissue damage. At the same time, the numbers of osteoclasts were also found to be reduced. In addition, treatment of periodontitis with resolvins systemically reversed the observed increase in CRP and IL-1β levels. Also, in established periodontal disease, resolvins prevented further tissue destruction, and both gingival and osseous tissues that were lost during disease were regenerated.

Finally, in in vitro bone cultures, resolvins significantly enhanced expression of osteoprotegerin (OPG) without inducing change in receptor activator of NF-κB ligand levels, whereas osteogenic markers alkaline phosphatase, bone sialoprotein, and Runt-related transcription factor 2 remained unchanged. These results indicate that resolvins may modulate osteoclast differentiation and bone remodeling by direct actions on bone, rescuing OPG production and restoring a favorable receptor activator of NF-κB ligand/OPG ratio.  

Resolvins, lipoxins, and protectins have also been shown in animal models to have beneficial impact on a variety of other inflammatory diseases. For example, lipoxins stopped neutrophil recruitment and promoted lymphatic removal of phagocytes in periodontitis. Moreover, in cystic fibrosis, lipoxins decreased neutrophil inflammation, pulmonary bacterial burden, and disease severity. Resolvins in a colitis model in mice decreased neutrophil recruitment and proinflammatory gene expression, improved survival, and reduced weight loss. In addition,
resolvs protected against neovascularization in retinopathy.\textsuperscript{51} Finally, in an asthma model, protectins protected against lung damage, airway inflammation, and airway hyperresponsiveness.\textsuperscript{52} Table 2 lists the impact of lipoxins, resolvins, and protectins on various inflammatory disease models.

It is conceivable that the use of proresolution mediators in managing periodontal and other inflammatory diseases may prove to be beneficial in humans as well. Mechanical debridement, which aims at the reduction of the bacterial load in the gingival pocket, may help the host/patient to clear the infection. In addition, it is possible that the use of locally applied proresolution mediators could prevent further tissue damage, enhance the resolution of inflammation (which would lead to healthy gingiva), and ideally result in periodontal tissue regeneration rather than in scarring and repair. Moreover, resolution of inflammation at the gingival level may minimize systemic inflammation induced by periodontal disease, thereby attenuating the possible negative effects of periodontal disease on systemic diseases.

**Figure 4.** Schematic Illustration of Lipid-Mediated Proinflammatory and Proresolution Pathways

**Origins of Proresolution Mediators**

To manipulate resolution of inflammation more effectively, it is imperative to understand the biologic origin of the proresolution mediators. Lipoxins (e.g., lipoxin A\textsubscript{4}) derive from arachidonic acid after activation of the 12-/5-LO or the 15-/5-LO pathways. Resolvins and protectins are biosynthesized from omega-3 essential polyunsaturated fatty acids (\(\omega-3\) PUFAs), such as eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). EPA and DHA can be metabolized by aspirin-modified COX-2 pathways to form resolvins, whereas DHA can be converted to protectins via an LO-mediated pathway (Figure 4).

Another aspect of current anti-inflammatory strategies was the discovery that disruption of biosynthesis of these proresolution mediators by either COX-2 or LO inhibitors may lead to a resolution deficit phenotype, which is characterized by impaired phagocyte removal, delayed resolution, and prolonged inflammation. This may explain why several anti-inflammatory agents, such as selective COX-2 inhibitors

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<table>
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<tr>
<th>Disease Model</th>
<th>Species</th>
<th>Action(s)</th>
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<tr>
<td><strong>Lipoxin A4/ATL</strong></td>
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| Periodontitis                       | Rabbit    | –Reduces neutrophil infiltration  
–Prevents connective tissue and bone loss                                                                                                  |
| Peritonitis                         | Mouse     | Stops neutrophil recruitment and lymphatic removal of phagocytes                                                                          |
| Dorsal air pouch                    | Mouse     | Stops neutrophil recruitment                                                                                                             |
| Dermal inflammation                | Mouse     | Stops neutrophil recruitment and vascular leakage                                                                                          |
| Colitis                             | Mouse     | –Attenuates proinflammatory gene expression  
–Reduces severity of colitis  
–Inhibits weight loss, inflammation, pulmonary dysfunction                                                                 |
| Asthma                              | Mouse     | Inhibits airway hyperresponsiveness and pulmonary inflammation                                                                            |
| Cystic fibrosis                     | Mouse     | Decreases neutrophilic inflammation, pulmonary bacterial burden, and disease severity                                                      |
| Ischemia-reperfusion injury         | Mouse     | –Attenuates hind-limb ischemia-reperfusion lung injury                                                                                      |
| Corneal disorders                   | Mouse     | –Accelerates cornea re-epithelialization  
–Limits sequelae of thermal injury (such as neovascularization and opacity)  
–Promotes host defense                                                                |
| Angiogenesis                        | Mouse     | Reduces angiogenic phenotype: endothelial-cell proliferation and migration                                                                  |
| Bone marrow transplant              | Mouse     | Protects against bone-marrow-transplant-induced graft-versus-host diseases                                                                    |
| Glomerulonephritis                  | Mouse     | –Reduces leukocyte rolling and adherence  
–Decreases neutrophil recruitment                                                                                                           |
| Hyperalgesia                        | Rat       | –Prolongs paw withdraw latency and reduces hyperalgesic index  
–Reduces paw edema                                                                                                                         |
| Pleuritis                           | Rat       | Shortens the duration of pleural exudation                                                                                                 |
| **Resolin E1**                      |           |                                                                                                                                            |
| Periodontitis                       | Rabbit    | –Reduces neutrophil infiltration  
–Prevents connective tissue and bone loss  
–Promotes healing of diseased tissues  
–Regenerates lost soft tissue and bone                                                                                                     |
| Peritonitis                         | Mouse     | –Stops neutrophil recruitment  
–Regulates chemokine and/or cytokine production  
–Promotes lymphatic removal of phagocytes                                                                                                   |
| Dorsal air pouch                    | Mouse     | Stops neutrophil recruitment                                                                                                             |
| Retinopathy                         | Mouse     | Protects against neovascularization                                                                                                        |
| Colitis                             | Mouse     | –Decreases neutrophil recruitment and proinflammatory gene expression  
–Improves survival  
–Reduces weight loss                                                                                                                      |
| **Resolin D1**                      |           |                                                                                                                                            |
| Peritonitis                         | Mouse     | Stops neutrophil recruitment                                                                                                             |
| Dorsal skin air pouch               | Mouse     | Stops neutrophil recruitment                                                                                                             |
| Kidney ischemia-reperfusion injury  | Mouse     | –Protects from ischemia-reperfusion kidney damage and loss of function  
Regulates macrophage                                                                                                                      |
| Retinopathy                         | Mouse     | Protects against neovascularization                                                                                                        |
| **Protectin D1**                    |           |                                                                                                                                            |
| Peritonitis                         | Mouse     | –Inhibits neutrophil recruitment  
–Regulates chemokine and/or cytokine production  
–Promotes lymphatic removal of phagocytes  
–Regulates T-cell migration                                                                                                                 |
| Asthma                              | Mouse     | Protects from lung damage, airway inflammation, and airway hyperresponsiveness  
Protectin D1 is generated in humans and appears to be diminished in asthmatics                                                              |
| Kidney ischemia-reperfusion injury  | Mouse     | Protects from ischemia-reperfusion kidney damage and loss of function  
Regulates macrophages function                                                                                                             |
| Retinopathy                         | Mouse     | Protects against neovascularization                                                                                                        |
| Ischemic stroke                     | Rat       | –Stops leukocyte infiltration  
–Inhibits nuclear factor-kB and cyclooxygenase-2 induction                                                                                   |
| Alzheimer’s disease                 | Human     | Diminishes protecting D1 production in human Alzheimer’s disease  
Promotes vascular remodeling                                                                                                               |
and certain LO inhibitors, have been shown to impair resolution of inflammation and lead to systemic inflammatory complications.

**Summary of Part III**

Theoretically, combining proresolving mediators and anti-inflammatory agents such as aspirin and statins—agents that decrease the extent of inflammation without interfering with the endogenous proresolving processes—may be a useful strategy to control excessive inflammation and restore homeostasis. More research is necessary to obtain solid information on the efficacy and safety of these interventions in humans. However, it is possible that in the future we can expect new treatment strategies to be available for the treatment of periodontal disease and its systemic complications.

**Supplemental Readings**


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CHAPTER 4

History of the Oral-Systemic Relationship

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INTRODUCTION

In the last decade, the possible association between oral and systemic health has been highlighted in numerous reports. The focus of attention is mainly periodontitis and its impact on certain conditions. Periodontitis is an infectious disease associated with a number of predominantly gram-negative bacteria, and it is now recognized that for the initiation and progression of this disease, a susceptible host is also required. It is also well documented that certain systemic conditions can modify the host’s susceptibility to periodontitis, but only recently has evidence surfaced about the possibility of a two-way relationship. Specifically, periodontitis has been implicated as a potential risk factor for cardiovascular diseases, respiratory diseases, diabetes mellitus, preterm labor, low birth weight, and renal disease.

Interest in the relationship of oral health/periodontal disease to general health is not new, but is more of a resurgence in the old and discredited concept of focal infection. Focal infection theory became popular in the beginning of the twentieth century because it explained a number of conditions for which there was no scientific explanation at the time. It eventually fell into disrepute because of a lack of scientific evidence.

This chapter examines the history of the hypothesis that microorganisms would localize from the source focus to the distant, systemic focus, and it follows, step by step, concepts of the oral-systemic relationship that have evolved over the years.

ANCIENT CIVILIZATIONS AND THE MIDDLE AGES

Throughout recorded history, many theories have been put forward to explain human illness. One area of the body that has been repeatedly implicated in the origin of human diseases is the oral cavity. Writings from as far back as those of the ancient Egyptians (2100 BC) mention tooth pain associated with women’s reproductive system diseases.1 In Assyria, the physician of King Ashurbanipal (669–626 BC) wrote about the troubles of his king: “The pains in his head, arms, and feet are caused by his teeth and must be removed.”2 In ancient Greece, Hippocrates (400 BC) recorded two cases in which eradication of the infections of the mouth appeared to relieve patients of rheumatic-like troubles of the joints.3 Aristotle, perhaps the first dental anatomist—especially from the standpoint of comparative anatomy—stated, “those persons who have the most teeth are the longest lived.”4 In his book, On Hygiene, the Roman physician Galen (166–201 AD) emphasized the interrelationship between the oral cavity and other illnesses.5

From the end of the Roman Empire until the Middle Ages, all sciences fell into abeyance. Had it not been for the Arabs (who had access to the learning and science contained in Greek manuscripts brought to their country by Nestorian exiles from Byzantium and Greeks who settled in southern Italy), the bulk of science and knowledge accumulated to that date might have been lost.4 The next notable advance in dentistry probably occurred in Italy in the 1400s when a physician named Giovanni d’Arcoli began filling decayed teeth with gold leaf, an admirably progressive step for that time. He is further credited with stating that for cases of severe dental pain, early intervention was advisable because “such violent pains are followed by syncope or epilepsy, through injury communicated to the
heart or brain."

In 1548, Ryff wrote a monograph that dealt exclusively with dental afflictions. In his pamphlet, *Useful Instructions on the Way to Keep Healthy, to Strengthen and Re-invigorate the Eyes and the Sight. With Further Instructions of the Way of Keeping the Mouth Fresh, the Teeth Clean and the Gums Firm*, he wrote, “The eyes and teeth have an extraordinary affinity or reciprocal relation to one another, by which they easily communicate to each other their defects and diseases, so that one cannot be perfectly healthy without the other being so too.”

In 1768, Berdmore, in *A Treatise on the Disorders and Deformities of the Teeth and Gums*, described the relation between the teeth and the entire body as one leading to the most “excruciating pains and dangerous inflammations and sometimes deep seated abscesses which destroy neighbouring parts and affect the whole system by sympathy, or by infecting the blood with corrupted matter.” In 1818, one of the most famous physicians in America, Benjamin Rush, reported the course of a disease in which a woman who was suffering from rheumatism of long standing had an aching tooth extracted and “she recovered in just a few days.”

All these statements over the course of history were made without sufficient supporting evidence; yet they were current beliefs at the time. The conclusions were usually drawn by repeated observation of a number of patients with similar symptoms and outcomes. Today these ancient theories—especially those related to oral systemic conditions—cannot be considered anything more than guesswork based on simple observation. However, it is of great interest that historically a suspicion or hunch existed of an interrelationship between oral disease and systemic conditions.

**ORAL SEPSIS AS A CAUSE OF DISEASE**

The importance of oral hygiene in relation to bacteriology was first detailed by Dutch scientist Antonie van Leeuwenhoek in 1683. However, it was with the discoveries of the late 1800s that the centuries-old debate about the influence of the mouth on the rest of the body began. One of the main reasons for interest in this area was due to strides made in the study of microbiology. Major contributors to advances in microbiology included Pasteur, Lister, and Koch. Koch was a physician working as a District Medical Officer in Wöllstein, a small city in what is now Germany. During the Franco-Prussian war, he began to study the disease anthrax, which was prevalent among farm animals in the community. Earlier, the anthrax bacillus had been discovered by Pollande, Royer, and Davine. Through a series of experiments, Koch demonstrated that pure cultures of the anthrax bacillus could cause the anthrax disease. His work was published in 1876 and the “germ theory of disease causation” was introduced to the world. Soon, scientists around the globe became interested in bacteria and their role in disease etiology.

Miller, an American dentist working at Koch’s Institute for Infectious Diseases, was convinced that the bacteria residing in the mouth could explain most illnesses. In 1880, to support his theory, Miller published a book, *The Microorganisms of the Human Mouth: The Local and General Diseases Which are Caused by Them*. In 1891, Miller published a classic article in the *Dental Cosmos* journal. The title of the article was “The Human Mouth as a Focus of Infection.” This article aimed to “call attention to the various local and general diseases which have been found to result from the action of microorganisms which have collected in the mouth and to various channels through which these microorganisms or their waste products may obtain entrance to parts of the body adjacent to or remote from the mouth.” It also aimed to “establish the great importance of thorough understanding on the part of the physician, no less than of the
dentist, of mouth germs as a factor in the production of disease.” The article was presented under three headings or sections:

- Diseases of the human body that have been traced to the action of mouth bacteria
- The pathogenic mouth bacteria
- Prophylactic measures

The diseases that Miller felt could be traced to bacteria colonizing the mouth included otitis, osteomyelitis, septicemia, pyemia meningitis, disturbance of alimentary tract, pneumonia, gangrene of the lungs, Ludwig’s angina, diseases of the maxillary sinus, actinomycosis, noma, diphtheria, tuberculosis, syphilis, and thrush. He described 149 cases, many of which he ascribed to a dental origin, such as fistulæ that opened on the neck, shoulder, arm, and breast. Thus was developed the concept of focus of infection, with organisms in the oral cavity being implicated in diseases of the body remote from the mouth. Although Miller did not mandate removal of teeth as a method of eradication of foci of infection, he sometimes suggested that the “treatment and filling of root canals” could serve this purpose. In Miller’s opinion, local collection of disease-producing organisms could produce “a metastatic abscess wherever a point of diminished resistance existed.” Moreover, he postulated that teeth were not the only source of aggregation of such bacteria but that foci in other organs, such as the tonsils and uterus, could be implicated.5,8

The next important figure in the history of oral sepsis as a cause of disease was the English physician, Hunter. At the time of Miller’s paper presentation, which Hunter attended, he was the senior assistant physician at the London Fever Hospital, and his attention was already drawn to the mouth as a possible source of infection. In 1900, he wrote “Oral Sepsis as a Cause of Disease,” an article published in the British Medical Journal.9 Hunter implicated poor oral hygiene, together with iatrogenic conservative dentistry, as causes of the multitude of diseases attributed to focal infection. He advocated oral antisepsis measures to diseased teeth or inflamed gums, the removal of “tooth stumps,” the boiling of every “tooth plate” worn, and the avoidance of restorations such as bridges, which can’t be cleanly maintained.5,9

In 1900, Godlee described how the signs and symptoms of other conditions, such as pleurisy, could be attributed to pyorrhea alveolaris and how all the signs and symptoms disappeared after careful removal of all calculus and regular syringing of the pockets with a hydrogen peroxide solution.5,10 In 1902, Colyer described the resolution of irregular heartbeat, gastric effects, and “general debility” after the treatment of any oral sepsis. He also suggested a good maxim with which a dentist should work—“better no teeth than septic ones.”5,11

In an article published by Wilcox in 1903, antral disease was put forward as an important sequela of oral sepsis.12 It was believed that prolonged antral suppuration could lead to extreme mental depression, often ending in suicidal tendency.5,12 Other relationships that were put forward were those between oral sepsis and migraine headaches, laryngal pain and spasm (which could induce cough, loss of voice, and wasting), blindness, and deafness, all of which Wilcox hypothesized could be cured by treating the oral sepsis.4 As the concept of oral sepsis became more popular, theories were put forward as to which organs were most susceptible to different types of oral sepsis, and how the treatment of oral sepsis could lead to recovery from tonsillitis, tuberculosis, and diabetes. It was also believed that oral sepsis could be transmitted by the licking of envelopes, use of contaminated telephone receivers, and men with beards.

In 1908, Merritt published an article in Dental Cosmos titled, “Mouth Infection: the
Cause of Systemic Disease.” He stated, “there is a general disposition on the part of the medical and dental professions to under-estimate the relations which exist between an unclean mouth and many local and systemic disorders of grave nature.” He felt that in many cases of malnutrition, the sole cause was a “filthy mouth” and that “no greater good could come to humanity than the full recognition of the dangers from this insidious, prolific and virulent infection in the human mouth.” Merritt also stated, “the adoption of proper oral hygiene practices would result in immediate and marked improvement to general health and notable increase in the average duration of human life.”

On October 3, 1910, Hunter was invited to McGill University in Montreal, Canada, to give the keynote address at the dedication of the Strathcona Medical Building. The title of his address was “The Role of Sepsis and Antisepsis in Medicine.” In his address, he blamed “oral sepsis” as the cause of a great many diseases, and made an attack on conservative dentistry or, as he called it, “septic dentistry.” His address was published in The Lancet, the leading British medical journal at the time, as well as in the Dental Register. Hunter is best remembered for the following statement in The Lancet report: “No one has probably had more reason than I have had to admire the sheer ingenuity and mechanical skill constantly displayed by the dental surgeon. And no one has had more reason to appreciate the ghastly tragedies of oral sepsis which his misplaced ingenuity so often carries in its train. Gold fillings, crowns and bridges, fixed dentures, built on and about diseased tooth roots form a veritable mausoleum of gold over a mass of sepsis to which there is no parallel in the whole realm of medicine.” He continued with “The worst cases of anaemia, gastritis, obscure fever, nervous disturbances of all kinds from mental depression to actual lesions of the cord, chronic rheumatic infections, kidney diseases, all those which owe their origin to, or are gravely complicated by the oral sepsis produced by these gold traps of sepsis. Time and again I have traced the very first onset of the whole trouble to the period within a month or two of their insertion.” Hunter’s condemnation of conservative dentistry appears to be based primarily on its poor standard. It was fashionable in London at the time to mimic complicated American dentistry. However, in many cases the results were of substandard quality. Some well-respected dentists, such as Edward Cameron Kirk, the editor of Dental Cosmos, recognized the potential systemic effects of oral sepsis, but felt that Hunter’s criticism of dentistry was unfair since Hunter’s observations were based primarily on the disastrous effects of a very low-standard dentistry.

In 1911, Billings, the long-serving Dean of Medicine at the University of Chicago and head of the focal infection research team at Rush Medical College and Presbyterian Hospital, replaced the term “oral sepsis” with “focal infection.” Soon after that, he was honored by being asked to give the annual Lane Memorial Lecture at Stanford University in 1915. There, he defined a focus of infection as a “circumscribed area of tissue infected with pathogenic organisms” and said that the term focal infection implied that: (1) such a focus or lesion of infection existed, (2) the infection was bacterial in nature, and (3) it was capable of dissemination, resulting in systemic infection of other contiguous or noncontiguous parts. The teeth, tonsils, adenoids, and mastoids were thought to be the usual sources of bacteremia, and certain bacteria, such as streptococcus and pneumococcus, had special affinities for target organs like the heart and lungs. Billings believed that chronic infectious arthritis was often associated with remote foci of streptococcus, gonococcus, or tuberculosis organisms, and suggested the
removal of all foci of infection and the improvement in patients’ immunity by absolute rest and improvement of population-wide and individual oral hygiene.\textsuperscript{17,18} One of the first studies measuring the clinical benefit of removing focal infection in 1917 confirmed Billings’ suggestions. The study was conducted as a retrospective postal survey, and 23% reported a cure for their arthritis after removal of infective foci. An additional 46% reported experiencing some improvement in symptoms.\textsuperscript{5,19}

One of Billings’ research associates was Rosenow, a graduate of the Rush Medical College where he had been a student of Billings. He used special methods for culturing material from various foci of infection. He obtained a number of pathogenic bacteria from patients, including streptococci and gonococci, which he injected in animals. He then tested whether these organisms would provoke lesions similar to the secondary manifestations noted in the patients from whom the foci had been removed. Billings used the term “elective localization” to note that certain strains of pathogenic bacteria (mostly streptococci) isolated from the oral cavity of the patients had localized to the joints, cardiac valves, or other areas of the animals.\textsuperscript{5}

Physicians such as Billings and Rosenow were prominent and convincing. More and more articles were published and many other physicians, such as Barker and Cecil, embraced the concept of focal infection. Cecil, best known for his textbook of medicine, reported in 1933 that “the keystone of the modern treatment of rheumatoid arthritis is the elimination of the infected foci.”\textsuperscript{20} In an article in 1938, Cecil quotes Rosenow who said “the prevention of oral sepsis in the future, with the view to lessening the incidence of systemic diseases, should henceforth take precedence in dental practice over the preservation of the teeth almost wholly for mechanical or cosmetic purposes.”\textsuperscript{21} Other leading members of the medical community, such as Mayo, also advocated the focal infection theory. He stated that “in children the tonsils and mouth probably carry eighty percent of the infective diseases that cause so much trouble in later life.” He went on to write “teeth with putrescent pulps may harbour green-producing streptococci and even though they show no redness at the gums they may be very dangerous to keep in the mouth.”\textsuperscript{1—5}

What followed in dentistry as the result of the “theory of focal infection” was an unprecedented wave of tooth extractions and the avoidance of conservative dentistry.\textsuperscript{22} All teeth that were endodontically or periodontally involved were extracted to prevent a possible focus of infection. This approach came to be known as the “hundred percenter.” The leading spokesperson for this radical approach was the physiologist, Fisher. He regarded a tooth with a root filling as a dead organ that needs to be extracted.\textsuperscript{5}

As biomedical research evolved in the early 1930s, it also started evaluating concepts on a scientific basis. It was then that the strong belief in the theory of focal infection began to decline. What stimulated this decline was the work of Holman, who noted that Rosenow’s work was fraught with contamination and that his data were inconsistent.\textsuperscript{22,23} Others noted that Rosenow inoculated animals with such high counts of bacteria that it was inevitable for every organ or joint to be affected.\textsuperscript{24,25} Grossman, in his book Root Canal Therapy, noted that Rosenow’s technique “so devastates the laboratory animal that lesions are sometimes produced in almost every tissue and organ of the body.” The fact that Rosenow’s work in animal models could not be reproduced by other investigators heavily discredited his theories.\textsuperscript{25}

Cecil, a great proponent of the focal infection theory, together with the rest of the medical community, started to reevaluate his approach. He and Angevine published an article in 1938 that reported a follow-up
study of 156 patients with rheumatoid arthritis who had teeth and/or tonsils removed because of foci of infection. They concluded that chronic focal infection was relatively unimportant in rheumatoid arthritis because of the 52 patients who had teeth removed, 47 did not get any better and 3 got worse. In their own words, they concluded that “focal infection is a splendid example of a plausible medical theory which is in danger of being converted by its enthusiastic supporters into the status of an accepted fact.”

In 1940, Reiman and Havens wrote a critical review of the theory of focal infection in the Journal of the American Medical Association. They reviewed the literature in detail and ended the report with the following paragraph: “It may be said, therefore, that: (a) The theory of focal infection, in the sense of the term used here, has not been proved, (b) the infectious agents involved are unknown, (c) large groups of persons whose tonsils are present are no worse than those whose tonsils are out, (d) patients whose teeth or tonsils are removed often continue to suffer from the original disease for which they were removed, (e) beneficial effects can seldom be ascribed to surgical procedures alone, (f) measures are often outweighed by harmful effects or no effect at all, and (g) many suggestive foci of infection heal after recovery from systemic disease, or when the general health is improved with hygienic and dietary measures.”

In 1951, a review by Williams and Burket concluded the following: “There is no good scientific evidence to support the theory that removal of these infected teeth would relieve or cure arthritis, rheumatic heart disease, and kidney, eye, skin, or other disorders.” The very strongly worded review by Reiman and Havens as well as overwhelming new evidence, brought the “era of focal infection” to an end. An editorial in the Journal of the American Medical Association in 1952 stated that this happened because “many patients with diseases presumably caused by foci of infection have not been relieved of their symptoms by removal of the foci. Many patients with these same systemic diseases have no evident focus of infection, and also foci of infection are, according to statistical studies, as common in apparently healthy persons as those with disease.” In looking back, it can be considered that the theory of focal infection not only was an easy way to explain the cause of many diseases, but also advocated treatment that was available to the patients at the time. According to Gibbons, the role of economics in the spread of the focal infection theory should not be underestimated. It is easy to understand that as the era of focal infection came to an end, the lucrative business of extracting teeth, removing tonsils, and treating sinuses as a way of treating human diseases gradually diminished. In his article “Germs, Dr. Billings and the Theory of Focal Infection,” Gibbons quotes one bacteriologist of the focal infection period saying “The age of specialization stimulates surgery. Operations carry the best fees with them, and without intimating that economics play a role in the specialist’s decision, nevertheless it is only reasonable to regard him as human—if he is the proud possessor of surgical skill, he is more prone to use it.”

In dentistry, for almost 50 years (1940–1989), there was little interest in the effect of the mouth on the rest of the body. However, throughout the second half of the twentieth century, dental scientists continued to question whether oral infection (and inflammation) might in some way contribute to a person’s overall health; however, the reasons given were mostly speculative. They continued to suggest that bacteria and bacterial products found in the mouth could enter the bloodstream and could in some way be harmful to the body as a whole. Not until the last decade of the twentieth century did dentistry and medicine start again to con-
sider the relationship of oral diseases, such as periodontal disease, as a contributor to risk factors for certain systemic diseases.

**Oral-Systemic Relationship Revisited**

The late 1980s saw an increasing number of publications implicating an association between periodontopathogenic bacteria and certain systemic conditions such as coronary artery disease, stroke, and preterm/low-birth-weight babies. Such insinuations had also been made early in the twentieth century, but this time reports were judged with a more measured response. According to Barnett, this response was a result of several factors: (a) greater analytical and statistical knowledge and a better understanding of the constraints of epidemiologic research in “establishing disease causality”; (b) increased awareness of the etiology and pathogenesis of oral diseases; (c) increased awareness of the etiology and pathogenesis of associated systemic diseases; (d) modern advances in the treatment of oral conditions; (e) realization that bacteria could in some way be implicated in the development of diseases that as yet have an undetermined etiology.

In 1989, Mattila and coworkers in Finland conducted a case-control study on 100 patients who had suffered an acute myocardial infarction. They compared these patients with 102 control subjects selected from the community. A full dental examination was performed on all the subjects studied. In addition, a dental index was computed. This index computed the sum of scores from the number of missing teeth, carious lesions, periapical lesions, probing depths, and the presence or absence of peri-coronitis. Dental health was found to be significantly worse in patients with a history of acute myocardial infarction than that of control subjects. This association remained valid even after adjustment for age, social class, smoking, serum lipid concentrations, and diabetes. It was mainly this study that renewed the interest of physicians and dentists in the relation of oral to systemic disease.

In retrospect, it is now clear that the advent of reports by Mattila and colleagues—followed soon thereafter by DeStefano et al. and Offenbacher et al.—was the beginning of a new era of understanding the impact of oral health and disease on overall health and disease. By 1996, the term “periodontal medicine” would emerge as scientists and clinicians in dentistry and medicine began to appreciate the tremendous effect that oral disease can have on the body.

Ironically, the situation over the last years is reminiscent of that at the beginning of the previous century. A large number of studies have been published relatively recently linking many diseases to oral infections. The most common oral infection mentioned is periodontitis, and it has been linked not only with the traditional diseases such as cardiovascular disease and diabetes, but also with other diseases such as cancer. Scientists now know that the existing evidence for a direct impact of oral infection on systemic disease outcomes is plausible and that where the evidence is strongest, as for diabetes, it is time to develop recommendations for dental and medical publications for comanagement of patients with both diseases.

The American Heart Association (AHA) released a report that concluded that periodontal disease is an independent risk factor for cardiovascular disease; however, evidence is not yet available that shows that treating periodontal disease actually reduces cardiovascular disease. The American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) jointly organized a workshop dedicated to periodontitis and its relation to systemic diseases to systematically evaluate the evidence for the association of periodontal diseases with diabetes, cardiovascular disease, and adverse pregnancy outcomes. In their conclusions, they stated, “the reported asso-
cation does not imply causality and establishment of causality will require new studies." According to Cullinan and Seymour, however, "such evidence will require expensive, long term intervention studies, which are extremely difficult to carry out and which may never be done." Since periodontitis is a very serious problem in its own right, it may be appropriate for dentists to concentrate on providing treatment to the patients affected and to provide treatment that contributes to the overall health of patients, since effective management of periodontal diseases is accompanied by reduction of risk factors common to chronic diseases such as periodontal disease and cardiovascular disease.

PERIODONTAL/ORAL DISEASE AS A RISK FACTOR FOR SYSTEMIC DISEASE

Despite many years of history demonstrating the influence of oral status on general health, recent decades have seen an accelerated effort for the prevention and management of these conditions through groundbreaking advances. Specifically, periodontitis, a chronic infectious and inflammatory disease of the gums and supporting tissues, has been associated with systemic conditions such as coronary heart disease and stroke, higher risk for preterm, low-birth-weight babies, and certain cancers. It has also been suggested periodontitis may pose threats to those with chronic disease, such as diabetes, respiratory diseases, and osteoporosis. Periodontal diseases are infections that are caused by microorganisms that colonize the tooth surface at or below the gingival margin. These infections affect the gingival tissues and can cause damage to the supporting connective tissue and bone. Periodontal disease can be caused by specific bacteria (e.g., Porphyromonas gingivalis) from the biofilm within the periodontal pocket. Several pathways for the passage of periodontal pathogens and their products into the circulation have been suggested and are currently the subject of intense research.

The focal infection theory, as proposed and defended the first time around, was mainly based on anecdotal evidence and the occasional case report. For the hypothesis not to fall into disrepute the second time around, different levels of evidence must be examined to establish a relation between the periodontal condition and the systemic health of the patient. Since not all scientific evidence is given the same weight, the stronger the evidence, the more likely it is that a true relation exists between these conditions.

Case reports provide us with very weak evidence and can only suggest a link, but not a relationship. Case-control studies are mainly used to identify factors that may contribute to a medical condition by comparing subjects who have the condition with patients who do not, but are otherwise similar. These studies may lead to cross-sectional analyses. Observational studies are used to examine associations between exposures and disease. These studies are relatively inexpensive and frequently used for epidemiologic studies. However, the fact that they are retrospective and not randomized limits their validity.

Cross-sectional analysis studies the relation between different variables at a point in time. These types of data can be used to assess the prevalence of acute or chronic conditions in a population. However, since exposure and disease status are measured at the same point in time, it may not always be possible to distinguish whether the exposure preceded or followed the disease. Stronger evidence is provided with a longitudinal study, in which subject populations are examined over time. A longitudinal study is often undertaken to obtain evidence to try to refute the existence of a suspected association between cause and disease; failure to refute a hypothesis strengthens confidence in
it. Longitudinal studies with controls are much stronger than those without controls. The same applies for intervention trials that provide the strongest form of evidence. Unfortunately, these are not only difficult to conduct, they are expensive, and they involve many ethical considerations.

**What Is Risk?**
Risk is the statistical likelihood that certain factors are associated with the development of disease. Risk can be divided into *absolute risk*, which is the likelihood of acquiring a certain disease, and *relative risk*, which is the likelihood of acquiring a disease when certain factors are modified, compared with the same likelihood if they are not. It is easy to understand that when true risk factors are identified, then intervention for those at risk can be planned and implemented.

The strength of association between putative risk factors and a disease state can be expressed in odds ratios. An odds ratio of 1 indicates an equal chance that an association will occur. An odds ratio of 2 indicates a twofold chance of an association being present. Care should be exercised in inferring causation from odds ratios. Association does not, in itself, imply causation. In the interpretation of odds ratios, it is important for the confidence interval of the odds ratio not to traverse 1. If it does, the odds ratio—regardless of magnitude—cannot be relied on.

There has long been an interest in the role of systemic factors as they affect periodontal disease. A series of studies were carried out looking at systemic risk factors for periodontal disease and were summarized by Genco in 1996. In this review, it was pointed out that in addition to preexisting diseases, systemic factors have been identified. These include reduced neutrophil function, stress and coping behaviors, osteopenia, age, gender (with more disease seen in males), hereditary factors, infection with periodontal pathogens, cigarette smoking, and diabetes. It should be noted that these risk factors are common to many chronic, noncommunicable diseases, such as heart disease, stroke, and diabetes, all of which are associated with periodontitis.

**Peri**

**odontitis/Oral Health as a Risk Factor for Specific Diseases: Evidence for an Association Cardiovascular**
Oral infections may contribute to cardiovascular disease by means of three possible mechanisms:

1. Direct effect of infectious agent in atheroma formation
2. Indirect or host-mediated responses
3. Common genetic predisposition

Bahekar and colleagues recently conducted a systematic review of the literature to evaluate whether such an association exists. This review revealed five prospective cohort studies involving 86,092 patients for at least 6 years. The authors considered that three of the five prospective studies were of good quality, and both the incidence and prevalence of coronary heart disease were increased in subjects with periodontal disease after adjustments for other variables known to increase the risk of coronary heart disease. Furthermore, five case-control studies involving 1,423 patients and five cross-sectional studies involving 17,724 patients were also evaluated. All supported a significant relation between periodontal disease and coronary heart disease. More prospective studies are needed, however, to prove the assumption that periodontitis may be a risk factor for coronary heart disease and to evaluate risk reduction with the treatment of periodontitis.

In planning prospective studies, it is important to remember that patients with periodontal disease share many of the same risk factors as patients with cardiovascular disease. These risk factors include age, gender, lower socioeconomic status, stress, and smoking. In addition, a large number
of patients with periodontal disease also exhibit cardiovascular disease; this could indicate that periodontal disease and atherosclerosis share similar or common etiologic pathways.\textsuperscript{46} The literature also suggests that a number of pathogens, antigens, endotoxins, and cytokines of periodontitis might be significant contributing factors.\textsuperscript{47,48} According to Williams et al.,\textsuperscript{49} controlling for such confounding factors when carrying out epidemiologic and observational studies requires large numbers of subjects to be enrolled, and these subjects need to be followed over a long period of time. Common periodontal pathogens such as \textit{Porphyromonas gingivalis} and \textit{Streptococcus sanguis} have been found in arterial plaques from carotid endarterectomy samples. Furthermore, periodontal disease has been associated with elevated levels of inflammatory markers, such as C-reactive protein. Although there is growing evidence that supports a role for C-reactive protein as a predictive, pathogenic factor for vascular risk, it is recognized that more research is needed.\textsuperscript{50}

Large-scale prospective intervention studies are needed to assess whether periodontitis can be considered an effective modifiable risk factor in the prevention of cardiovascular disease.

\textbf{Adverse Pregnancy Outcomes}

Several studies on laboratory animals in the 1970s and 1980s revealed that bacterial endotoxin (a cell wall component isolated from \textit{Escherichia coli}) is capable of producing spontaneous abortion, low fetal weight, and malformations.\textsuperscript{50} Collins and colleagues\textsuperscript{51,52} successfully demonstrated that oral anaerobes such as \textit{P. gingivalis} had similar effects.

In 1996, Offenbacher and colleagues\textsuperscript{53} constructed a case-control study with the title “Periodontal Infection as a Possible Risk Factor for Preterm Low Birth Weight.” In this investigation, they sought to determine whether the prevalence of mater-nal periodontal infection could be associated with preterm low birth weight, while controlling for known risk factors such as smoking and poor nutrition. Results observed from the 124 pregnant or postpar-tum mothers who took part in this study indicated that periodontal disease represents a clinically significant risk factor for preterm low birth weight. This landmark report by Offenbacher and colleagues was the first of its kind.

In the last 7 years, an explosion of data was released from case-control studies, cohort studies, and clinical trials, as well as from systematic reviews. Many studies have reported a positive association, but it must be concluded that because of different study designs, heterogeneity in the way adverse pregnancy outcomes were measured, as well as a lack of adequate analysis for confounders, there is still no consistent evidence for or against this association.

Large-scale prospective intervention studies are needed in which adverse pregnancy outcomes and the severity of periodontal disease can be clearly defined.

\textbf{Diabetes: A Two-Way Relationship}

It is clear from epidemiologic studies that diabetes mellitus increases the risk for periodontal disease.\textsuperscript{53,54} The available literature highlights the importance of oral health in subjects with diabetes, and demonstrates an increased prevalence of periodontitis among patients with poorly controlled diabetes.\textsuperscript{49} Patients with controlled diabetes show periodontal conditions similar to those of the healthy population.

The current literature does not provide us with conclusive evidence to support a causal relationship between periodontal disease and risk for type 2 diabetes. There is evidence of an increased risk of periodontitis in patients with diabetes, but Taylor and coworkers\textsuperscript{55} also showed that patients with type 2 diabetes who suffer from periodontitis
have worse glycemic control, suggesting that not only does diabetes affect periodontitis, but when a diabetic has periodontitis, it leads to worsening diabetes or glycemic control. This was followed by a paper by Grossi and Genco,\textsuperscript{56} in which periodontal disease and diabetes mellitus were presented in a two-way relationship. This began a long line of investigation in which treatment of periodontal disease in diabetes was found to contribute to glycemic control, with one of the first studies reported by Grossi and colleagues.\textsuperscript{57} In 2008, a meta-analysis of nine control studies on the subject confirmed that the reduction of glycated hemoglobin with periodontal therapy can be significant, comparable to other attempts to control glycated hemoglobin.\textsuperscript{49} Researchers tried to evaluate the effects of periodontal therapy on systemic inflammatory markers and on glycemic control.\textsuperscript{58} Several randomized control trials and a number of longitudinal and observational studies provided some evidence to support the concept that periodontitis can adversely affect glycemic management. Overall though, it is inconclusive that periodontal treatment results in improvement of metabolic control and of markers of systemic inflammation.

Emerging evidence suggests that periodontitis predicts the development of overt nephropathy and end-stage renal disease in patients with type 2 diabetes.\textsuperscript{41,59} A prospective study by Shultis and colleagues\textsuperscript{41} was conducted exclusively in individuals with diabetes. It also included a proportionally large number of individuals with kidney disease. Whether treatment of periodontitis will reduce the risk of diabetic kidney disease has not yet been determined, but this study provides a rationale for further investigation into the connections between periodontal disease and diabetic progression.

There is a need for large-scale prospective intervention studies, mainly in specific high-risk groups because, according to Williams and colleagues,\textsuperscript{49} these groups can provide more immediate answers than studies with a more heterogeneous diabetic population.

Respiratory Infections
Scannapieco\textsuperscript{60} describes four possible mechanisms of the presence of oral bacteria in the pathogenesis of respiratory infections:

1. The oral cavity might be a reservoir for microorganisms that contaminate saliva and is then aspirated into the lungs.
2. Periodontal disease-associated enzymes in saliva may facilitate the adherence of respiratory pathogens in the mucosal surfaces.
3. Periodontal disease-associated enzymes may destroy protective salivary pellicles, resulting in fewer nonspecific host defense mechanisms in high-risk patients.
4. Cytokines and other molecules originating from untreated periodontal tissues are continuously released in saliva. Aspiration of these may alter respiratory epithelium and promote respiratory pathogen colonization.

A systematic review published in 2006 by Azarpazhooh and Leake\textsuperscript{61} investigated evidence for a possible etiologic association between oral health and pneumonia or other respiratory diseases. They concluded that there is fair evidence of an association between pneumonia and oral health, and poor evidence of an association between chronic obstructive pulmonary disease and oral health. In addition, there is good evidence that implementation of high-quality and frequent oral health care decreases the occurrence and progression of respiratory diseases among elderly hospitalized or institutionalized persons.\textsuperscript{61}

There is a need for large-scale prospective intervention studies targeting high-risk people of the community, nursing homes, and intensive care units.
**Osteoporosis**

Over the last decade, it has been speculated that by decreasing the patient’s alveolar bone mass, osteoporosis makes teeth more susceptible to resorption by the periodontal inflammatory reaction. Human studies have addressed this relationship, and several large-scale studies showed an association between osteoporosis and reduced alveolar crest height in postmenopausal women. In another study, osteoporosis and periodontal infection were found to be independent risk factors for oral bone loss. Other studies, especially longitudinal studies, are necessary to determine the temporal nature of this association and to further evaluate it.

Some studies investigated the effect of hormone replacement therapy or vitamin D intake on tooth loss. In almost all studies, there was a positive correlation between the number of teeth retained and medical treatment, but it must be kept in mind that confounding factors such as age, smoking, socioeconomic status, and many other factors may have affected the results.

There is a need for large-scale prospective studies with as many confounding factors as possible to be factored into these investigations.

**CONCLUSIONS**

A long-standing and well-accepted principle is that good oral health is an integral component of good general health. In recent years, there has been an attempt to tie oral conditions to systemic diseases in a causal relationship, but existing data support only an association. Evidence for this relationship is growing, and a scientifically based understanding of how oral health may pose a risk for certain systemic diseases is developing. Certain linkages are stronger than others, but until a number of well-constructed, controlled intervention studies can provide “hard” evidence, treatment recommendations need to be guarded.

**Supplemental Readings**


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CHAPTER 5
Diabetes Mellitus: A Medical Overview
Srividya Kidambi, Shailendra B. Patel

INTRODUCTION
Diabetes mellitus (DM) is a quintessential metabolic disease whose characteristic phenotype is loss of control of glucose homeostasis, but the pathophysiology also affects fat and protein metabolism.1 Resulting hyperglycemia is associated with both short-term and long-term complications, making early diagnosis and treatment of this condition essential. The key hormonal disturbance causing DM can be a defect in insulin secretion, in insulin action, or both. Several pathogenic mechanisms have been proposed for the disease, and more than one mechanism may be at play for the disease to become clinically evident. This chapter describes the classification, epidemiology, pathogenesis and pathophysiology, clinical presentations, complications, and diagnosis of DM and provides a brief overview of treatment options.

Key educational objectives are to understand the following:
• Diabetes is a true metabolic disorder caused by disrupting insulin action.
• Both genetic and environmental factors are involved in causing diabetes.
• There are two main forms, type 1 and type 2, distinguished upon absolute and relative insulin deficiency, respectively.
• Insulin action is intimately tied to many other counterregulatory actions.
• Long-term complications of diabetes affect every organ in the body.
• Controlling glycemia levels in addition to cardiovascular risk factors is important in preventing, delaying, and ameliorating disabling or life-threatening complications.

CLASSIFICATION OF DIABETES MELLITUS
Diabetes mellitus is classified into several subtypes, which are based on etiology. This classification can help in understanding clinical manifestations and in providing a rationale for the treatment offered (Table 1). Most patients with DM (85–90%) have type 2 disease (defective insulin action and a relative defect in insulin secretion), whereas another 5%–10% have type 1 DM (absolute defect in insulin secretion, which requires insulin from the time of diagnosis). Remaining subtypes are rare (see Table 1). This chapter focuses on the major subgroups: type 1 DM, type 2 DM, and gestational diabetes mellitus (GDM); the latter affects fetal and maternal health and is a risk factor for later development of type 2 DM.

EPIDEMIOLOGY
According to 2010 estimates, 25.8 million people (or 8.3% of the population) in the United States have DM.3,4 About 7 million of these do not know they have DM and present to healthcare providers after a point of no return in preventing complications.3 Prevalence increases with increasing age with almost 27% of individuals over the age of 65 having DM.5 An epidemic of type 2 DM is underway in both developed and developing worlds, but the brunt is being felt sharply in developing countries.6,9 Globally, the number of people with diabetes is expected to rise from the current estimate of 371 million in 2012 to 552 million in 2030, making the cost of treating DM and its complications a pressing economic concern.

Patients with DM have a two- to four-fold higher risk for stroke and death from heart disease compared with people without
Table 1. Etiologic Classification of Diabetes Mellitus

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<tr>
<td>I.</td>
<td>Type 1 diabetes (B-cell destruction, usually leading to absolute insulin deficiency)</td>
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<td>A. Immune mediated</td>
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<td></td>
<td>B. Idiopathic</td>
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<td>II.</td>
<td>Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)</td>
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<td>III.</td>
<td>Other specific types</td>
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<td>A. Genetic defects of B-cell function</td>
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<td>2. Chromosome 7, glucokinase (MODY2)</td>
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<td>8. Others</td>
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<td>Genetic defects in insulin action</td>
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<td>1. Lipodystrophic syndromes</td>
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<td>3. Leprechaunism</td>
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<td>Diseases of the exocrine pancreas</td>
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<td>1. Pancreatitis</td>
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<td>2. Trauma/pancreatectomy</td>
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<td>3. Neoplasia</td>
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<td>5. Hemochromatosis</td>
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<td>6. Fibrocalculous pancreatopathy</td>
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<td>Endocrinopathies</td>
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<td>1. Cushing’s syndrome</td>
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<td>2. Acromegaly</td>
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<td>3. Glucagonoma</td>
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<td>4. Pheochromocytoma</td>
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<td>E.</td>
<td>Drug- or chemical-induced</td>
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<td>1. Glucocorticoids</td>
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<td>2. Atypical antipsychotics</td>
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<td>3. Pentamidine</td>
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<td>5. α-Interferon</td>
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<td>F.</td>
<td>Infections</td>
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<td>1. Congenital rubella</td>
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<td>G.</td>
<td>Uncommon forms of immune-mediated diabetes</td>
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<td></td>
<td>1. Stiff-man syndrome</td>
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<td>2. Anti-insulin receptor antibodies</td>
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<td>3. Others</td>
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<td>H.</td>
<td>Other genetic syndromes sometimes associated with diabetes</td>
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<td>1. Down syndrome</td>
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<td>2. Turner’s syndrome</td>
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<td>3. Wolfram’s syndrome</td>
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<td>4. Laurence-Moon-Biedl syndrome</td>
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<td>5. Prader-Willi syndrome</td>
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<td>6. Others</td>
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<td>IV.</td>
<td>Gestational diabetes mellitus (GDM)</td>
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Periodontal diseases are also more common in people with DM. Among young adults, those with DM have about twice the risk of developing periodontal disease compared with those without DM. Persons with poorly controlled diabetes (HbA1c > 9%) are nearly three times more likely to have severe periodontitis than those without diabetes. Almost one-third of people with DM have severe periodontal disease with loss of attachment of the gums to the teeth measuring 5 mm or more.

In addition to the enormous morbidity associated with DM, it was the seventh leading cause of death listed on US death certificates in 2011. Overall, the risk of death among people with DM is about twice that of those of similar age without DM.

**PATHOPHYSIOLOGY**

The pathophysiology of DM revolves around impairment of insulin secretion, insulin resistance, or both, resulting in reduced utilization of glucose, hyperglycemia, and impairment of fatty acid metabolism. Symptoms and complications of DM are due to hyperglycemia as well as to lack of adequate insulin action.

**Glucose Metabolism**

Carbohydrates, broken down mainly into glucose, are one of the main energy sources in most organisms including humans. Consideration of glucose and insulin metabolic pathways is crucial to understanding the pathophysiology of DM.

Glucose is derived from three sources: intestinal absorption following digestion of dietary carbohydrates; glycogenolysis, the

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient. (Modified with permission, American Diabetes Association. *Diabetes Care* 2009;31;(Suppl 1).
breakdown of glycogen, which is the polymerized storage form of glucose; and gluconeogenesis, the formation of glucose from precursors including lactate (and pyruvate), amino acids (especially alanine and glutamine), and, to a lesser extent, glycerol. Only the liver and kidneys are capable of releasing glucose into circulation by glycogenolysis and gluconeogenesis. All tissues can use glucose as a substrate for energy production, but only the brain is wholly dependent on glucose as its main energy source. Thus, mechanisms to maintain a steady-state supply of glucose to the central nervous system are integral to metabolic control.

Both insulin-dependent and insulin-independent pathways can determine whole-body clearance of glucose. Glucose is transported into the cells by specific transporters, and the next step is phosphorylation to glucose-6-phosphate by enzymes hexokinase (insulin-regulated) or glucokinase (glucose-induced and regulates insulin secretion). Only then, glucose can enter metabolic pathways such as glycolysis, glycogen synthesis, hexosamine biosynthesis (alternative pathway to glycolysis), or pentose phosphate pathway (for generation of nicotinamide adenine dinucleotide phosphate [NADPH] and to reduce cellular oxidative stress). It is important to note that entry of glucose into different tissues is regulated by expression of different glucose transporters; in muscle and fat, glucose entry is allowed only via an insulin-dependent translocation of the glucose transporter, GLUT4, to the cell surface, whereas in the brain the glucose transporter, GLUT1, is constitutively active and not dependent on insulin action. Insulin regulates many of these processes; it increases cell surface glucose transporters in insulin-sensitive tissues such as adipose and muscle, induces hexokinase, and inhibits expression of enzymes involved in glycogenolysis and gluconeogenesis. Glucagon action results in the opposite effects. Hence, deficiency of insulin, absolute (as in type 1 DM) or relative (as in type 2 DM), is associated with decreased clearance of blood glucose from the body and hyperglycaemia (Figure 1).

**Role of Insulin in the Body**

Insulin is secreted by β-cells of the islets of Langerhans, an endocrine organ in the pancreas. The pancreatic islet comprises a group of cells, termed α-, β-, and δ-cells, surrounded by exocrine pancreas. These islets synthesize and release a number of hormones, the classic ones being insulin and amylin from the β-cell, glucagon from the α-cell, somatostatin from the δ-cell, and a number of other bioactive polypeptides not discussed here. Insulin (as well as amylin) is synthesized as a prohormone, transported to granules where it is processed by a proprotein convertase, resulting in mature insulin, C-peptide (byproduct of proinsulin processing), and amylin. These are stored in the mature granules until released on stimulation of the β-cell. Insulin production usually exceeds the need, so the unreleased granules are destroyed in the lysosomal compartment of the β-cell. Glucose is the primary stimulant of insulin secretion, and oxidative metabolism of glucose is required for glucose to stimulate granule exocytosis. A number of other secretagogues, including hormones, gut peptides, and amino acids, also have the ability to provoke insulin secretion.

Insulin’s primary physiologic function in the body can be described as anabolic, resulting in storage of fuels from ingested carbohydrate and fat (e.g., glycogen and triglycerides) and regulating catabolism of stored fuel. Its main target tissues are skeletal muscle, liver, and adipose tissue, and its action on these tissues (or lack thereof) is responsible for systemic effects of insulin. If insulin is the Yin, a group of hormones such as glucagon, cortisol, and growth hormone
Figure 1. Action of Insulin and Glucagon Under Feeding and Fasting Conditions

Feeding, satiety, and the neurohormonal response to feeding are integrated by the brain, especially the hypothalamus (1A). This consists of the vagal system, incretin hormone secretion, and gut motility hormones, among other mechanisms. Upon feeding (1A), the neurohormonal response, as well as direct glucose stimulation of the pancreas, results in activation of pathways that lead to efficient insulin secretion as well as a decrease in glucagon secretion from the islets of Langerhans in the pancreas into the portal tract. This results in increased liver uptake of glucose, inhibition of hepatic gluconeogenesis, increased fatty acid synthesis, and very-low-density lipoprotein (VLDL) secretion and increased glycogen storage. Although most insulin is cleared by the liver, it also reaches the central circulation where in the fat, it increases glucose uptake and triglyceride storage, and inhibits free fatty acid release. In muscle, insulin increases glucose uptake and glycogen storage; in the kidney it inhibits gluconeogenesis. Under fasting conditions (1B), the neurohormonal response is switched to maintenance of glucose levels, resulting in decreased insulin and increased glucagon secretion, with the resultant opposite effects on the above-described target organs. In the liver, gluconeogenesis, glycogenolysis, and fatty acid breakdown is stimulated. In adipose tissues, fat is mobilized with increased lipolysis and free-acid release. In muscle, decreased glucose uptake and increase fatty acid catabolism take place. All these actions are tightly regulated and coordinated to account for all physiologic processes, ranging from short-term energy expenditure (e.g., exercise) to both short- and long-term fasting. In addition, many other hormones (e.g., cortisol, growth hormones, catecholamines) are involved, but are not described here.

Insulin exerts its action by binding to a cell-surface receptor, the insulin receptor (IR), which has an extracellular and an intracellular domain. Intracellular domain possesses tyrosine-specific protein kinase activity, which is activated by insulin binding, and phosphorylates several intracellular proteins, specifically insulin receptor substrate (IRS)-1, -2, -3 and -4 (Figure 2). The phosphorylated IRS lead to activation of multiple downstream signaling pathways and ultimately to several activated protein kinases. Activation of these protein kinases is responsible for mediating many of the eventual metabolic actions of insulin, including translocation of glucose transporters, activation of glycogen synthesis, and suppression of gluconeogenesis by the liver.27

In addition to carbohydrate metabolism, insulin has several other actions. Its
Insulin signaling occurs via many pathways and leads to the various actions of insulin. These signaling pathways interact with many other pathways that are not depicted (e.g., cortisol, epinephrine, glucagon), and the concept of critical nodes has been evoked to explain some key interactions. Critical nodes form an important part of the signaling network that functions downstream of the insulin receptor (IR—black arrows) and the insulin growth factor-1 receptor (IGF1R—blue arrows). Signaling pathways that are activated by cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and leptin interfere with insulin signaling through cross-talk (orange and red arrows). Three important nodes in the insulin pathway are the IR, the IR substrates (IRS 1-4—light blue box), the phosphatidylinositol 3-kinase (PI3K) with its several regulatory and catalytic subunits (light green box), and the three AKT/protein kinase B (PKB) isoforms (pink box). Downstream or intermediate effectors as well as modulators of these critical nodes include:

- Akt substrate of 160 kDa (AS160)
- atypical protein kinase C (aPKC)
- Cas-Br-M (murine)
- Cbl-associated protein (CAP)
- Cotropic retroviral transforming sequence homologue (Cbl)
- Cell-division cycle 42 (CDC42)
- c-Jun-N-terminal kinase (JNK)
- Extracellular signal-regulated kinase 1 and 2 (ERK1 and ERK2)
- Forkhead box O1 (FOXO1)
- Glycogen synthase kinase 3 (GSK3)
- Janus kinase (JAK)
- Mammalian target of rapamycin (mTOR)
- p90 ribosomal protein S6 kinase (p90RSK)
- Phosphatase and tensin homologue (PTEN)
- Phosphoinositide-dependent kinase 1 and 2 (PDK1 and 2)
- Protein tyrosine phosphatase-1B (PTP1B)
- Rac
- Ras
- Ras homologue gene family, member Q (ARHQ; also called TC10)
- Signal transducer and activator of transcription (STAT)
- Src-homology-2-containing protein (Shc)
- Suppressor of cytokine signaling (SOCS)

Note: Dashed arrows represent an activation process with less intensity. Reproduced with permission from Nat Rev Mol Cell Biol 2006;7:85–96.
principle effect on adipose tissue is to suppress lipolysis and keep circulating free fatty acid levels in check. These elevated free fatty acids are thought to inhibit glucose utilization by peripheral tissues and also increase hepatic gluconeogenesis. The disordered metabolism of fatty acids has been proposed as having a major effect on pathophysiology in diabetes. Insulin’s effect on adipose tissue appears to be as important as its effects on carbohydrate metabolism.

The development of DM thus involves not only pancreatic islet β-cell dysfunction/destruction, but also action of insulin in the periphery. Although attention is usually focused on insulin, it is important to acknowledge the role that counterregulatory hormones (the Yang) play to fully understand the pathophysiology of DM.

**Type 1 DM**

In most patients, type 1 DM is an autoimmune disorder (type 1A) with selective destruction of the β-cells in the pancreatic islets occurring in genetically susceptible individuals and resulting in absolute insulin deficiency. Autoantibodies are detected as epiphenomenon in 85% to 90% of persons in the beginning stages of the disease, but the immune damage is cell-mediated, involving CD4+ T-cell dysfunction. Autoantibodies are directed against islet cell, insulin, other islet cell antigens such as glutamic acid decarboxylase (GAD65), tyrosine phosphatase–related proteins such as insulinoma associated protein 2 (IA-2 and IA-2b), and zinc transporter 8 (ZnT8). Although there are no good markers to predict impending development of type 1 DM, the presence of these autoantibodies is helpful in making a diagnosis, and testing for one or more of these antibodies is recommended to make an accurate diagnosis. In a few patients, autoantibodies may have dissipated by the time of diagnosis or an alternate pathway for destruction of pancreatic β-cells is present. A minor subgroup of patients with type 1 DM are classified as having idiopathic DM (nonimmune-mediated or idiopathic or type 1B).

Note also that the presence of type 1 or type 2 DM is not mutually exclusive. With an increase in prevalence of obesity even among patients with type 1 DM, insulin resistance is being increasingly noted among patients with type 1 DM and may require some of the strategies used for type 2 DM.

**Latent Autoimmune Diabetes in Adults**

A small subgroup of patients share genetic and clinical features of both type 1 and type 2 DM, and tend to become insulin-dependent a few months to years into diagnosis, rather than at the outset. This group has an increased risk for developing diabetic ketoacidosis (DKA), although many maintain minimal insulin secretion required to stave off DKA. These patients have variable titers of autoantibodies, usually with a lower body mass index (BMI) compared with that of a typical type 2 DM patient, and they respond poorly to oral hypoglycemic agents. Insulin treatment is recommended since there is progressive absolute insulin deficiency in latent autoimmune diabetes in adults, secondary to the progressive autoimmune damage to the islets.

**Genetics of Type 1**

Type 1 DM develops in the background of strong genetic susceptibility in the context of poorly defined environmental factors. Susceptibility to type 1 DM seems to be determined by multiple genetic loci, and recent advances in genome-wide scanning has begun to elucidate many of these genes. There is a robust association (still < 50% of genetic contribution) between type 1 DM and the major histocompatibility complex (MHC) genes (HLA-DR and HLA-DQ), whereas other loci (e.g., pre-proinsulin, PTPN 22 gene, and CTLA-4) have small
effects\textsuperscript{34,45} Specific alleles of both DR and DQ can either increase or decrease the risk of type 1 DM. The function of these HLA molecules is to present antigens to the immune cells, specifically T lymphocytes, and sensitize them to autoantigens.

The prevalence of type 1 DM in Western populations is approximately 0.3\% in the general population,\textsuperscript{46} whereas it is 6\% if the father is affected, 4\% if a sibling is affected, and 3\% if the mother is affected.\textsuperscript{47,48} Although the risk of DM is much greater for relatives of patients with type 1 DM, more than 85\% of people who develop type 1 DM do not have a first-degree relative with the disease. The risk for an identical twin is estimated to be 30\% to 50\%,\textsuperscript{49-52} suggesting a strong environmental effect.\textsuperscript{53}

Patients with type 1 DM are also prone to other autoimmune diseases such as Hashimoto’s thyroiditis (hypothyroidism), vitiligo (loss of skin pigmentation), Addison’s disease (cortisol and aldosterone deficiency), celiac disease (malabsorption of nutrients), and pernicious anemia (vitamin B\textsubscript{12} deficiency).\textsuperscript{54}

Several environmental factors including viral infections, vaccinations, and certain dietary factors such as cow’s milk and cereals have been proposed as the putative triggers to the initiation of destruction of pancreatic islets in the setting of appropriate genetic background.\textsuperscript{55-60} However, except for congenital rubella infection, robust evidence of association is lacking.\textsuperscript{61}

**Type 2 DM**

Type 2 DM, previously known as noninsulin-dependent DM or adult-onset DM, is the predominant form of DM comprising up to 90\% of total world cases. This form of DM is associated with impairments in both insulin action (in other words, insulin resistance) and insulin secretion.\textsuperscript{3} Insulin resistance requires elevated levels of insulin to perform functions of glucose and lipid homeostasis, and a person can maintain normoglycemia as long as his or her pancreas can increase the production of insulin. However, in genetically predisposed individuals, beta-cells are unable to increase the insulin production to the levels required to compensate for insulin resistance, a condition occasionally termed \textit{β-cell exhaustion}, and results in increasing hyperglycemia.

**Insulin Resistance**

The complicated insulin pathway (see Figure 1) highlights multiple points in which disordered action in any one of the gene products involved in the pathways could result in impaired insulin action, in turn resulting in insulin resistance. Despite identifying several of these processes, the molecular mechanisms causing insulin resistance in the majority of the patients remain unknown. Apart from the latter intrinsic component of insulin resistance, certain acquired factors may contribute to the development of insulin resistance and are reversible to some extent. These include obesity, drugs, and glucose toxicity.

Obesity predisposes a person to develop insulin resistance and thereby type 2 DM. Obesity can cause insulin resistance via several mechanisms, although other mechanisms remain to be elucidated.\textsuperscript{67} One of the mechanisms attributed to increased insulin resistance in obesity was decreased insulin receptor tyrosine kinase activity in the skeletal muscle\textsuperscript{68} and possibly in other tissues.\textsuperscript{69,70}

Weight loss improves the activity of the receptor tyrosine kinase activity.\textsuperscript{71} This and other studies provide evidence that insulin resistance does not always have to be genetically determined, but can be acquired and reversed to some extent.\textsuperscript{72,73} Another hypothesis posits that substances secreted by adipose tissue cause tissues to become insulin-resistant (such as paracrine, autocrine, and endocrine factors). These substances
include free fatty acids (which inhibit glucose transport, glucose oxidation, and glucose utilization)\textsuperscript{20,30,74} and leptin and tumor necrosis factor (TNF-\(\alpha\)).\textsuperscript{75-80} Some products such as free fatty acids may create a vicious cycle in which insulin resistance increases free fatty acid levels, which in turn increase insulin resistance. A break in the cycle of progressively increasing free fatty acids either by decrease in weight (thus reducing the insulin resistance) or by treatment with insulin or insulin sensitizer may alleviate the degree of insulin resistance defects related to obesity, some of which seem to be acquired and partially reversible.\textsuperscript{81}

A number of drugs can impair glucose tolerance, either by decreasing insulin secretion (e.g., octreotide, diazoxide, and organ transplant rejection medications such as cyclosporine and tacrolimus), or by increasing insulin resistance (glucocorticoids, oral contraceptives, several classes of antihypertensive drugs such as beta blockers, thiazide diuretics, nicotinic acid, protease inhibitors used for treatment of HIV infection, and some of the atypical antipsychotic agents, such as clozapine and olanzapine).

Glucose toxicity results from chronic exposure of the pancreatic islet cells to supraphysiologic concentrations of glucose in the blood leading to cellular dysfunction, \(\beta\)-cell toxicity, which is to some extent reversible, but may become irreversible over time.\textsuperscript{82} In addition, in animals, hyperglycemia is also associated with insulin resistance by decreasing the glucose transport into the cells.\textsuperscript{83,84} Thus, high glucose concentrations can cause secretory defect as well as increase insulin resistance, but with timely treatment, this can be reversible.

The relative secretory defect in type 2 DM is not associated with immune-mediated destruction of \(\beta\)-cells but amyloid deposits in the islet that are associated with reduction in islet cell mass.\textsuperscript{85-87} The protein component of these deposits was found to be the \(\beta\)-cell secretory product amylin.\textsuperscript{88,89} However, the mechanism for the initiation of amyloid formation and the deposition in the islets is not yet clear. It may have both a genetic and environmental etiology.\textsuperscript{90} A number of types of insulin secretory abnormalities have been described in type 2 DM, including the timing and height of response to glucose challenge and other secretagogues.\textsuperscript{91-99}

### Genetics of Type 2

Much like type 1 DM, type 2 DM is also thought to occur in genetically predisposed individuals with superimposed environmental influences.\textsuperscript{100-103} Type 2 DM is a complex trait that is transmitted with a pattern of polygenic inheritance,\textsuperscript{104-106} which means that abnormalities or polymorphisms need to occur concurrently in multiple genes for the disease to develop. Several aspects of the development of type 2 DM are under genetic control including intra-abdominal obesity, insulin resistance, and insulin secretory defects.\textsuperscript{107-116} Studies on monozygotic twins show an extremely high concordance rate of close to 90\%, which is much higher than that of type 1 DM, thus suggesting higher heritability.\textsuperscript{117} However, it is not known which genes predispose to insulin deficiency or insulin resistance. Genetic linkage methods have been used to try to identify type 2 DM genes and have succeeded in mapping genes to several loci.\textsuperscript{118-123} However, unlike type 1 DM, environmental influences are well characterized.

### Ketosis-Prone Diabetes

A subclass of patients presents with diabetic ketoacidosis, which is typically associated with an absolute insulin deficiency, but these subjects, on recovery, do not require insulin for management. They have no features of autoimmunity and show a robust ability to secrete insulin when tested in the postrecovery phase.
CLINICAL PRESENTATION
In general, type 1 DM patients present in a more acute and dramatic fashion (in part, because they have an absolute insulin deficiency) compared with type 2 DM patients, who usually have a more insidious presentation. In both cases, the most common symptoms are polyuria (and new-onset nocturia), polydipsia, and weight loss. However, type 2 DM is an insidious disease and may fester for years before a diagnosis is made. Blurry vision can result from changes in the osmolality of the lens from hyperglycemia. In addition, frequent skin and vaginal infections, slow healing of skin lesions, or occasionally distal neuropathy may be presenting features. Any of the above-mentioned symptoms in an undiagnosed patient should prompt checking of blood glucose concentrations.

Type 1 DM
Type 1 DM, though commonly known as juvenile diabetes, can occur at any age, but typically presents around the age of puberty. There is a short prodromal phase with fatigue, weight loss, polyuria, and polydipsia. In young children, new-onset bedwetting may be a presenting feature. If these symptoms go unrecognized, the condition could progress to ketoacidosis, with tachypnea, tachycardia, hypotension, and diabetic ketoacidosis (DKA) and may lead to altered mental state and coma. Frequently, an intercurrent illness or an infection may be a trigger event. Because there is an absolute deficiency of insulin, the presentation is acute (days) and needs urgent medical attention. In adults who have an autoimmune disease or who have had damage (typically alcohol) or surgery to the pancreas gland, a diagnosis of diabetes should be considered for failure to gain weight or unexplained weight loss.

Type 2 DM
Type 2 DM has long been considered an adult disease, although children and young adults with this disease are now being increasingly diagnosed. The disease can evolve over several years, and the natural history may differ among patients. Many patients with type 2 DM are older than 40 years, are overweight or obese, and have an increased waist circumference (a surrogate marker for visceral fat accumulation). The presence of metabolic syndrome markers (increased waist–hip ratio, hypertension, low HDL-cholesterol, impaired fasting glucose) is strongly predictive of development of type 2 DM. Although insulin resistance is the primary cause of type 2 DM, it is not sufficient to cause DM as long as the pancreas can secrete enough insulin to compensate. Presentation is usually insidious and goes unrecognized for years, since mild to moderate hyperglycemia may not cause any noticeable symptoms. However, this mild hyperglycemia-associated lipid and blood pressure abnormalities are not entirely benign because they increase the risk of macro- and microvascular complications.

Up to 20% of newly diagnosed type 2 DM patients can manifest signs of diabetic complications. With worsening hyperglycemia, symptoms of polyuria, weight loss, and other symptoms may then result in the condition coming to light. It is not uncommon for an intercurrent illness, such as stroke, myocardial infarction (MI), or infection to also uncover diabetes. Rarely, acute severe hyperglycemia (over 1–2 days) can lead to a hyperosmolar (hyperosmolar, hyperglycemic nonketotic state [HHS]) with altered mental state and coma as an acute presenting feature. Hence, screening in high-risk individuals is essential to minimize the risk of these complications. Presentation with ketoacidosis occurs rarely in these patients, but may occur in conjunction with other illnesses such as infection or in stressful situations such as acute MI. Type 2 DM could be considered to evolve in two stages.
Stage 1 is development of impaired glucose tolerance or impaired fasting glucose (also termed prediabetes), and stage 2 is the development of overt diabetes (Table 2).

**Table 2. Diagnostic Criteria for Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Test Criteria</th>
<th>Prediabetes Mellitus</th>
<th>Overt Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>≥ 5.7</td>
<td>≥ 6.5</td>
</tr>
<tr>
<td>Fasting plasma glucose* (mg/dL)</td>
<td>≥ 100</td>
<td>≥ 126</td>
</tr>
<tr>
<td>Plasma glucose 2-hour post 75 g oral glucose tolerance test† (mg/dL)</td>
<td>140–199</td>
<td>2 hours: ≥ 200</td>
</tr>
<tr>
<td>Random plasma glucose‡ with symptoms of hyperglycemia* (mg/dL)</td>
<td>≥ 200</td>
<td></td>
</tr>
</tbody>
</table>

*Fasting defined as no caloric intake for 8 hours.

*Oral glucose tolerance test involves measurement of plasma glucose at specified time after consuming a glucose load of 75 g or 100 g dissolved in water.

†Random plasma glucose defined as anytime of the day without any temporal association to caloric intake.

‡Symptoms of hyperglycemia include polyuria, polyphagia, polydipsia, and unexplained weight loss.

**Gestational Diabetes**

Gestational diabetes mellitus (GDM) is a form of DM that has its initial onset during the later stage of the second trimester of pregnancy and that resolves at the end of pregnancy. Up to 4% of pregnancies in the United States are complicated by the development of gestational diabetes. GDM during pregnancy increases both fetal growth (macrosomia) and obstetric complications. Although screening guidelines differ among various groups of physicians, most agree that screening should be undertaken between 24 and 28 weeks of pregnancy in women who are obese, have a first-degree relative with diabetes, are older than 25 years, and come from a higher risk ethnic group (Hispanic, African American, Native American). Many of the risk factors and the pathophysiologic process for GDM are similar to those of type 2 DM. With the increase in insulin resistance during pregnancy, women who are susceptible to developing type 2 DM owing to a concomitant secretory defect may indeed develop type 2 DM. Although the risk of fetal developmental abnormalities is higher in women who are diabetic before becoming pregnant, with GDM, the diabetes develops at the end of the second trimester, a time when organogenesis has already been completed. Most women revert to normal glucose tolerance postpartum. Approximately 50% of patients who have had GDM have a recurrence in future pregnancies and a 30% to 60% risk of developing established diabetes long term. GDM provides a unique opportunity to educate women about the need for lifestyle changes (weight loss, exercise, and improved diet) to prevent overt DM in the future.

**Acute Complications**

DKA and HHS are potentially fatal but largely preventable acute complications of untreated DM. DKA is most common in patients with type 1 DM, although it can occur in patients with type 2 DM as well; whereas HHS is more common in patients with type 2 DM. Although these two conditions are discussed as two separate entities, they are part of the same spectrum of diseases characterized by inadequate insulin. DKA results when there is *absolute* insulin deficiency, whereas HHS develops with relative insulin deficiency. However, they do differ in the degree of dehydration, ketosis, and metabolic acidosis. For both disorders, the precipitating factors could be the same, including missed insulin doses, dehydration, infection, certain medications, or other major illnesses. However, restricted water intake resulting from ill health or immobilization, compounded by altered thirst response, may contribute to the dehydration and HHS in elderly patients with type 2 DM.
**Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is characterized by varying degrees of hyperglycemia, ketonemia, and metabolic acidosis.\(^{126,131}\) When combined, these three elements give rise to the clinical syndrome of DKA, which is associated with dehydration, electrolyte abnormalities, and altered sensorium.

As a result of severe insulin deficiency, unchecked gluconeogenesis, glycogenolysis, and decreased glucose utilization result in hyperglycemia.\(^{132}\) Gluconeogenesis is also fueled by increased availability of amino acids that are a result of increased catabolism, again because of decreased insulin. Elevated blood glucose results in increased plasma osmolality levels (hyperosmolar state) causing shift of water from the intracellular space and intracellular dehydration. The increased plasma osmolality promotes osmotic diuresis, resulting in net loss of body water and thus initiating a vicious cycle of increased plasma osmolality and progressive dehydration. The progressive dehydration also leads to reduced tissue perfusion, hypoxia, and thus the generation of lactic acid, which contributes to the acidosis (see text that follows). Decreased blood pH leads to reduced insulin action, setting up a vicious cycle. Osmotic diuresis also promotes loss of multiple minerals and electrolytes, including sodium, potassium, phosphate, calcium, magnesium, and chloride, all of which need to be replaced.

Loss of insulin action results in an increase in lipolysis and an increase in free fatty acid production; these fatty acids are metabolized by the liver into ketone bodies (acetone, acetoacetate and beta-hydroxybutyrate, a source of energy for the heart and brain during starvation).\(^{133}\) Initially, the ketonemia may be mild as the body tries to metabolize them.\(^{134,135}\) As the acidosis from tissue hypoxia with further reduced insulin action occurs, excessive ketone bodies are produced. Acidosis promotes movement of potassium from intracellular to extracellular space, from where it could be excreted in urine along with osmotic diuresis, resulting in hypokalemia. Ketones may be detected clinically in the breath, as these are volatile. Laboratory abnormalities helpful in making the diagnosis are hyperglycemia, an increased anion gap (indicative of acidosis), a low arterial blood pH (< 7.4 to as low as 6.9), a low bicarbonate level, elevated lactic acid levels, as well as ketone bodies. Since ketone body production is part of a normal response to starvation, their detection, per se, is not indicative of DKA.

In addition, DKA may be associated with increased levels of proinflammatory cytokines and procoagulant factors. These along with dehydration also create a fertile ground for prothrombotic state.\(^{136}\)

**Hyperglycemic Hyperosmolar Nonketotic State**

This condition, HHS, is similar to DKA, but differs due to the presence of sufficient insulin to prevent lipolysis, and thus acidosis is not a major factor. Only a tenth of concentration of insulin in the blood is required to prevent lipolysis; therefore, ketoacidosis, compared with the amount needed to stimulate glucose utilization and prevention of hyperglycemia is rare in type 2 DM. Since patients with type 2 DM do have this residual insulin, they are less likely to develop DKA but are prone to develop severe hyperglycemia and dehydration.\(^{137}\) Note that ketosis should not be confused with ketoacidosis: the former occurs during any period of starvation, whereas the latter reflects absolute insulin deficiency. Mortality from HHS is higher owing to older age, comorbid illnesses, and severity of dehydration.

Clinically, those with DKA and HHS present with well-known symptoms of hyperglycemia and dehydration, such as polyuria, polydipsia, polyphagia, weight loss, weakness, dry mucosal membranes, tachycardia, and hypotension in severe cases. Altered sensorium and, frequently, precom-
atose or comatose situation can be seen in both conditions as a result of dehydration. Kussmaul respiration (rapid shallow breathing), acetone breath, nausea, vomiting, and abdominal pain can also occur in DKA because of the acidosis. Laboratory evaluation reveals high blood glucose and renal and other electrolyte abnormalities. The goals of therapy in these patients are restoration of the circulatory volume and tissue perfusion, gradual reduction of serum glucose (rapid reduction may result in cerebral edema), and correction of electrolyte abnormalities and ketosis when present. Precipitating causes such as infection should be identified and treated. Intravenous fluids and insulin infusion form the mainstay of treatment along with frequent monitoring of clinical and laboratory parameters and adjustment of treatment.

**COMPLICATIONS OF DIABETES MELLITUS**

Diabetes is a true metabolic disease and can affect many organ systems over the course of the disease. Such chronic complications are responsible for considerable morbidity and mortality. These complications can be divided into microvascular, macrovascular, and nonvascular and are summarized in Table 3. The risk of these complications increases as a function of hyperglycemia and duration of DM and are usually first seen 10 years after diagnosis.

**Microvascular Complications**

Large, randomized clinical trials of individuals with type 1 or type 2 DM, such as the Diabetes Control and Complications Trial (DCCT)\(^{18}\) and the United Kingdom Prospective Diabetes Study (UKPDS)\(^{19}\) have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays these complications (see Table 3). It must be noted that not all people with poor diabetes control develop these complications, suggesting that other factors such as genetics and environment may modulate the development of these complications.

**Ophthalmic Complications**

Diabetic retinopathy (DR) is the leading cause of blindness in persons between ages 20 and 74. Chronic hyperglycemia is thought to be the primary cause of retinal injury because of impaired autoregulation of retinal blood flow, accumulation of sorbitol, and advanced glycosylation end products within the retinal cells and extracellular fluid. The severity and progression of DR are variable in each patient; however, one important predictor of DR is duration of DM. DR is divided into two forms and further classified based on severity. Nonproliferative DR is characterized by retinal vascular microaneurysms, blot hemorrhages, intraretinal microvascular abnormalities with increased retinal vascular permeability, and alterations in retinal blood flow—all of which lead to retinal ischemia. Proliferative retinopathy is characterized by neovascularization in response to retinal hypoxia, mediated by action of insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). These newly formed blood vessels lack sufficient strength, rupture easily, resulting in intravitreous hemorrhage, and subsequently lead to fibrosis and retinal detachment, resulting in blindness. In addition, macular edema can occur at any stage of diabetic retinopathy.

Intensive glucose control since the time of diagnosis of DM is necessary for the prevention of onset and progression of retinopathy. Since most patients are asymptomatic until late in the disease process, an annual exam for early detection and laser photocoagulation (panretinal or focal) can prevent blindness.

**Renal Complications**

Diabetes is the most common cause of renal failure in the United States. The earliest
### Table 3. Complications of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Complication</th>
<th>Salient Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disease:</strong></td>
<td>Annual screening should begin at the time of diagnosis in patients with type 2 DM and 5 years after onset of type 1 DM. Rectangular retinal detachment and proliferative changes. Laser photocoagulation is the major modality of treatment to prevent further loss. Both are more common in patients with DM, occur at a younger age, and progress faster.</td>
</tr>
<tr>
<td>Retinopathy (DR)</td>
<td>Retinopathy progresses in two stages: Nonproliferative and proliferative (see text). Laser photocoagulation of retina is the major modality of treatment to prevent further loss. Both are more common in patients with DM, occur at a younger age, and progress faster.</td>
</tr>
<tr>
<td>Macular edema</td>
<td></td>
</tr>
<tr>
<td>Cataracts and glaucoma</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney disease:</strong></td>
<td>Annual screening of urine for microalbumin. Microalbuminuria (30–300 mg/24 h), potentially reversible. Overt proteinuria: &gt;300 mg /24 h, irreversible. Major cause of renal failure and dialysis requirement.</td>
</tr>
<tr>
<td>Nephropathy</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td><strong>Generalized symmetric neuropathy:</strong></td>
<td>Annual screening for neuropathy by examination of feet and monofilament testing. Podiatry referral should be considered in all patients with neuropathy for custom footwear. Pharmacotherapy management of pain remains a challenge.</td>
</tr>
<tr>
<td>Acute sensory</td>
<td></td>
</tr>
<tr>
<td>Chronic sensorimotor</td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
</tr>
<tr>
<td>Focal or multifocal neuropathy:</td>
<td></td>
</tr>
<tr>
<td>Cranial, truncal</td>
<td></td>
</tr>
<tr>
<td>Diabetic amyotrophy</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary artery, peripheral arterial, and cerebrovascular disease</strong></td>
<td>Leading cause of premature death in type 2 DM. Well-developed treatment guidelines and medications for lipid and blood pressure management. Smoking cessation is vital.</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>Strict glycemic control reduces the chance for infections.</td>
</tr>
<tr>
<td><strong>Skin changes</strong></td>
<td>Most are self-limiting. Skin infections can be prevented with good glycemic control. Moisturizing can prevent dryness of the skin. Necrobiosis lipoidica seen occasionally in type 1 DM patients.</td>
</tr>
<tr>
<td><strong>Gum and periodontal disease, tooth loss</strong></td>
<td>Poor oral health associated with increased cardiovascular morbidity/mortality.</td>
</tr>
<tr>
<td><strong>Hearing loss</strong></td>
<td>Increased sensorineural hearing loss.</td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>No evidence-based guidelines for management, risk of bone loss increased by diabetes.</td>
</tr>
<tr>
<td><strong>Musculoskeletal complications</strong></td>
<td>Stiff joints and arthralgias much more common than previously suspected. Diabetic cheiroarthropathy, flexor tenosynovitis, Dupuytren’s contracture, and Charcot’s joints (secondary to neurologic deficits) require some intervention.</td>
</tr>
</tbody>
</table>

Pathologic changes alter the microcirculation, with structural changes in the glomerular matrix resulting in an increase in glomerular filtration rate (GFR). This increases excretion of small amounts of albumin in the urine (microalbuminuria 30–300 mg/d). Fifty percent of these individuals progress to overt proteinuria (300 mg–1 g/d).
or nephrotic syndrome (urine protein > 1 g/d). Urinary protein excretion is exacerbated considerably by uncontrolled hypertension, and the combination of diabetes and hypertension is the most common predisposing factor for end-stage renal disease (ESRD).

In addition to nephropathy, type IV renal tubular acidosis (and resulting hyperkalemia) and predisposition to radiocontrast-induced nephrotoxicity are also seen in patients with DM. Intensive control of blood glucose, dyslipidemia, and blood pressure is recommended to prevent the onset of microalbuminuria and to prevent progression to overt proteinuria or renal failure.

Once ESRD ensues, patients are usually placed on dialysis. Kidney transplantation is generally the optimal renal replacement therapy for patients with DM and ESRD, and timing of transplantation influences patient survival, with better survival rates for patients who undergo transplantation without ever going through dialysis.

**Neurologic Complications**

Approximately 50% of patients with type 1 or type 2 DM develop neuropathy. It is usually symmetric sensory polyneuropathy, but may also be focal mononeuropathy and/or autonomic neuropathy, with loss of both myelinated and unmyelinated nerve fibers. Up to 50% of individuals with neuropathy may not be symptomatic. The pathogenesis has been attributed to ischemic injury from a nonsystemic microvasculitis; metabolic and hormonal factors may also contribute to the nerve fiber damage.\(^{40,141}\)

*Generalized symmetric polyneuropathy* is characterized by progressive loss of distal sensation in glove and stocking distribution followed by, in severe cases, motor weakness. Symptoms include pain, tingling, and numbness, and physical exam reveals loss of fine touch, vibration, and position sense initially, which may later progress to wasting of small muscles of the hands and feet resulting in Charcot’s joints, arch collapse, and sensory ataxia. *Mononeuropathy* is associated with pain and weakness in one nerve distribution that is self-limiting. *Diabetic amyotrophy*, seen mainly in type 2 DM patients, is associated with pain in the lower limbs followed by muscle weakness in major muscles of buttocks and thighs. It is a self-limiting condition and improves partially in 12 to 24 months; treatment is supportive. *Autonomic neuropathy*, though not well diagnosed, can affect all the major organ systems. Many cardiovascular abnormalities are noted, including resting tachycardia, diminished heart rate variability, silent myocardial ischemia, defective heart rate and blood pressure response to exercise, and postural hypotension. Altered small and large bowel motility (constipation or diarrhea), gastroparesis (anorexia, nausea, vomiting, and bloating), and gastroesophageal reflux disease are the common manifestations of gastrointestinal system involvement. Genitourinary systems are also involved and manifest as bladder hypotonia (incomplete emptying, dribbling, and overflow incontinence), erectile dysfunction, and female sexual dysfunction. Abnormal sweat production may result in xerosis, cracking of feet, and decreased sweating in response to hypoglycemia.

Tight glycemic control from the time of onset of DM is necessary for prevention of neuropathy. Treatment is difficult once the disease affects various organ systems. Fortunately, painful polyneuropathy is infrequent and often self-limited. For symptomatic treatment of painful neuropathy, several therapies have been tried with limited efficacy, such as tricyclic antidepressants, anticonvulsants, selective serotonin and norepinephrine reuptake inhibitors, and topical therapies. Treatment of Charcot’s foot and arch deformities may involve avoidance of weight bearing, special orthotic shoes to prevent ulceration, and, rarely, surgical correction. Treatment for organ-specific complications of autonomic neuropathy is symptomatic.
Macrovascular Complications
Association of macrovascular complications with hyperglycemia is less conclusive and appears to be more related to coexisting conditions such as dyslipidemia and hypertension. Cardiovascular disease (CVD) risk is increased in those with type 1 and type 2 DM by twofold in men and fourfold in women. In addition, patients with diabetes and CVD have worse outcomes and poorer long-term survival compared with those without DM and CVD. Type 2 DM patients with no prior MI have a similar risk for coronary artery-related events as do nondiabetic individuals who have had a prior MI. Patients with insulin resistance and type 2 DM have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis. Risk is increased when retinopathy, nephropathy, hypertension, and dyslipidemia are associated with DM. DM also increases the risk of silent MI owing to associated autonomic dysfunction. Even though the risk of both asymptomatic and symptomatic heart disease is increased in patients with DM, all major societies (American Diabetes Association [ADA] and the American College of Cardiology/American Heart Association [ACC/AHA]) do not recommend routine screening for CVD by either treadmill or pharmacologic stress test. New imaging techniques such as calcium scoring and noninvasive coronary angiography with computed tomography can detect the presence of CVD in asymptomatic patients. However, DM is already considered a CVD risk equivalent, and maximum medical therapy is recommended to control the risk factors.

Dyslipidemia frequently coexists with DM, especially type 2 DM, with a typical pattern of increased triglycerides, decreased HDL cholesterol, and increased small-dense low-density lipoprotein (LDL) cholesterol particles. The goals of therapy are to reduce LDL cholesterol to < 100 mg/dL and triglycerides to < 150 mg/dL.

Hypertension is frequently associated with DM and can hasten the onset of complications, especially for CVD and nephropathy. Management includes aggressive control of blood pressure and may require multiple medications.

Patients with DM also are at high risk for congestive heart failure (CHF) (diabetic cardiomyopathy) independent of CVD and hypertension, perhaps because of reduced left ventricular compliance. In addition, some drugs such as thiazolidinediones may increase the risk of CHF.

As a preventive measure, aspirin should be prescribed for all type 2 DM patients, unless contraindicated, although newer guidelines recommend the use of aspirin only in subjects with clinical evidence of thrombovascular disease.

Miscellaneous Complications
Infections
DM is associated with greater frequency and severity of common infections; in addition, some infections are exclusively seen in patients with DM. Hyperglycemia results in impaired cell-mediated immunity and colonization and growth of various bacterial and fungal species. Apart from hyperglycemia, vascular insufficiency and peripheral and autonomic neuropathies noted in patients with DM form perfect host factors that predispose to infections. Bacterial infections such as styes, boils, carbuncles, and surgical-site infections are the most common. Common fungal infections include intertrigo, caused by Candida albicans, and ringworm infections. Asymptomatic bacteriuria is also commonly seen in patients with DM but does not necessitate treatment.

Sexual Dysfunction
Male erectile dysfunction and female sexual dysfunction are commonly seen in patients
with DM. Male erectile dysfunction can be related to multiple factors including autonomic nervous system dysfunction, impaired blood flow to penis from vasculopathy, and psychological factors such as depression. All men with DM should be asked about erectile dysfunction and should be examined for the presence of hypogonadism along with usual DM-related complications.

**Dermatologic Manifestations**

Dermatologic problems are common in diabetes, with approximately 30% of patients experiencing some cutaneous involvement during the course of their illness. Several skin conditions are more common among patients with DM, such as bacterial infections, fungal infections, and itching, but are not exclusive to patients with DM. Skin manifestations generally appear during the course of the disease in patients known to have diabetes, but they may also be the first presenting sign of diabetes or may even precede the diagnosis by many years.

Some conditions occur exclusively in patients with DM. **Diabetic dermal ulcer** is a harmless condition that arises owing to small vessel changes and manifests as oval or circular pigmented and scaly patches on the front of the legs. These lesions are usually asymptomatic and do not need to be treated. Another disease caused by changes in blood vessels is **necrobiosis lipoidica diabetorum**. This rare disorder begins in the pretibial region as painful erythematous papules that enlarge into glossy plaques with irregular borders and atrophic centers. These patches are deeper than in dermal ulcer, can be itchy and painful, and can ulcerate. No treatment is necessary prior to the ulceration. **Bullous diabetorum** is a condition in which blisters can occur on the backs of hands and feet and are self-limiting. One third of people who have type 1 DM can develop tight, thick, and waxy skin on the backs of their hands, known as **digital sclerosis**. No specific treatment exists for this condition other than to achieve adequate glycemic control. Another condition known as **disseminated granuloma annulare** can occur in patients with DM and is a benign, asymptomatic, self-limited papular eruption found in patients of all ages. The primary skin lesion usually is grouped papules in an enlarging annular shape, with color ranging from flesh-colored to erythematous and is widespread. Disseminated granuloma annulare may be treated with one of several systemic therapies such as dapsone, retinoids, niacinamide, antimalarials, psoralsen plus ultraviolet A therapy, fumaric acid esters, tacrolimus, and pimecrolimus. Consultation with a dermatologist is recommended because of the possible toxicities of these agents.

In addition, **vulgaria** (autoimmune destruction of melanocytes) may coexist with type 1 DM owing to a common pathologic process. **Acanthosis nigricans** (hyperpigmentation seen on the neck, axilla, groin, and extensor surfaces) is associated with insulin resistance and type 2 DM and is due to melanocyte replication. Treatment of this condition is not necessary except for cosmetic reasons. The best treatment for this condition is weight loss, which is typically the underlying cause, though trials with topical or systemic retinoids or a topical vitamin D analogs may help.

**Complications Related to the Musculoskeletal System**

DM is associated with osteoporosis and fracture risk, particularly among those with type 1 DM. Bone disease in DM is characterized by reduced bone turnover and formation, along with increased resorption. The pathogenesis has been attributed to impaired osteoblast function secondary to reduced insulin and IGF-1 levels and reduced bone formation due to accumulation of advanced glycosylation end products (AGEs) in collagen from hyperglycemia. In
patients with type 2 DM, general bone density seems to be preserved; however, an increased risk of fracture has been attributed to several reasons including poor bone quality, falls following hypoglycemia, poor balance due to diabetic neuropathy, foot ulcers and amputations, poor vision due to cataracts and retinopathy, and orthostatic hypotension.\textsuperscript{144,148–151}

Patients with DM are also at increased risk for hand and shoulder disorders such as painless limited joint mobility, Dupuytren’s contracture, flexor tenosynovitis, adhesive capsulitis, diabetic muscle infarction, and carpal tunnel syndrome.\textsuperscript{152} Limited joint mobility (diabetic cheiroarthropathy) has been attributed to deposition of glycosylated collagen in connective tissue around joints, resulting in stiffening. The prevalence increases with increased duration of DM and probably poor glycemic control.\textsuperscript{153,154} Available treatment options include physical therapy, corticosteroid injections, and surgical repair when indicated.\textsuperscript{155–157}

\textbf{Periodontal Disease}

Oral health is now increasingly recognized as an important part of diabetes management; there is a mutually reciprocal relation between glycemic control and oral health. Periodontal infection worsens metabolic control of DM, and improving oral hygiene improves glycemic control.\textsuperscript{158,101} People with poorly controlled DM are more likely to develop gingivitis, dry mouth, dental abscess and fungal infections, and slow wound healing.\textsuperscript{159} This topic is reviewed in depth elsewhere in this book.

\textbf{The Diabetic Foot}

Diabetic foot is a term commonly used to refer to foot complications in diabetic patients and is characterized by slow-healing plantar ulcers from minor trauma. About 15\% of diabetic patients may experience foot ulceration in their lifetime. This condition represents a result of multiple systems gone wrong, beginning with neuropathy and loss of sensation in the feet, vascular disease with poor circulation and consequently impaired healing, and susceptibility to infections as a result of impaired immune response and poor glycemic control. In addition, foot deformities from muscle weakness and visual defects add to the predisposing factors for foot injury. The manifestations could begin as cellulitis and progress to abscess formation, osteomyelitis, and gangrene, which may ultimately lead to a need for amputation. Preventive care is essential and should include not only professional care (as listed in Table 4) but also self-care on a day-to-day basis. Daily inspection of the feet and wearing clean soft socks and properly fitting shoes are among many precautions to take to prevent foot ulceration. Once the ulcer is formed, antibiotics, relief of pressure to the ulcerated area, and control of blood glucose form the mainstay of treatment.

\textbf{Mechanisms of Complications}

Several mechanisms have been proposed to explain the role of hyperglycemia in the development of chronic complications. Higher blood glucose levels seem to channel glucose into pathways other than glycolysis, thus resulting in products that are detrimental to various tissues, especially connective tissues and vasculature. The following theories all have some supportive evidence for their role in pathophysiology:

1. Chronically elevated blood glucose levels result in interaction of glucose with intra- and extracellular proteins, a process called \textit{nonenzymatic glycosylation} and results in advanced glycosylation end products (AGEs). AGEs have been shown to cross-link proteins and promote glomerular dysfunction and accelerate atherosclerosis.

2. Elevated blood glucose levels may be converted to sorbitol by the enzyme
### Table 4. Comprehensive Principles for Preventing DM Complications

<table>
<thead>
<tr>
<th>Lifestyle changes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diet: Sugar-free diet for type 2 DM, No restrictions for type 1 DM</td>
</tr>
<tr>
<td>◦ Fat 20–35% of total calorie intake, saturated fat &lt; 7% of calories, &lt; 200 mg/d dietary cholesterol</td>
</tr>
<tr>
<td>• Exercise: At least 150 minutes/week of aerobic physical activity</td>
</tr>
<tr>
<td>• Optimum weight (BMI &lt; 25)</td>
</tr>
<tr>
<td>• Smoking cessation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modifiable risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Glycemic control:</td>
</tr>
<tr>
<td>◦ Glycosylated hemoglobin—measured at least twice a year (HbA1c &lt; 7%)</td>
</tr>
<tr>
<td>◦ Self-monitoring of blood glucose (SMBG)—no recommended optimal frequency, but probably should be measured 3–4 times a day in patients who are administering insulin for blood glucose control (preprandial plasma glucose 90–130 mg/dL, 2-hour postprandial plasma glucose of &lt; 180 mg/dL)</td>
</tr>
<tr>
<td>• Lipid management (LDL &lt; 100 mg/dL, optional goal &lt; 70 mg/dL, HDL &gt; 45 mg/dL in men and &gt; 55 mg/dL in women and triglycerides &lt;150 mg/dL)</td>
</tr>
<tr>
<td>• Blood pressure control (&lt;130/80 mm Hg, but &lt;125/75 mm Hg is preferred in those with nephropathy)</td>
</tr>
<tr>
<td>• Aspirin prophylaxis (primary prevention in diabetics over 40 years)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Preventive care:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Annual screening</td>
</tr>
<tr>
<td>◦ Screening for microalbuminuria</td>
</tr>
<tr>
<td>• Annual eye exam</td>
</tr>
<tr>
<td>• Podiatric exam</td>
</tr>
<tr>
<td>• Annual influenza vaccination</td>
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<tr>
<td>• Pneumococcal vaccination</td>
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</tbody>
</table>

aldo reductase, after usual pathway of glycolysis is saturated. Increased intracellular sorbitol results in alteration of cellular osmolality and generates reactive oxygen species, both of which can result in cellular dysfunction. Although this theory is logical, treatment with aldose reductase inhibitors has not demonstrated a great clinical benefit in preventing microvascular complications in clinical trials except, possibly, diabetic neuropathy.160–162

3. Elevated blood glucose levels result in activation of protein kinase C (PKC), which in turn can alter the transcription of genes of certain connective tissue elements and neurons, resulting in micro- and macrovascular complications. Inhibition of PKC is another therapeutic target being studied to prevent these complications; however, clinical benefit is not yet clear.

4. Hyperglycemia also increases glucose flux through the hexosamine pathway, generating fructose-6-phosphate, and alters the glycosylation process of certain proteins.

5. In addition, various growth factors such as VEGF and TGF are produced in excess and cause damage to the tissues.

**DIAGNOSIS OF DIABETES MELLITUS**

Screening for diabetes is suggested for adults over 45 years or for all adults with a BMI of 25 kg/m² or more who have one or more risk factors for diabetes (e.g., first-degree relatives with DM, GDM, hypertension, dyslipidemia, or physical inactivity). Diagnostic criteria are summarized in Table 2. Recent addition of HbA1c for diagnosis of diabetes makes it convenient for patients to be screened.163,164 Threshold values for diagnosis are not chosen arbitrarily but based on their ability to predict retinopathy.165,166 Owing to intra-individual variation in laboratory
values, it is essential to confirm abnormal results on a separate day.

**MANAGEMENT OF DIABETES MELLITUS**

Management of prediabetes should be given as much importance as DM itself. Lifestyle modifications (predominantly exercise and weight loss) as noted in the following text, and metformin therapy can decrease the risk of type 2 DM. Hence all patients should be counseled regarding healthy lifestyle changes regardless of their diabetes status.

Goals of management of DM should be to achieve near-normal glucose homeostasis, prevent long-term complications, and possibly prevent progression of the disease. Treatment goals are listed in Table 4 and require a multidisciplinary approach.

**Diabetes Education**

Every patient with DM should be taught diabetes self-management skills. Education should include teaching about self-monitoring of blood glucose (SMBG) using glucometers, about acute and chronic complications and how to prevent them, about treatment options, insulin administration (if applicable), recognition and treatment of hypoglycemia, and about risk behavior modification such as smoking cessation.

**Monitoring the Level of Glycemic Control**

Good glycemic control can minimize the risk of retinopathy, nephropathy, and neuropathy in both type 1 and type 2 DM and can reduce the risk of CVD in patients with type 1 DM. SMBG, with the help of glucometers, helps day-to-day monitoring of blood glucose needed for insulin dosing, prevention, and treatment of hypoglycemia (see Table 4). Continuous glucose monitoring system (CGMS) is a relatively new method that uses an indwelling subcutaneous catheter to monitor interstitial fluid glucose and provide either real-time or retrospective glucose values used for the management of type 1 DM. Considerable expertise is necessary on the part of the diabetes management team to interpret the large amount of data generated.

Long-term assessment of glycemic control is made by measurement of levels of glycosylated hemoglobin A1c (HbA1c). Nonenzymatic glycosylation of hemoglobin A1 (A1 being the predominant subtype of hemoglobin in adults) by blood glucose is increased when blood glucose levels are persistently elevated. Normal concentrations are between 4% and 6%, and values above 6% represent the presence of elevated blood glucose. Since erythrocyte life span is 3 months, HbA1c represents glycemic control over the previous 8 to 12 weeks. In patients achieving their glycemic goal, the ADA recommends measurement of HbA1c at least twice per year. In general, the target A1c should be less than 7.0%, but it may be individualized with both lower (e.g., during pregnancy) and higher (elderly with multiple comorbidities) goals being acceptable in some patients. In addition to SMBG, some patients with type 1 DM may need to monitor ketones in their urine, especially in the event of illness or pregnancy.

**Lifestyle Modification**

Medical nutrition therapy (MNT or diet) and exercise are the central components of the management of DM. Patient education regarding these aspects should be continuous and reinforced at every healthcare visit.

MNT is important to prevent onset of type 2 DM by promoting healthy eating habits and weight loss in those with obesity and prediabetes (primary prevention), to manage existing type 1 and type 2 DM (secondary prevention), and to prevent complications of DM (tertiary prevention). Although the goals of MNT should be individualized, certain general principles are discussed here. Certain dietary recommendations issued for the general population are also applicable to patients with DM. Diet
should be balanced including fruits, vegetables, and fiber and should be lower in saturated fats (< 7%) and trans fats, with avoidance of high-protein foods according to ADA recommendations.

In overweight and obese individuals, even a modest weight loss of 5% to 10% is associated with improvement in insulin resistance and will prevent development of DM in those with prediabetes or improve treatment requirements in those who already have DM. Weight loss may be achieved by either low-calorie diet or low-carbohydrate diets (such as the Atkins diet), although effects of the latter may be short-lived. Nevertheless, some form of dietary modification is essential for weight loss. Increased physical activity is also an essential component, especially for maintaining the weight loss achieved by dietary modification. Weight loss medications may be considered in a few obese individuals in whom they can help achieve weight loss of 5% to 10% as recommended; however, the effects may also be short-lived. Bariatric surgery may be the only option for weight loss for some severely obese persons and can be very successful in improving glycemic control as well as weight loss. Detailed discussion of weight loss strategies is beyond the scope of this textbook.

The goal of secondary prevention is to maintain normoglycemia in those with established DM, in addition to promoting weight loss in overweight and obese persons. Monitoring carbohydrate intake by carbohydrate counting, exchanges, or any other method is essential for achieving glycemic control. Mixed meals (those with protein/carbohydrate combination or fat/carbohydrate combination) decrease postprandial excursion of blood glucose and low glycemic index foods (associated with lower postprandial rise in blood glucose) may improve glycemic control. Patients who are on insulin should learn to estimate carbohydrate in their diet and match the insulin dose to this carbohydrate.

When complications set in, certain dietary restrictions may be necessary, such as limiting protein intake to 0.8 g/kg body weight per day in patients with overt diabetic nephropathy with proteinuria.

Exercise is essential to maintain weight loss, improve physical fitness, and reduce plasma glucose concentrations. Older diabetics starting a new exercise program may need to have medical clearance because of the high prevalence of asymptomatic CVD.

Control of hypertension is important in diabetic patients to prevent CVD and progression of diabetic retinopathy and nephropathy,167,168 and benefits may be even greater than glycemic control in patients with type 2 DM. The choice of antihypertensive therapy among patients with DM, being the focus of investigation in a number of large clinical trials, has evolved considerably. At least in patients with nephropathy, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) seem to be the preferred initial therapy. Chlorothalidone, long-acting dihydropyridine calcium channel blockers, and carvedilol have been associated with better cardiovascular and renal outcomes in combination with ACE inhibitors or ARBs.

**Pharmacologic Treatment**

Insulin is the required treatment for type 1 DM (oral agents are not indicated for use in patients with type 1 DM), whereas patients with type 2 DM can be managed with diet therapy alone or may require oral hypoglycemic agents and/or insulin or a combination thereof. Treatment of DM has been revolutionized by the introduction of several new agents in the last decade that act on different aspects of diabetes pathology (Table 5).

For insulin therapy, there are now many types of insulins that can allow for different onset, peak time, and duration of action, and there are many ways to administer these. All the insulins used currently are manufac-
Table 5. Oral Hypoglycemic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Characteristic</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Secretagogues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas (SU):</td>
<td>• Bind and activate the sulfonylurea receptor on β-cells • Duration of action and daily doses vary by agent • May be excreted by liver (glimepiride, glipizide) or kidney (glyburide)</td>
<td>• Hypoglycemia • Weight gain</td>
</tr>
<tr>
<td>-Glipizide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Glyburide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Glimepiride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides:</td>
<td>• Bind and activate the sulfonylurea receptor on β-cells • Short duration of action, quick onset of action, can be taken 15 min before meals to target postprandial hyperglycemia • Contraindicated in those with gastroparesis and chronic renal insufficiency</td>
<td>• Generally none, but possible hypoglycemia</td>
</tr>
<tr>
<td>-Repaglinide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Nateglinide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin Sensitizers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides:</td>
<td>• Exact mechanism not characterized, likely a low-grade mitochondrial poison and leads to activation of AMP kinase • Decreases hepatic gluconeogenesis and increases peripheral glucose uptake • Contraindicated in renal insufficiency (GFR &lt; 40 mL/min), age &gt; 80 years, heart failure, hepatic failure, alcohol abuse, acute illness • Promotes modest weight loss and has low risk for hypoglycemia</td>
<td>• GI distress with diarrhea, nausea, crampy abdominal pains, and dysgeusia. Rarely, lactic acidosis can develop in patients with renal insufficiency • Can cause contrast nephropathy • Levels of vitamin B₁₂ are lowered, but may not be clinically significant</td>
</tr>
<tr>
<td>-Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinediones:</strong></td>
<td>• Activate nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPARγ) • Improve peripheral glucose uptake in skeletal muscle and fat and reduce free fatty acid levels, thus reducing insulin resistance • Take up to 6–12 weeks to attain optimal therapeutic effect • Contraindicated in those with heart failure • No significant risk of hypoglycemia</td>
<td>• Weight gain • Fluid retention, may precipitate congestive heart failure in susceptible individuals • Possible increase in risk of bone loss</td>
</tr>
<tr>
<td>-Pioglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Rosiglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agents That Decrease Glucose Absorption</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors:</td>
<td>• Inhibit alpha-glucosidase in the gut and thus prevent breakdown of some complex carbohydrates into simple sugars, which then cannot be absorbed • Prevent postprandial glucose excursions</td>
<td>• Bloating, diarrhea, and flatulence due to action of colonic bacteria on undigested carbohydrates</td>
</tr>
<tr>
<td>-Acarbose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Miglitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agents That Increase Renal Glucose Excretion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2 inhibitors:</td>
<td>• Inhibits SGLT2 in kidney to prevent reabsorption of filtered glucose</td>
<td>• Dehydration on initiation • Urinary tract infections • Genital tract infections</td>
</tr>
<tr>
<td>-Canagliflozin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agents That Augment Incretin Pathways</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dipeptidyl peptidase IV inhibitors:</td>
<td>• Inhibit degradation of native GLP-1 and GIP, enhancing incretin effect • Clinical experience with this agent is limited</td>
<td>• Well tolerated and safe in renal failure • Possible angioedema in rare cases</td>
</tr>
<tr>
<td>-Sitagliptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-receptor agonists:</td>
<td>• Injectable only • Acts by mimicking incretins • Can act centrally as well as peripherally • Causes satiety and leads to weight loss</td>
<td>• Rash, skin reactions • Nausea • Pancreatitis has been reported</td>
</tr>
<tr>
<td>-Exenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Liraglutide</td>
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</tbody>
</table>
tured; animal source insulins are exceptionally rarely used.

**Oral Antidiabetic Agents**

**Sulfonylureas:** These time-honored drugs have been available since the 1950s, and although some older-generation agents (glyburide) continue to be used, the more commonly used agents (first-line) are glipizide and glikemipride. Unlike the former, which is excreted primarily through the kidneys, they are metabolized in the liver and are relatively safer in the face of deteriorating renal function. The sulfonylureas result in increased insulin secretion from β-cells by binding to the sulfonylurea receptor (SUR) and are dosed once or twice a day. The major side effect of these agents is hypoglycemia, especially when they are used in combination with other agents, or when renal or liver disease exists. The sulfonylureas (together with metformin, see following text) are the most frequently prescribed agents for type 2 DM and are now generic.

**Miglitidinides:** These agents also stimulate the SUR, but they have very different kinetics; they bind, stimulate, and have a very short action time, allowing them to be used as meal-time agents. Two such agents, repaglinide and nateglinide, are particularly useful in the elderly or in subjects in whom inconsistent eating patterns are an issue.

**Insulin Sensitizers:** These drugs act by improving the action of insulin on target tissues (e.g., liver, skeletal muscle, and adipose tissues). This group includes the biguanide metformin (whose principle action is to inhibit hepatic gluconeogenesis, but also improves skeletal muscle uptake of glucose and decreases intestinal glucose uptake) and thiazolidinediones (pioglitazone and rosiglitazone), which act primarily on adipose and skeletal muscle to improve insulin action. Metformin is one of the most commonly used oral agents (if not first-line), since it promotes some weight loss, or weight maintenance (an issue for most type 2 DM patients). However, the major side effects of gastrointestinal upset (pain and/or diarrhea) can limit its use. In addition, a potential side effect is lactic acidosis, an effect that can occur in the context of significant major organ (kidney, liver, or heart) failure, which is almost negligible when metformin is used per prescribing guidelines. Because metformin is excreted through the kidneys, it is not used in subjects with renal impairment and its use is suspended when intravenous contrast agents for radiologic reasons are to be used, since contrast nephropathy can result.

Thiazolidinediones (pioglitazone and rosiglitazone) act in the adipose and muscle tissues to sensitize the action of insulin. Like metformin, insulin sensitizers have also been shown to delay and/or prevent the onset of diabetes when used in prediabetic subjects in clinical trials (thiazolidinediones are not indicated for this use). The main side effect of these agents is weight gain (both fluid retention and adipose tissue) and has been associated with potential bone loss, limiting widespread use of these agents. However, in subjects with considerable insulin resistance, thiazolidinediones are particularly useful to limit or reduce insulin therapy.

**Alpha-Glucosidase Inhibitors:** These inhibitors act by decreasing the glucose absorption from the intestine. Though effective, their major side effects are intestinal upset (e.g., diarrhea and flatulence). Their cost also limits their use.

**Incretins and Incretin-Mimetics:** Incretins are the hormones that, upon a dietary challenge, amplify glucose-stimulated insulin secretion, decrease glucagon action, and may improve islet cell health (though the latter has been demonstrated only in animal models). There are two known incretins; glucagon-like-peptide-1 (GLP-1) and gastric-inhibitory-peptide (GIP). Incretins are produced in intestinal L cells (GLP-1) or K cells (GIP). In response to nutrients, they stimu-
late insulin secretion in a glucose-dependent fashion, inhibiting glucagon secretion, slowing gastric emptying, reducing appetite, and improving satiety. They act by binding to their cognate receptors and are inactivated in the bloodstream by dipeptidyl peptidase IV (DPP-IV). Inhibitors to DDP-IV have now been created that increase their activity. One FDA-approved inhibitor to DPP-IV is sitagliptin, although others are likely to be approved in the near future (e.g., vildagliptin, alogliptin). Because the mechanism of action is related, one injectable agent, exenatide, is discussed here; it also uses the incretin pathway. This drug was identified as the active agent in the saliva of the Gila monster that causes hypoglycemia. Exenatide binds and activates the GLP-1 receptor and in addition acts in the hypothalamus to suppress feeding and increase satiety. Sitagliptin is generally well tolerated, although it has not been on the market long enough to conclude it is generally safe. Exenatide is also generally well tolerated, although nausea, vomiting, and diarrhea are common, but may settle down with continued use. Rarely, pancreatitis has been reported with exenatide and is under review.

**Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors**: This is a new class of drugs recently approved by the FDA for treatment of type 2 DM. SGLT2 is expressed in the proximal tubule and mediates reabsorption of 90% of filtered glucose; its inhibitors promote the renal excretion of glucose, thereby modestly lowering elevated blood glucose levels in patients with type 2 DM. These agents promote urinary excretion of glucose; the kidney filters glucose when the blood glucose is higher than ~200 mg/dL, but this glucose is reabsorbed via SGLT2 in the proximal tubules. These inhibitors prevent the filtered glucose reabsorption. As a result of increased glucose and sodium in the filtrate, a mild diuresis results. This process affects only filtered glucose; thus, it seems ideal to prevent blood glucose from remaining at levels higher than the renal threshold for glucose filtration. As a result of the induced glycosuria, some weight loss is also observed since calories will be lost.

**Combination Therapy**: It is common (and often necessary) to use combination therapy for management of type 2 DM. Combination therapy is predicated on ensuring that each of the components acts in a different pathway, thereby ensuring synergism of action. The most common combinations are a sulfonylurea agent and an insulin sensitizer, but triple therapies with a sulfonylurea agent, insulin sensitizer, and a DDP-IV inhibitor are used. Metformin and thiazolidinediones can be used together, since they target different tissues to improve insulin sensitivity and act through different pathways.

With all combination therapies, the risk of hypoglycemia is increased and may require appropriate dose titration. In general, when insulin therapy is initiated, many of the oral agents, except the insulin sensitizers, are discontinued.

**Insulin Therapy**

Exogenous insulin can be administered to replace or supplement endogenous production of insulin. It is usually administered by injection, which is the cause of much phobia associated with insulin therapy. For type 1 DM patients, insulin is the mainstay and in most patients, frequent multiple dosing (basal and bolus) is common. Insulin should also be considered as the initial therapy in certain individuals with type 2 DM, such as those with renal or hepatic disease and any acute illness. However, most patients with type 2 DM may eventually need insulin as the disease progresses and relative insulin deficiency develops. A significant disadvantage of currently available preparations and methods of delivery is that the insulin directly enters the systemic circulation; this is
unlike the action of endogenous insulin, which is released into the portal venous system. No insulin regimen or method of delivery can mimic the pancreas. However, insulin therapy should mimic physiologic release of insulin, which is characterized by a continuous basal secretion to prevent fasting hyperglycemia and gluconeogenesis and by prandial insulin release with meals to prevent postprandial hyperglycemia, especially in patients with type 1 DM, who lack endogenous insulin production. In the fasting state, long-acting basal insulin is used, which has a flat profile without a peak. At mealtime, a bolus injection of fast-acting insulin is given to produce a peak coinciding with the absorption of ingested carbohydrate. In patients with type 2 DM, some endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake. Insulin is usually initiated in a single long-acting dose, given either in the evening or just before bedtime. However, other doses may need to be added later.

In the past, insulin was derived from porcine and bovine sources. This has been replaced by recombinant human insulin (e.g., NPH or regular insulin) or analog insulins, which are modified to produce varying levels of onset of action ranging from fast-acting (analog insulins such as aspart, lispro, and glulisine) to longer-duration (glargine, detemir) insulins (Table 6). Duration and peak of action are altered by changing the chemical characteristics of the human insulin molecule. For example, regular insulin aggregates to form hexomers, which requires the body to break it down into monomers before its action. Therefore, a longer time to onset of action is required compared with that of rapid-acting analog insulins, which have full biologic activity but less tendency to aggregate and remain as monomers. Several different premix insulins, containing a mixture of an intermediate-acting insulin (typically NPH) and a short-acting insulin (regular

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristic</th>
<th>Action in Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting insulin:</td>
<td>• Analog insulins</td>
<td>Onset of action: &lt; 1 hour</td>
</tr>
<tr>
<td>- Lispro</td>
<td>• Altered amino acid sequence promotes insulin monomers that are rapidly absorbed</td>
<td>Peak action: 1–2 h</td>
</tr>
<tr>
<td>- Aspart</td>
<td>• Injected shortly before meals</td>
<td>Duration of action: 2–3 h</td>
</tr>
<tr>
<td>- Glulisine</td>
<td>• Shorter duration of action results in fewer hypoglycemic episodes</td>
<td></td>
</tr>
<tr>
<td>Short-acting insulin:</td>
<td>• Soluble human insulin, generic</td>
<td>Onset of action: 0.50–1 h</td>
</tr>
<tr>
<td>- Regular</td>
<td>• Injected 30–60 minutes before meals for optimal action; failing to do so results in postprandial hyperglycemia</td>
<td>Peak action: 2–4 h</td>
</tr>
<tr>
<td></td>
<td>• Less convenient than rapid-acting analogs</td>
<td>Duration of action: 4–6 h</td>
</tr>
<tr>
<td>Intermediate-acting insulin:</td>
<td>• Formed by adding protamine to human insulin, generic</td>
<td>Onset of action: 2–3 h</td>
</tr>
<tr>
<td>- NPH (isophane suspension)</td>
<td>• Acts as both basal and bolus insulin due to a peak at 4–6 h</td>
<td>Peak action: 4–6 h</td>
</tr>
<tr>
<td></td>
<td>• Hypoglycemia a problem due to these peaks</td>
<td>Duration of action: 6–8 h</td>
</tr>
<tr>
<td>Long-acting insulin:</td>
<td>• Insulin analogs</td>
<td>Onset of action: 1–4 h</td>
</tr>
<tr>
<td>- Glargine</td>
<td>• Lesser incidence of hypoglycemia than NPH insulin</td>
<td>Peak action: none</td>
</tr>
<tr>
<td>- Detemir</td>
<td>• Glargine: Provides consistent level in plasma over long duration</td>
<td>Duration of action: up to 22 h</td>
</tr>
</tbody>
</table>
insulin or newer short-acting analogs), are available to provide basal-bolus insulins in a predetermined ratio for convenience.

The basis for any successful insulin therapy is the ability of the patient to monitor his or her own blood glucose using glucometers, with the information that equips the patient to adjust the insulin dose, diet, and exercise to allow for normoglycemia and prevent hypoglycemia. Insulin therapy is associated with the risk of significant weight gain and hypoglycemia.

**Insulin Delivery Systems**

All of the currently used delivery systems inject insulin through the skin and into the subcutaneous tissue. As previously mentioned, the most commonly used technique is administration by syringe and hypodermic needle. These needles now have a special coating to help them enter the skin as painlessly as possible. Another device is an insulin pen, which looks like a pen with cartridges, but the cartridges are filled with insulin rather than ink. A short needle is attached to the tip of the pen. Users need to turn a dial to select the desired dose of insulin and press a plunger on the end to deliver the insulin just under the skin. This method is frequently used now with patients who are on the run; the pen is safely stored at room temperature and is convenient to keep in one’s pocket or purse.

Continuous subcutaneous insulin infusion (CSII), also known as insulin pump therapy, delivers insulin through a tiny soft tube attached to a cannula that is implanted under the skin through a needlestick (infusion set). The tubing on the other end is connected to an external device containing a computer chip, an insulin reservoir that can hold up to 300 units of rapid-acting insulin and a pumping system. The infusion set needs to be changed once every 3 days. First developed in 1976, the prototype was large and inconvenient to use. Since that time, tremendous advances in computer technology have enabled the infusion set to be reduced to the size of a pager and at the same time perform exceptional tasks.\(^{171}\)

Typically, the abdomen is the site where the cannula is implanted; however, it can be implanted in any convenient location on the body. A normal pancreas secretes a basal amount of insulin continuously throughout the day to keep blood glucose in the desired range between meals and overnight and a bolus is secreted with food intake to control postprandial hyperglycemia. The pump can be programmed to mimic this endogenous pancreatic secretion and allows multiple basal rates based on exercise and activity level. The pump is an open-loop system, which requires the pump-wearer to decide how much basal or bolus dose is to be given. In addition to eliminating multiple daily injections, it can deliver small amounts of insulin with great accuracy\(^{172}\) and can decrease hypoglycemia due to the peakless nature of rapid-acting continuous insulin infusion.\(^{172-174}\) CSII can and should probably be used in all patients with type 1 DM, since these patients have physiologic insulin requirements.\(^{175}\) However, it can be especially advantageous to certain patients who are runners, pregnant, shift workers, or those who have gastroparesis.\(^{171,176-179}\) CSII may also be used in patients with type 2 DM and who may limit weight gain.\(^{180}\) Even though a host of patients may be candidates for pump therapy, not all of them would be eligible to receive one. Patients must be well motivated and able to understand basic insulin pharmacology and insulin pump technology. In addition, they must recognize that this technology does not substitute for their good decision-making and involves frequent checks of blood glucoses, interpreting them, and deciding whether and how to treat them. Typically, those who are able to follow intensive multiple-dose regimen but not able to achieve glycemic control because of obvious disadvantages of bolus regimens will benefit most from CSII.
Several innovations are coming to pump technology at a rapid pace, with remote controls to program the dose to those that wirelessly connect glucometers and the pump. However, the most anticipated technology for a long time has been a closed-loop device like a closed-loop pancreas system. Such a system would include a continuous glucose sensor that would transmit glucose readings in real time to the insulin pump, which in turn would respond by infusing the exact amount of basal and bolus insulin required to reach glycemic targets. Some prototypes of this technology are already commercially available.

Other Therapies

Pramlintide: Amylin is a hormone that is usually cosecreted with insulin in response to glucose by pancreatic β-cells. Its effects are mostly on the gut and include suppression of glucagon secretion, retardation of gastric emptying, and promotion of satiety, complementing insulin’s action in establishing glucose homeostasis. Patients with type 1 and type 2 DM have been shown to have deficiency of amylin as well as of insulin. However, amylin is relatively insoluble in aqueous solution and aggregates on plastic and glass. A synthetic amylin analog, pramlintide is currently approved for use along with insulin in patients with type 1 and type 2 DM who are inadequately controlled with their current regimens. It is given before meals, usually in conjunction with prandial insulin, but in a separate subcutaneous injection. The major role of pramlintide is to decrease postprandial glucose excursions, stabilizing glycemic control. In clinical trials, the absolute reduction in HbA1c is modest (0.3%–0.5%), although it is associated with mild weight loss, which distinguishes it from insulin therapy. Side effects are nausea and vomiting, especially at higher doses. A common dosing schedule (3 times daily) also makes it inconvenient for many patients. At this time, its niche appears to be in poorly controlled type 1 (and type 2) DM for patients already on intensive insulin regimens but whose glucose profile shows postprandial hyperglycemia not adequately addressed by increasing the dose of pre-meal rapid-acting insulin. Because of its effect on body weight, pramlintide seems to be most attractive for patients who are overweight. Insulin dosage may need to be reduced because of an increased risk of hypoglycemia.

Pancreas and Islet Transplantation: Transplantation of whole pancreas or isolated islet cells is a treatment option for patients with type 1 DM to restore glucose-regulated endogenous insulin production. Islet cell transplantation is still performed in a controlled research setting, whereas solid organ pancreas transplantation is usually carried out in conjunction with renal transplantation (thus most patients are those with renal failure). If successful, both forms of transplantation eliminate or reduce the need for intensive insulin therapy to attain near normal glycemic control, which has been associated with severe hypoglycemia.181 Whole pancreas transplantation, performed alone or in combination with kidney transplantation or after kidney transplantation, is limited by organ availability, graft failure, and morbidity associated with immunosuppressive therapy and surgical complications.182 Improvements in surgical techniques and immunosuppressive therapy regimens have helped reduce morbidity and mortality, making this a viable therapeutic alternative for treatment of DM.183 The greatest promise of islet cell transplantation is the possibility of immunosuppression-free transplantation, allowing for the prevention of the high rates of side effects associated with these medications. As of now, pancreas transplantation has a higher rate of insulin independence (55% at 3 years) compared with islet cell transplantation (35% at 3 years), although there are no direct comparison studies.
COMPLICATIONS OF TREATMENT

Intensive control of DM is recommended to prevent microvascular complications, but it is important to recognize the limitations of such intensive therapy. Goals of treatment should be individualized based on age, comorbidities, and financial restrictions. Aggressive attempts to achieve glycemic control can be associated with hypoglycemia, weight gain, transient worsening of diabetic retinopathy and neuropathy in the short term, and the need for increased healthcare services. Most serious of these is hypoglycemia, which occurs most frequently with insulin therapy, and may also occur with secretagogues. Other agents are less likely to cause hypoglycemia unless given in combination with insulin or secretagogues. Weight gain occurs with most (insulin, insulin secretagogues, and thiazolidinediones) but not all (metformin, alpha-glucosidase inhibitors, and exenatide) therapies that improve glycemic control. This is partially due to the anabolic effects of insulin and the reduction in glycosuria. In the DCCT, individuals with the greatest weight gain were found to exhibit increases in LDL cholesterol and triglycerides as well as increases in blood pressure (both systolic and diastolic) similar to those seen in individuals with type 2 DM and insulin resistance. These effects could increase the risk of CVD.

Hypoglycemia

Hypoglycemia (low blood glucose) may occur as a result of absolute insulin excess or insulin/glucose mismatch. Risk factors include increased dose of insulin, administration at the wrong time, exercise (increased glucose utilization), decreased food intake (missed meals), alcoholism (which interferes with gluconeogenesis), and renal failure (decreased insulin clearance). When blood glucose levels reach a threshold of around 70 to 80 mg/dL, counterregulatory hormones such as glucagon, epinephrine, growth hormone, and cortisol increase. These hormones stimulate glycogenolysis and gluconeogenesis in an attempt to correct hypoglycemia. In individuals with DM, these thresholds may not be the same as for healthy individuals. The blood glucose level at which the counterregulatory mechanisms are initiated changes to a higher level in those with poorly controlled DM (who often have symptoms of hypoglycemia at normal glucose levels) and to lower levels in people with recurrent hypoglycemia. A continuing fall in blood glucose levels results in autonomic symptoms initially (due to noradrenaline, acetylcholine, and epinephrine released from adrenal gland and sympathetic nervous system) and then to neuroglycopenic symptoms.

Autonomic symptoms and signs are palpitations, tremors, anxiety, sweating, intense craving for food, and rise in blood pressure and pulse rate. Neuroglycopenic symptoms are the direct result of central nervous system neuronal glucose deprivation. They include behavioral changes, confusion, fatigue or weakness, visual changes, seizure, loss of consciousness, and, rarely if hypoglycemia is severe and prolonged, death or permanent neurologic damage. Clearly adrenergic symptoms serve as a warning sign for the patient to recognize developing hypoglycemia and abort the downward spiral by ingesting carbohydrate before hypoglycemic neuroglycopenia symptoms develop. Once neuroglycopenia develops, patients are no longer able to take care of themselves and need assistance (severe hypoglycemia). However, some patients may have hypoglycemia unawareness, which is characterized by impairment of sympathoadrenal response against hypoglycemia. These impaired responses create a vicious cycle of recurrent iatrogenic hypoglycemia. Hypoglycemia unawareness, and to some extent the reduced epinephrine component of defective glucose counterregulation, is reversible within as few as 2 to 3 weeks of scrupulous avoidance of
hypoglycemia in most affected patients.

Risk for hypoglycemia should be minimized in every patient by education, inquiry about hypoglycemia at every healthcare visit, and assessment of hypoglycemia awareness. Hypoglycemia occurs more frequently in patients who are being treated with intensive insulin therapy. It can be minimized by reducing the glycemic control goal to that which can be accomplished safely and by making sure the patient’s glucometer is accurately calibrated.

Most episodes of hypoglycemia are mild to moderate (with or without symptoms) and can be effectively treated by oral glucose supplementation; parenteral treatment is necessary in patients who are unwilling or unable to take carbohydrate orally (Table 7). The duration of a hypoglycemic episode is a function of the pharmacodynamic profile of the drug that induced it. A severe episode caused by a sulfonylurea overdose can be prolonged, and hospitalization for prolonged treatment and observation is often necessary. Glucagon, which forms an important part of the treatment plan, apart from correcting hypoglycemia rapidly, may result in transient hyperglycemia, nausea, and vomiting. The glycemic response with glucagon is transient, and hence should be followed by either glucose infusion or a meal, depending on the patient’s mental status. The patient should be prescribed a glucagon kit, and friends and family should be taught to recognize the symptoms of hypoglycemia and to be familiar with the use of glucagon kits.

Table 7. Identification and Treatment of Hypoglycemia

<table>
<thead>
<tr>
<th>Symptoms of Hypoglycemia</th>
<th>Signs of Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Shakiness</td>
<td>• Tremors</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>• Tachycardia</td>
</tr>
<tr>
<td>• Palpitations</td>
<td>• Sweating</td>
</tr>
<tr>
<td>• Increased sweating</td>
<td>• Confusion, inappropriate behavior</td>
</tr>
<tr>
<td>• Hunger</td>
<td></td>
</tr>
</tbody>
</table>

General Principles:
• Treatment should be initiated as soon as possible
• All patients should be given instructions as to how to treat hypoglycemia.
• In a healthcare institution, staff should not wait for lab results or wait for response from a physician
• If blood glucose is extremely low on the glucometer, e.g., < 40 mg/dL, blood should be drawn and sent to the lab for accurate blood glucose level, since the precision of glucometers is low at extremely low blood glucose levels

Treating the Conscious Hypoglycemic Patient:
• Treat with ~ 15 g of simple carbohydrates orally
  • ½ can of regular soda
  • 4 oz of regular fruit juice or
  • 3–4 glucose tablets
• Repeat fingerstick glucose in 15 minutes
• If blood glucose is < 60 mg/dL, repeat 15 g of simple carbohydrates and check blood glucose in 15 minutes. Continue this protocol until blood glucose is > 60, then follow with a mixed snack
• Ascertain cause and if hypoglycemia not likely to recur, ask patient to discuss the hypoglycemia with his or her physician

Treating the Unconscious Hypoglycemic Patient or Otherwise Unable to Consume Oral Carbohydrate:
With IV access
• 25–50 g of 50 % dextrose can be given immediately
Without IV access
• Glucose gel can be applied to the mouth or rectum in the semi-obtunded patient
• Treat with 1 mg glucagon intramuscularly or subcutaneously; patient should regain consciousness in 15–20 minutes
• Repeat the blood glucose in 15 minutes
Pregnancy and DM
Maternal hyperglycemia at the time of conception from either type 1 or type 2 DM greatly increases the risk of spontaneous miscarriages and multiple congenital birth defects. In addition, DM in pregnancy is an independent risk factor for pregnancy-induced hypertension and preeclampsia.\textsuperscript{136} Women with DM who become pregnant are at considerable risk for the development and/or progression of DM during pregnancy. They need frequent and additional examinations during pregnancy and 1 year postpartum even if they have had dilated eye exam prepregnancy. Uncontrolled blood glucose in the last trimester are associated with fetal macrosomia (due to high blood glucose reaching the fetus and stimulating fetal insulin production, which increases fetal growth), polyhydramnios (increased amniotic fluid due to high blood glucose), and sudden fetal death. Intensive control of DM from the prepregnancy period to throughout the pregnancy along with aggressive fetal surveillance and perinatal care can improve the outcomes.\textsuperscript{126} Insulin requirement increases throughout the pregnancy because the pregnancy is an inherently insulin-resistant state. The precise mechanisms for increase in insulin resistance are not known, but placental hormones such as human placental lactogen and progesterone and, to some extent, increased fat deposits during the pregnancy seem to mediate the insulin resistance. These factors may interfere with binding of insulin to its receptor or may act at the level of cell signaling pathway behind the insulin receptor. The glucose targets during the pregnancy are more stringent so that fetal macrosomia can be avoided.

Insulin is the preferred treatment for management of DM during pregnancy, not only in those with type 1 DM but also in those with type 2 DM and GDM. Insulin requirements drop precipitously in the immediate postpartum period, so necessary adjustments should be made preemptively. More frequent antenatal fetal testing is recommended to recognize signs of fetal distress. In addition, timing of delivery is closely monitored to avoid peripartum complications, with most obstetricians choosing to deliver before 41 weeks.

CONCLUSIONS
DM is an ancient disease that is becoming more prevalent throughout the world. Although there is a strong genetic predisposition toward developing type 1 or type 2 DM, environmental factors are a critical component because the rise in incidence is occurring at a much faster pace than genetics alone can produce. The key pathophysiologic disturbance is centered on insulin action, which is intimately involved with almost every metabolic process and endocrine pathway. Understanding the pathophysiology necessitates a comprehension of all disrupted metabolic pathways. For example, insulin regulates not only glucose metabolism, but also fatty acid, cholesterol, and amino acid metabolism in cell growth and cell division, acting as a balance to other hormones that perform the opposite function.

Long-term disturbances of these pathways are responsible for devastating complications: diabetes is a major cause of retinopathy and blindness, renal failure and dialysis requirement, premature CVD (heart attacks, stroke, and peripheral vascular disease), and loss of limbs. Many other organs or systems are now recognized to be affected by diabetes, such as all aspects of oral health. Although diabetes is diagnosed with well-defined biochemical criteria, it is increasingly appreciated that any level of elevated glycemia (an indication of reduced insulin action) leads to greater cardiovascular morbidity and mortality. An increasingly sophisticated group of therapies are available to manage this disorder to improve the health of the patient.
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CHAPTER 6
Hyperglycemia/Diabetes Mellitus and Periodontal Infection Adversely Affect Each Other

Wenche S. Borgnakke

INTRODUCTION
Diabetes, prediabetes, and periodontal diseases are common chronic diseases worldwide. This chapter provides a description of the evidence regarding the two-way relationship between periodontal disease and hyperglycemia in both otherwise healthy individuals and in those with prediabetes or manifest diabetes.

This mutually adverse relationship shows the following characteristics:
1. Elevated blood glucose level (hyperglycemia) adversely affecting periodontal health.
2. Periodontal infection adversely affecting blood glucose levels, leading to:
   a. Decreased glycemic control in people with diabetes
   b. Increased risk for diabetes complications
   c. Elevated blood glucose levels or development of prediabetes in otherwise healthy individuals, development of type 2 diabetes in those with prediabetes, and possibly development of gestational diabetes

All healthcare professionals should understand the role and importance of oral health in managing patients with diabetes or those who are at risk. Attaining or maintaining healthy periodontal tissues to be as free of infection and its subsequent inflammation as possible—including nonsurgical periodontal treatment if needed—may amount to an important, novel avenue for improving glucose control in people with type 2 diabetes or for helping to prevent development or progression of prediabetes and manifest diabetes with its complications. Through such relatively simple and straightforward but concerted effort, a potentially large gain may be obtained in improving the quality of life of those with diabetes while reducing the immense burden of diabetes and its sequelae on patients, their families, and employers, as well as society as a whole.

The educational objective is to provide an overview of the current evidence among humans regarding the following topics, reflecting the organization of the chapter:
I. Effect of Hyperglycemia on Periodontal Health
II. Effect of Periodontal Infection on Blood Glucose Levels in Health, Prediabetes, Diabetes, and Diabetes Complications:
   A. Nonintervention, descriptive studies
   B. Intervention studies: effect of nonsurgical periodontal therapy on glycemic control in type 2 diabetes
III. Advice for Patients with (or at Risk for) Diabetes and Their Healthcare Providers

I. EFFECT OF HYPERGLYCEMIA ON PERIODONTAL HEALTH
Periodontitis had for many years been known as a complication of diabetes and in 1993 was suggested to be considered the sixth such complication by the Director of the National Institute of Dental Research, Dr. Harold Löe.1 However, this notion had not gained sufficient attention in the medical community until rather recently, despite efforts to disseminate the concept in the
medical community, for instance, by including such information in medical textbooks and other books and publications targeted to both medical and dental healthcare students and practitioners. It has become increasingly evident in the last few years that the presence of high blood glucose levels, that is, hyperglycemia, as seen in those with uncontrolled diabetes, is the important factor, rather than simply a diagnosis of diabetes. This realization is contrary to the still widespread belief that merely having diabetes predisposes to periodontitis. In those with type 2 diabetes, the level of hyperglycemia positively correlates with periodontal probing depth (PPD). That is, the higher the average blood glucose level is over time, the deeper the PPD. On the contrary, the clinical periodontal health status in people with well-controlled diabetes is usually similar to that observed in those without diabetes, and their periodontium responds similarly to periodontal treatment and extractions.

Because of the high—and steadily increasing—prevalence of diabetes globally, the medical and dental practitioner will likely encounter many patients with diabetes. The International Diabetes Federation (IDF) estimates that 382 million (8.3%) people worldwide have diabetes mellitus, with almost 50% of these (175 million) being undiagnosed. Another 316 million with impaired glucose tolerance (IGT) are at risk. By 2035, the IDF expects 592 million people to live with manifest diabetes, with another 471 million having impaired glucose tolerance, totaling almost 1 billion persons globally.

According to the most recent estimates by the Centers for Disease Control and Prevention (CDC), diabetes affects 29.1 million or 9.3% of the US population, of whom 20 million are diagnosed with diabetes, and 8.1 million are unaware of their disease. Similar to that found in many other countries, Figures 1 and 2 illustrate the US parallel population prevalence trends in obesity and manifest diabetes, based on representative data from the National Health and Nutrition Examination Survey (NHANES).

As can be seen in the dotted graph, over one third are obese. An additional one third are overweight with BMI between 25 and < 30 kg/m², leaving only one third of adults as underweight or of normal weight. Just 20 years ago, only in two states were as many as one in five adults obese. Figure 2 shows parallel trends in obesity and diabetes by state. Not only is the prevalence of diagnosed diabetes increasing at an alarming rate over time, the number of states in which ≥ 7.5% of individuals have diabetes now outnumbers those with lower prevalence. This has severe consequences for premature mortality, lost productivity, and human suffering, and results in immense costs to society.

Obesity and Periodontitis

Not only are obesity and hyperglycemia linked through underlying inflammatory mechanisms, obesity also affects the periodontium. For example, among 186 French subjects 35 to 64 years of age, BMI was statistically associated with missing teeth, PPD, and plaque index after adjustment for potential confounders including insulin resistance.

Similarly, obesity—especially central (abdominal) adiposity assessed by waist-to-hip ratio—was associated with a greater risk of periodontitis in a population of adults 70 years and older in the San Juan metropolitan area of Puerto Rico. Therefore, it is important to control for obesity when interpreting study results, since obesity functions as a confounder. That is, observed differences in outcomes between groups may be due to differing obesity rates in the study groups and not to the agent under study.

An intervention study not only identified overweight/obesity (BMI) as an independent predictive factor for poorer outcomes of nonsurgical periodontal treatment, it also suggested that this negative effect was
**Figure 1.** Prevalence of Total Confirmed Diabetes* and Obesity† in US Adults ≥ 20 years in NHANES (7,385 participants for 1988–1994; 5,680 participants for 1999–2004; and 6,719 participants for 2005–2010)

*Both hemoglobin A1c ≥ 6.5% and fasting glucose ≥ 126 mg/dL (≥ 7.0 mmol/L).† Body mass index (BMI) ≥ 30 kg/m².*


**Figure 2.** Prevalence of Obesity and Diabetes Among US Adults ≥ 18 Years by State

of a magnitude similar to that of cigarette smoking.\textsuperscript{19} Another study demonstrated that obese individuals who had undergone bariatric surgery and lost at least 40% of their presurgery body weight showed a significantly improved response to periodontal treatment.\textsuperscript{20}

**Hyperglycemia/Diabetes Types**

The terms hyperglycemia, prediabetes, and diabetes refer to states in which blood glucose levels are elevated. Only recently has it become apparent that hyperglycemia also plays a role in otherwise healthy individuals, as well as in those with prediabetes and diabetes. Table 1 shows various types of hyperglycemia and their case definitions.\textsuperscript{21-23} Based on a systematic review, the World Health Organization (WHO) recommended as recently as 2011 the use of HbA\textsubscript{1c} for diagnosing—not only screening—diabetes, and selected the cut-point as 6.5%. That is, persons with 6.5% HbA\textsubscript{1c} or higher are classified as having diabetes\textsuperscript{21} (Table 1).

The degree to which diabetes is controlled or managed is usually assessed by measuring the percent of glycated hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) in the blood, also known as “long-term blood sugar,” rather than the momentary concentration of glucose when fasting or at random. HbA\textsubscript{1c} is a measure of how much glucose has been present in the blood and has irreversibly bound to the hemoglobin in the red blood cells over their lifetime. A miniscule amount of blood from a simple fingerstick can be analyzed chair-side, and the result indicates the level of control of glycemia during the previous 60 to 90 days, measured as percent of HbA\textsubscript{1c}. Healthy persons have an HbA\textsubscript{1c} level of ≤ 5.6%.\textsuperscript{23}

**Table 1. Glycated Hemoglobin Levels (HbA\textsubscript{1c}) and Plasma Glucose Levels: (A) HbA\textsubscript{1c} and Corresponding Average Plasma Glucose;\textsuperscript{22} (B) Classification of Diabetes Status by HbA\textsubscript{1c}\textsuperscript{21} and Fasting Plasma Glucose Levels\textsuperscript{23}**

<table>
<thead>
<tr>
<th>HbA\textsubscript{1c} %</th>
<th>A) Average Plasma Glucose$^{\text{22}}$</th>
<th>B1) HbA\textsubscript{1c} %$^{\text{21}}$</th>
<th>B2) Fasting Plasma Glucose$^{\text{23}}$</th>
<th>Diabetes Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>~68</td>
<td>~3.8</td>
<td>≤5.6</td>
<td>Healthy</td>
</tr>
<tr>
<td>5</td>
<td>97 (76–120)</td>
<td>5.4 (4.2–6.7)</td>
<td>&lt;100</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>5.6</td>
<td>~114</td>
<td>~6.4</td>
<td>&lt; 100</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>5.7</td>
<td>~117</td>
<td>~6.5</td>
<td>5.7–6.4</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>6</td>
<td>126 (100–152)</td>
<td>7.0 (5.5–8.5)</td>
<td>100–125</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>6.4</td>
<td>~137</td>
<td>~7.7</td>
<td>5.6-6.9</td>
<td>Prediabetes</td>
</tr>
<tr>
<td>6.5</td>
<td>~140</td>
<td>~7.8</td>
<td>≥ 6.5</td>
<td>Diabetes</td>
</tr>
<tr>
<td>7</td>
<td>154 (123–185)</td>
<td>8.6 (6.8–10.3)</td>
<td>≥ 126</td>
<td>Diabetes</td>
</tr>
<tr>
<td>8</td>
<td>183 (147–217)</td>
<td>10.2 (8.1–12.1)</td>
<td>≥ 7.0</td>
<td>Diabetes</td>
</tr>
<tr>
<td>9</td>
<td>212 (170–249)</td>
<td>11.8 (9.4–13.9)</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>240 (193–282)</td>
<td>13.4 (10.7–15.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>269 (217–314)</td>
<td>14.9 (12.0–17.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>298 (240–347)</td>
<td>16.5 (13.3–19.3)</td>
<td></td>
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</tbody>
</table>

Panel (A): Translating glycated hemoglobin level (HbA\textsubscript{1c}) into estimated average blood glucose concentration.

Each percentage point HbA\textsubscript{1c} is equivalent to a mean glucose level of ~29 mg/dL or ~1.6 mmol/L.

Numbers in italics are estimates.

CI, confidence interval.

**Source:** Modified from Nathan DM et al. *Diabetes Care* 2008;31:1473–8.\textsuperscript{22}

Panel (B): Diabetes classification based on HbA\textsubscript{1c} and fasting plasma glucose concentration.

Fasting: defined as no caloric intake for at least 8 hours; prediabetes: increased risk for development of manifest diabetes.

**Source:** Modified from *Diabetes Care* 2014;37(Suppl 1):S81–90.\textsuperscript{21}
current general therapeutic target for HbA$_1c$ is to achieve a level less than 7%, but this is tailored to the individual patient.\textsuperscript{24}

**Evidence from Epidemiologic Studies**

There is growing evidence that hyperglycemia/diabetes adversely affects periodontal health, in particular that the degree of hyperglycemia in health or in prediabetes, and level of glycemic control in manifest diabetes, is associated with poorer periodontal health.

The evidence that diabetes adversely affects periodontal health and vice versa is provided by studies conducted in various parts of the world. The variety in the body of evidence stems not only from the geographic origins of the reports, but is also determined by the designs and methods of conducting the studies, because these factors help determine the kinds of conclusions about causality that can be inferred from the results.\textsuperscript{25} However, with today’s chronic diseases that are multifactorial in nature, it is often difficult to identify one specific cause, since many risk factors are at play simultaneously.

**Analytic Epidemiologic Study Designs**

The three main types of analytic, nonexperimental study designs used to explore or identify potential relations in human health are the cross-sectional, case-control, and cohort study designs.\textsuperscript{25} These three study designs are considered observational studies because they do not include treatment or intervention, even though one also “observes” the effect of the intervention in the latter. Therefore, the term epidemiologic (among people) is used in this chapter rather than observational.

The study designs differ in the way study participants are selected and the relation in time between the occurrence of exposure to the putative (suspected) causal factor and the occurrence of the disease or condition (outcome). They also differ with respect to the highest level of strength of the evidence for a relation between the suspected putative agent and the outcome, with cross-sectional studies providing the lowest level of strength, followed by case-control and cohort studies; well-conducted systematic reviews and meta-analyses of well-conducted randomized controlled trials (RCTs) provide the strongest available evidence. Intervention studies are described in a separate section. Because of ethical, methodologic, and practical limitations of experimental studies for answering questions about causation for many types of health-related issues, other study designs are also used. It is important to keep in mind that RCTs would not be appropriate for addressing the question of whether diabetes/hyperglycemia (putative agent) causes periodontitis (outcome) in initially healthy individuals. This is because it would be unethical to use an intervention in humans that causes diabetes in the experimental group. Results from studies of the following epidemiologic, nonintervention design provide evidence with increasing level of strength for potentially causal relationships.

**Cross-Sectional Studies**

Most scientific reports are cross-sectional studies that provide information about the association between diabetes and the prevalence of periodontal diseases. The latter may be assessed by using one or more of several measures of periodontal health (e.g., gingivitis, bleeding on probing [BOP], periodontal probing depth [PPD], clinical attachment loss [CAL], and radiographic bone loss). Cross-sectional studies can provide information on the prevalence, extent, and severity of periodontal disease in people with hyperglycemia/diabetes at a single point in time. Studies of prevalence additionally allow us to compare the differences in percent or proportions of individuals with periodontal disease between those with and without diabetes or between those with diabetes with
differing levels of glycemic control. The studies reporting the extent of periodontal disease assess the number of teeth or sites affected: How many? or Which proportion? Studies of severity assess the periodontal destruction by considering the magnitude of pocket depth or attachment loss: How serious is the worst periodontal breakdown?

The majority of cross-sectional studies report that more persons with hyperglycemia have periodontal disease, and in a dose-dependent manner, that is, severity of periodontal diseases increases with higher blood glucose levels. A few illustrative reports on special topics are briefly mentioned in the following text.

Authors reported from a study conducted among 350 children 6 to 13 years of age with and without diabetes (99% had type 1) a statistically significant association between number of bleeding sites and degree of glycemic control; that is, the number of bleeding sites increased with increasing HbA1c values (with higher HbA1c indicating poorer control). Around the primary teeth, the risk for bleeding was increased by 35% and around permanent teeth by 57% in children with diabetes, compared with children without diabetes. Hence, children with diabetes have a higher risk for gingival bleeding than that of their healthy peers, especially in those with higher BMI and longer duration of diabetes. A study among adolescents in Chile showed that diabetes is a potential predisposing factor for necrotizing ulcerative gingivitis (NUG), with double the chance for NUG in those with diabetes.

Javed and colleagues have conducted cross-sectional studies among persons with prediabetes that merit attention. One was specifically designed to study the relative effect of hyperglycemia and cigarette smoking on periodontitis in people with prediabetes. It confirmed that BOP was significantly reduced in smokers with and without prediabetes. More importantly, it concluded that in persons with prediabetes, the hyperglycemia seemingly overshadowed the severity of periodontal disease. This was also the case in another study pertaining to habitual chewing of gutka (betel nut), in which periodontal inflammation was heightened in healthy individuals, but obscured in gutka users with prediabetes. When the severity of periodontal disease is obscured by elevated glucose levels, poor periodontal health can go unnoticed by clinicians. Nonetheless, nonchewers with type 2 diabetes still had poorer clinically assessed periodontal health than both gutka chewers and nonchewers without type 2 diabetes.

A fourth study explored the effect of glycemic control in those with prediabetes on perceived oral health, clinical parameters, and radiographic alveolar bone loss. Participants with prediabetes had more self-assessed gingival bleeding, pain on chewing, dry mouth, and oral burning sensations, as well as poorer clinically and radiographically assessed periodontal health.

Case-Control Studies
In case-control studies of Puerto Rican children ages 6 to 12 years and Kuwaiti children ages 4 to 14 years with type 1 diabetes, those with diabetes, particularly those with high HbA1c levels, had a higher risk for plaque and gingivitis measured as BOP, compared with that of similar children without diabetes.

Cohort Studies
Since cohort (longitudinal) studies follow the same individuals over time, they can assess incidence (development of new cases) and progression of periodontal disease, where incidence is a measure of the rate of new cases and progression is a measure of the worsening of already existing periodontal disease over time. Longitudinal studies allow quantification of the degree to which hyperglycemia/diabetes increases the risk for periodontal disease, as well as its extent, severity,
or progression. Cohort studies provide descriptive, noninterventional evidence supporting the role of hyperglycemia/diabetes contributing to poorer periodontal health. Because the time sequence is known—that is, the researchers know whether hyperglycemia or periodontal disease existed first—this study design can allow for conclusions that contribute to establishing a causal relationship between hyperglycemia/diabetes and poorer periodontal health. Such temporality-based directionality allows us to speak about “effect” of the agent on the outcome—in this case, the effect of hyperglycemia on periodontal health. Consequently, the evidence from longitudinal studies can support a causal relationship.

Most studies conclude that people with poorer glycemic control have worse periodontal health than those with better glycemic control who again have better periodontal health than those without elevated blood glucose levels. Only a few examples of such studies are given to illustrate the type of studies.

The first study of its kind followed 92 patients with chronic, moderate to advanced periodontitis over 5 years of periodontal maintenance therapy. They were matched for sex and smoking into three groups: 23 had poorly controlled (HbA1c ≥ 6.5%) and 23 had well-controlled (HbA1c < 6.5%) diabetes, whereas 46 belonged to a nondiabetes control group. Those with poor control had about three times greater risk for progression of periodontitis (odds ratio [OR] 2.9), especially among those who smoked (OR 3.7), and for tooth loss (OR 3.1) when compared with the groups with well-controlled diabetes or those without diabetes. Remarkably, those with well-controlled diabetes had the same risk as those without diabetes. This example highlights the influence of glycemic control and the importance of maintaining a good periodontal status (Figure 3).

A total of 35,247 male participants of the Health Professionals Follow-Up Study (HPFUS) who were on average 54 years old, dentate, and free of periodontitis at baseline, were followed up from 1986 to 2006 by biennial questionnaires. The 2,285 men (6%) with type 2 diabetes had a significant, adjusted 29% greater risk of developing periodontitis. Furthermore, this risk was 49% greater with less than the median total intake of fruit and vegetables.

**Tooth Loss**

The ultimate result of untreated periodontal infection would be losing a tooth. Periodontitis is widely assumed to be the main cause of tooth loss in adults, even though caries is responsible for more lost teeth, even among the very old, in some studies. Although most clinical studies on oral health in people with diabetes provide some information of the number of teeth present, only a few focus on exploring the relation between diabetes and tooth loss.

**Cross-Sectional Studies**

Patel and coworkers analyzed data from 2,508 persons 50 years and older who participated in the national population study NHANES 2003–2004 cycle. They concluded that the percentage of people with diabetes who were edentulous was much higher than that in persons free of diabetes. A full 20% of edentulous individuals also had diabetes. The adjusted chance of having no natural teeth was 2.25 times higher in people with diabetes than among those without; and among the dentate with diabetes, the average number of missing teeth was 9.8 compared with 6.7 among those with no diabetes. Regrettably, the authors did not report tooth loss by level of glycemic control.

Similarly, a Thai study of 605 adults (379 with and 226 without diabetes) ages 20 to 86 years concluded that diabetes and tooth loss were directly associated, with those with diabetes having 1.7 times greater chance for having lost teeth. Among 1,354 Finnish men
Figure 3. Periodontal Measures over 5 Years in Patients in Periodontal Maintenance with Poor (PGC) and Good (GGC) Glycemic Control Compared with Healthy Individuals (NDC, No Diabetes Control): A, Mean PPD. B, Mean CAL. C, BOP. D, Plaque Index

45 to 74 years of age, 534 or 39% had metabolic syndrome. More specifically, on adjustment for potential confounders, tooth loss was found to be significantly associated with glycemic control.

Mexicans between 30 and 60 years with type 2 diabetes of at least 5 years’ duration and with mean HbA1c of 8.0 (± 1.38)% had significantly greater tooth loss than the nondiabetes control group, namely 5.7 (± 3.7) versus 3.5 (± 2.9) teeth (P = .034). Similar findings were reported among Croatians with a mean age of 55 years and having had diabetes an average of 10.6 years, with the number of missing teeth increasing with disease duration. Moreover, 154 Sudanese with type 2 diabetes had lost more teeth than the 303 without diabetes, with 74.0% versus 90.4% having more than 21 natural teeth remaining. A study in Colombia demonstrated that high blood glucose levels were associated with poorer periodontal health status (PPD and CAL) and more tooth loss in men and women on average 50 years old.

Persons with periodontitis and diabetes had a mean of 20 natural teeth compared with 25 in the diabetes-free persons.

**Longitudinal Studies**

In the US HPFUS mentioned earlier, the men with type 2 diabetes lost significantly more teeth over the 20-year span, namely, 10% more than their diabetes-free colleagues. The first prospective study on glycemic control-related progression of periodontitis and loss of teeth for individuals in periodontal treatment maintenance therapy was conducted in Brazil with the results published in 2013. During the 5-year maintenance period, persons with poor glycemic control (HbA1c > 6.5%) experienced greater tooth loss, compared with those with good glycemic control or no diabetes. Those
with poor control had a 3.1 times greater risk of losing teeth. An even greater risk, namely 4.1 times, was seen in those who also smoked.

**SUMMARY: I. EVIDENCE FOR EFFECT OF HYPERGLYCEMIA ON PERIODONTAL HEALTH**

Although there are exceptions, the majority of studies conclude that the prevalence, extent, or severity of periodontal disease is greater in people who have elevated blood glucose levels, especially in those with poor glucose control. People with poorly controlled diabetes are more likely to have deeper periodontal pockets, greater attachment loss, and more radiographic bone loss than people who do not have diabetes. A dose-response relation exists, such that the worse the hyperglycemia is, the more negatively it affects the periodontium. Also, people who have had uncontrolled diabetes for longer periods tend to have poorer periodontal health, particularly more clinical attachment or radiographic bone loss.

The preponderance of studies reporting on the mutually adverse associations between hyperglycemia and periodontal health are cross-sectional and involve convenience samples of patients—principally from hospitals, dental schools, and clinics, but also from larger population-based studies. However, a growing body of evidence from longitudinal studies provides additional support for the association between diabetes and periodontal disease. These studies were conducted in different settings and different countries, with different ethnic populations and age mixes, and with a variety of measures of periodontal disease status (e.g., gingival inflammation, pathologic PPD, loss of periodontal attachment, and radiographic evidence of alveolar bone loss). The studies use different parameters to assess periodontal disease occurrence (prevalence, incidence, extent, severity, and progression). Hence, this inevitable variation in methodology and study populations limits the possibility that the same biases or confounding factors apply in all the studies and therefore provides support for concluding that diabetes is a risk factor for periodontal disease incidence, progression, and severity. In addition, substantial evidence supports a dose-response relationship. That is, with increasing levels of hyperglycemia, the adverse effects on periodontal health become greater. Finally, there are no studies with superior design features to refute this conclusion. Examples of comprehensive reviews of the studies in this body of literature are presented in reports by Mealey and Ocampo, Lamster et al., Taylor and Borgnakke, Taylor et al., and Borgnakke and Genco.

**II. EFFECT OF PERIODONTAL INFECTION ON BLOOD GLUCOSE LEVELS IN HEALTH, PREDIABETES, DIABETES, AND DIABETES COMPLICATIONS**

The next section describes an effect going in the opposite direction, namely, periodontal infection adversely affecting blood glucose levels. Only recently are we beginning to understand that this is important also in healthy persons who may eventually develop prediabetes and ultimately type 2 diabetes if the elevated glucose levels persist and increase.

Periodontal infection contributes to the chronic systemic inflammatory burden. As part of the general immune response to infection for which energy is needed to combat the “intruder,” periodontal infection elevates the concentration of sugar in the blood, just like any other infection elsewhere in the body. Effects of periodontal infection on the local and general systemic inflammatory responses are described in more detail in Chapter 3.

A growing body of evidence supports the long-time clinical observation that periodontal infection adversely affects glycemic control. We recognize that making every
effort to decrease elevated blood glucose levels is very important, to improve glycemic control and prevent complications not only in persons with diabetes due to the chronic hyperglycemia, but also in individuals with prediabetes—and even in healthy individuals. Periodontal infection ultimately contributes to a greater risk of complications of diabetes that are caused by persistently high levels of blood glucose. Diabetes complications are potentially fatal, such as heart disease and other cardiovascular events; stroke; nephropathy (diseases of the kidney, ultimately leading to end-stage renal disease [ESRD] that requires renal dialysis for survival); neuropathy (diseases of peripheral and autonomic nerves); retinopathy (diseases of the retina, possibly leading to partial or complete blindness); extremely decreased wound healing; and amputations.

Mediators important in periodontal inflammation, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1-beta (IL-1β), are shown to have important systemic effects on glucose and lipid metabolism as well as on insulin action, resulting in development of insulin resistance and diabetes, as suggested by Grossi and Genco in 1998. Genco et al. proposed a model that linked inflammation to obesity, diabetes, and periodontal infection in 2005.

Metabolic and immune systems are among the most fundamental for survival. Their regulations are highly integrated, and the proper function of each is dependent on the other. Dysfunctions of this central interface can lead to several chronic metabolic diseases, particularly obesity, type 2 diabetes, and cardiovascular disease. Collectively, these diseases currently constitute the greatest threat to global human health and welfare.

A. Evidence from Nonintervention Studies

Periodontal infection is a risk factor for elevation of blood sugar level. In 2013, Borgnakke, Ylöstalo, Taylor, and Genco conducted a systematic review of epidemiologic observational evidence for the effect of periodontal disease on diabetes-related measures. Studies that permitted determination of directionality of observed effects and that met the eligibility criteria were included. The authors concluded that a small body of evidence supports significant adverse effects of periodontal disease on glycemic control, diabetes complications, and development of type 2 (and possibly gestational) diabetes. However, there were only a limited number of eligible studies, several of which included small sample sizes. Furthermore, exposure (periodontal parameters) and outcome (glycemic measures) parameters varied among the studies; therefore, the generalizability of their results was limited. Also, the heterogeneity among the studies prevented any meaningful meta-analysis to be conducted. The authors concluded that the current evidence suggests that periodontal disease adversely affects diabetes outcomes and that further longitudinal studies are warranted.

Glycemic Control in Type 2 Diabetes

The first—now classic—longitudinal epidemiologic study was conducted by the National Institute of Diabetes and Digestive and Kidney Diseases among the Pima Indians in Arizona, USA, whose diabetes prevalence is unusually high. Reports from this study are the first to provide evidence for the formerly expressed hypothesis that periodontal infection can adversely affect diabetes. One report found that subjects with type 2 diabetes in good to moderate control and with severe periodontitis at baseline were about six times more likely to have developed poor glycemic control 2 years later than those without severe periodontitis at baseline.

Even though the cross-sectional study design cannot indicate causality, one unique such study conducted in Mexico merits
mention. Among 127 pregnant women with type 2 diabetes, those with periodontitis were more likely to have poorer glycemic control, after controlling for presence of a urinary tract infection and/or cervicovaginal infection and a measure of compliance with recommended medical treatment for the diabetes. Consequently, the authors speculate that periodontal infection may present a hitherto unnoticed factor contributing to lack of glycemic control and therefore should be considered by prenatal care teams.

Development of Hyperglycemia in Healthy Persons
Recent evidence has demonstrated that periodontal infection leads to elevated blood glucose levels also in healthy individuals who do not have diabetes or even prediabetes.

Cross-Sectional Studies
Analyzing NHANES 1999–2004 data from 3,616 persons with periodontal examinations, Demmer’s group found periodontal infection to be associated with insulin resistance, which increased linearly with each 1 mm increase in mean PPD, but was unassociated with CAL. A study in India comprising 200 diabetes-free persons 50 years and older compared four sex- and age-matched groups of 50 with increasing periodontitis severity assessed by tooth mobility from none to grade 3. Levels of both glycohemoglobin and serum C-reactive protein increased significantly with periodontitis severity in a dose-response fashion, except that the mobility increase from grade 1 to 2 was not statistically significant.

Longitudinal Studies
A large population-based study (N = 2,793; age range 20–81) was conducted in Pomernia in former East Germany among people who did not have diabetes at baseline. Those with periodontitis at baseline had approximately a fivefold increase in HbA1c compared with individuals who were periodontally healthy at both baseline and 5 years later. Similarly, in another prospective cohort study among 1,023 Japanese systemically healthy persons 20–56 years of age (mean 37.3 years), having baseline pathologic PPDs was associated in a dose-response manner with having developed one or more components of metabolic syndrome 4 years later. In a retrospective cohort study among 961 Japanese 40–79 years of age, Saito et al. concluded that each additional millimeter mean probing depth corresponded to an increase of 0.13 percentage points of HbA1c over the previous 10 years. Moreover, increasing mean probing depth, but not CAL, corresponded to the development of glucose intolerance.

Development of Type 2 Diabetes
In addition to evidence supporting periodontal disease as a potential risk factor for developing diabetes complications, evidence is also emerging that periodontal disease may be a risk factor for type 2 diabetes and possibly for gestational diabetes. Demmer and colleagues investigated the association between periodontal disease and the development of new (i.e., incident) diabetes cases in a representative sample of the US population, analyzing data from the first National Health and Nutrition Examination Survey (NHANES I) and its Epidemiologic Follow-up Study (NHEFS). The average follow-up period for the 9,296 individuals in the analysis was 17 years—the period from 1971 to 1992. The study was a cohort study design because the information on the exposure (i.e., the hypothesized causal factor), the presence or absence of periodontal disease, was known at the time the study began, and the outcome (development of diabetes) was assessed subsequently. This study concluded that having periodontal disease was significantly associated with a 50% to 100% (up to twofold) greater risk for type 2 diabetes after
controlling for other established risk factors for diabetes.

One prospective and two retrospective longitudinal studies were conducted in Japan and explored the effect of periodontitis on the development of type 2 diabetes. The prospective study over 5 years among 6,125 employees 30 to 69 years old and 77% males found that having a PPD ≥ 6 mm led to type 2 diabetes. Another workplace screening study over 6.5 years (range: 2–7 years) among 5,848 persons between 30 and 59 years also concluded that such deep pockets lead to type 2 diabetes. However, after adjustment for potential confounders, only women with PPD of 4–6 mm were statistically significantly more likely to develop type 2 diabetes. In a community-based study in Hisayama, Japan, among almost 1,000 individuals ages 40–79, baseline deep pockets (mean > 2.0 mm) as well as high CAL (mean > 2.5 mm) were significantly associated with impaired glucose tolerance and with manifest diabetes 10 years later. The relationship was dose-dependent, so that each additional millimeter PPD corresponded to an increase of 0.13 HbA1c percentage points.

Diabetes Complications

It is widely recognized that long-term poor glycemic control is a major determinant for the development of chronic complications of diabetes. Results from the landmark Diabetes Control and Complications Trial (type 1 diabetes) and the UK Prospective Diabetes Study (UKPDS, type 2 diabetes) demonstrated that attaining and maintaining good glycemic control can reduce the risk for and slow the progression of microvascular complications in patients with types 1 and 2 diabetes, respectively. In addition, the UKPDS observed a 16% reduction (P = .052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death. Further epidemiologic analysis from the UKPDS showed a continuous association between the risk of cardiovascular complications and glycaemia; every percentage point decrease in HbA1c (e.g., from 9% to 8%), was associated with a 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and 18% reduction in combined fatal and nonfatal myocardial infarction.

The following examples are provided to illustrate the types of studies that constitute the evidence that associates diabetes complications with periodontal disease by diabetes type.

Two reports do not specify diabetes type. The only US national survey that assessed microvascular hemorrhaging at two different body locations is the NHANES 1988–1994. Persons with 20% or more sites with gingival bleeding on probing had a 57% significantly increased chance of also having bleeding in the retina, a sign of systemic microvascular injury and a common complication of diabetes. A study of 73 Japanese indicated 2.8 times greater risk for retinopathy in those with radiographic alveolar bone loss greater than the median compared with those at or below the median, with the severity of retinopathy increasing with magnitude of bone loss.

Type 1 Diabetes

There is emerging evidence from observational studies regarding the association between periodontal disease and risk for diabetes complications. Thorstensson and colleagues studied 39 case-control pairs of individuals with mostly type 1 diabetes for 6 years median follow-up time in Jönköping, Sweden. In each pair, the cases had severe alveolar bone loss and controls had gingivitis or minor alveolar bone loss. The authors found at their follow-up medical assessments that cases were significantly more likely than controls to have prevalent proteinuria and cardiovascular complications including transient ischemic attacks, angina, myocardial
infarction, and intermittent claudication, as well as stroke.

**Type 2 Diabetes**

Two reports from the longitudinal study of type 2 diabetes and its complications in the Gila River Pima Indian Community in Arizona address nephropathy and cardiovascular disease. Saremi and colleagues studied a cohort of 628 individuals for a median follow-up time of 11 years. Individuals with severe periodontal disease had 3.2 times greater risk for cardiorenal mortality (i.e., ischemic heart disease and diabetes-related nephropathy combined) than those with no, mild, or moderate periodontal disease. This estimate of significantly greater risk persisted while controlling for several major risk factors of cardiorenal mortality including age, sex, diabetes duration, HbA1c, body mass index, hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macroalbuminuria, and smoking. In the second report, Shultis et al. found in a group of 529 adults that periodontitis and edentulism were significantly associated with the risk of developing overt nephropathy and ESRD. The incidence of macroalbuminuria was 2.0, 2.1, and 2.6 times greater in individuals with moderate or severe periodontitis or in those who were edentulous, respectively, compared with those with no or mild periodontitis. The corresponding incidences of ESRD were 2.3, 3.5, and 4.9 times greater.

A comparison of 791 persons 52–74 years of age with type 2 diabetes with 5,257 persons without diabetes participating in the Atherosclerosis Risk in Communities (ARIC) study in four communities in as many US states showed that those with severe periodontal disease had greater incidence of coronary heart disease and subclinical heart disease. The latter was assessed by increased carotid intima media thickness (≥1 mm) and acoustic shadowing revealing calcification of advanced atherosclerotic plaque. In a study in Iran among 213 persons with type 2 diabetes with and without diabetic retinopathy and 73 healthy controls, the risk for retinopathy was significantly higher in those with periodontitis, and the severity of the two conditions was strongly correlated. In Brazil, a study among 122 persons with type 2 diabetes showed that those with PPDs of 4 mm or more had over six times greater risk of having neuropathic foot ulcers (OR: 6.6; CI: 2.3–18.8; \( P \leq .001 \)), compared with those with no pathologic periodontal pockets.

**Importance of Diabetes Complications**

The crucial importance of preventing the development or at least the severity of complications of diabetes can be illustrated by a 2014 study of Swedish data from 20,836 individuals with type 2 diabetes derived from the National Diabetes Registry. The life expectancy at the time of experiencing their first major diabetes complication (myocardial infarction, stroke, heart failure, amputation, or renal failure) could be calculated and changed over time by complication type. In addition to cigarette smoking, renal failure manifested as low estimated glomerular filtration rate and albuminuria, significantly increases mortality risk. As mentioned, studies have demonstrated that periodontal disease is associated with such mortality factors, so it could be speculated that attainment of periodontal health could positively affect the mortality rate.

**Development of Gestational Diabetes**

Two US case-control studies explored the potential role of periodontitis in developing gestational diabetes (GDM). Regardless of which of three case definitions for periodontitis was applied, Xiong and colleagues demonstrated that among 53 women with GDM and 106 pregnant women without, that GDM, in a dose-response manner, was
associated with both PPD and attachment loss. Dasanayake’s team investigated whether pregnant women who develop GDM, compared with pregnant women who do not develop GDM, had poorer clinical periodontal health and/or demonstrated higher levels of other biologic markers of periodontal disease approximately 2 months before their GDM diagnosis. The other biologic markers included bacteriologic (dental plaque and cervicovaginal samples), immunologic, and periodontitis-related inflammatory mediator analytes. Women who had higher vaginal levels of Tannerella forsythia, a bacterium known to be associated with periodontitis, were statistically significantly more likely to develop GDM than women with lower levels. Therefore, the authors conclude that Tannereilla forsythia in the vaginal flora is a potential risk factor for gestational diabetes.

SUMMARY: II. EVIDENCE FOR EFFECT OF PERIODONTAL INFECTION ON GLUCOSE LEVELS
A. NON-INTERVENTION STUDIES
A small, but growing body of evidence suggests that periodontal infection contributes to the systemic inflammatory burden and subsequently is associated with increased blood glucose levels. Such periodontal disease-initiated hyperglycemia contributes to elevated glucose levels in healthy individuals and to the development of prediabetes, type 2 diabetes, and possibly gestational diabetes, as well as diabetes complications.

B. EVIDENCE FROM INTERVENTION STUDIES
Nonsurgical periodontal treatment decreases blood sugar level. The most important question of relevance to clinical practice and management of diabetes is whether it is possible to improve blood sugar control by minimizing the periodontal infection by means of professional nonsurgical periodontal treatment that can be provided in general dental offices and supplemented with home oral hygiene measures.

The majority of nonsurgical treatment studies report a statistically significant decrease in HbA1c, whereas others do not demonstrate any decrease or one that is not significant. The latter result often occurs because of a lack of statistical power provided by the small number of study subjects. The relatively small numbers of participants in most of the studies are primarily due to the immense resources required for conducting clinical trials, especially those with a long follow-up period. Table 2 displays systematic reviews that include meta-analyses conducted by pooling results from sufficiently similar studies to attain more statistical power and hence gain more strength to support the conclusions.

Before publication of results from several subsequently conducted confirmatory RCTs that show similar results, especially for initially uncontrolled diabetes, the well-respected Cochrane Review Group concluded in 2010, based on only three eligible RCTs: “The evidence gathered suggested that there may be small but significant improvement in blood sugar control from treating preexisting gum disease in people with Type 2 diabetes mellitus.”

A study of periodontal treatment called Diabetes and Periodontal Therapy Trial (DPTT) was recently published, in which the authors reported finding no significant effect on HbA1c in persons with type 2 diabetes 3 and 6 months after nonsurgical periodontal treatment. The recruitment was ended early “due to futility.” Of the 1,756 people screened, 514 were randomized, of whom 240/257 in the treatment group and 236/257 in the control group completed the study. The treatment consisted of scaling and root planing completed during at least two sessions. Oral hygiene instruction (OHI) was provided together with 0.12% chlorhexidine gluconate for twice-daily rinsing for the
following 2 weeks. The participants returned
3 and 6 months later for one session of
about 1 hour of scaling and root planing
and OHI, whereas the control group at their
baseline, 3-, and 6-month visits received OHI
only. At the conclusion of the study, control
group participants were offered scaling and
root planing.

The authors claim that their treatment
resulted in significantly improved periodontal
health, but did not mention that this signif-
cance was statistical in nature only. Unfortu-
nately, the treatment provided did not cli-

cally improve the periodontal status suffi-
ciently, per commonly accepted standards
for nonsurgical periodontal therapy. At the
end of the study, the treatment group had a
plaque score of 72.1% sites/person (down
from 86.7% at baseline), and 41.6% of the
sites had BOP (down from 60.6%). More-
over, 30.6 sites and 15.7 sites per person,
respectively, had PPD ≥ 4 mm and PPD ≥ 5
mm, respectively, which corresponds to
20.1% and 10.2% of the sites that still had
pathologic pockets. The gingival index had
decreased by 0.4, namely, from 1.4 to 1.0.
These clinical periodontal measures fall short
of the generally accepted standards for clini-
cally successful nonsurgical periodontal

therapy. When periodontal health, or near
health, is not attained, no significant effect
can be expected on the HbA1c level, simply
because periodontal infection and the elicited
host inflammatory responses persist.

The researchers and their study partici-
pants were not able to obtain acceptable
periodontal health and therefore could not
draw any firm conclusions regarding any
effect on HbA1c. These and other shortcom-
ings of this study are described in three
Letters to the Editor, which appear in the
May 14, 2014 issue of JAMA, along with
the DPTT authors’ response thereto. In
addition, a more detailed review was
posted online on May 22, 2014, ahead of
publication of the printed version in the Sep-
tember 2014 issue of the Journal of Evidence-
Based Dental Practice. A plain summary of the DPTT report was published in the May 2014 issue of the Journal of the American Dental Association (JADA) without comments or critique.

**Effect of Prophylaxis Only**
A study with particular clinical relevance,
especially for populations with limited access
to advanced professional dental services,
merits special mention. In collaboration

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**Table 2. Effect of Nonsurgical Periodontal Treatment on Glycemic Control in People with Type 2 Diabetes: Meta-Analyses Published August 6, 2014**

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th># Studies</th>
<th># RCTs</th>
<th>Pooled # Subjects</th>
<th>HbA1c Change</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janket et al. 2005⁵⁵</td>
<td>5</td>
<td>1</td>
<td>268</td>
<td>-0.66%</td>
<td>-2.2; 0.9</td>
<td>ns</td>
</tr>
<tr>
<td>Darré et al. 2008⁵⁶</td>
<td>9</td>
<td>9</td>
<td>485</td>
<td>-0.46%</td>
<td>-0.82; -0.11</td>
<td>.01</td>
</tr>
<tr>
<td>Tewu et al. 2010⁻⁵⁷</td>
<td>5</td>
<td>3</td>
<td>180</td>
<td>-0.40%</td>
<td>-0.77; -0.04</td>
<td>.03</td>
</tr>
<tr>
<td>Simpson et al. 2010⁻⁸</td>
<td>3</td>
<td>3</td>
<td>244</td>
<td>-0.40%</td>
<td>-0.78; -0.01</td>
<td>.04</td>
</tr>
<tr>
<td>Cochrane Review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sgolastra et al. 2013⁻⁹</td>
<td>5</td>
<td>9</td>
<td>315</td>
<td>-0.65%</td>
<td>-0.88; -0.43</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Engebretson &amp; Kocher 2013⁻¹⁰</td>
<td>9</td>
<td>9</td>
<td>775</td>
<td>-0.36%</td>
<td>-0.54; -0.19</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Liew et al. 2013⁻¹</td>
<td>6</td>
<td>6</td>
<td>422</td>
<td>-0.41%</td>
<td>-0.73; -0.09</td>
<td>.013</td>
</tr>
</tbody>
</table>

¹Weighted.
²Remaining two non-RCT studies are clinical controlled trials.
³Standardized mean difference.
⁴CI, confidence interval; HbA1c, glycated hemoglobin; ns, nonsignificant; RCT, randomized controlled trial.
between a Chilean dental school and a private dental practice, Lopez and team\(^27\) studied subjects with moderate and severe periodontitis in groups with no diabetes and with type 2 diabetes, the latter divided by glycemic control into subgroups with good [mean HbA\(_{1c}\) = 6.2 (±0.0%) \(\text{range 4.8–6.9\%}\)] and poor [mean HbA\(_{1c}\) = 8.6 (±1.3%) \(\text{range 7–10.5\%}\)] glycemic control, respectively. Even though the glycemic control did not change, all the periodontal parameters (mean CAL and PPD; proportions of sites with CAL ≥3 mm, PPD ≥ 4 mm, BOP; plaque) improved significantly in both groups, with and without diabetes, with remarkable similarity in periodontal health at the end of the 9-month study, despite the nondiabetes group being nonsignificantly heavier [mean BMI = 31.1 (±3.9) kg/m\(^2\); range 23.0–40.0 kg/m\(^2\)] versus [28.8 (±4.0) kg/m\(^2\); range 24.0–37.7 kg/m\(^2\)]. This study demonstrates that 3-monthly, routine prophylaxis (scaling and coronal plaque removal and polishing), supported with home care instructions, can successfully prevent any progression of periodontitis in every participant, regardless of the presence of diabetes and the level of glycemic control. This finding is interesting, not only because routine prophylaxis was demonstrated to maintain periodontal health—and possibly to prevent deterioration of glycemic control, provided all other factors were stable during the study—but also because these findings contradict the results of a well conducted systematic review by the Cochrane Collaboration.\(^90\)

This comprehensive review concluded: “There is insufficient evidence to determine the effects of routine scale and polish treatments,” when attempting to determine whether the routine “prophylaxis” usually provided at regular dental check-ups, also in people with low risk for periodontitis, actually are clinically effective for periodontal health.\(^90\)

**Effects of Full-Mouth Extraction**

Randomizing 58 patients with serious, incurable periodontitis requiring full-mouth extraction into one group receiving such removal of all teeth and the other group not receiving any care, Khader and colleagues\(^91\) reported that the HbA\(_{1c}\) level and fasting blood glucose levels decreased significantly from 8.6\% at baseline to 7.4\% after 3 months and continued to decrease to 7.3\% at 6 months after extraction. Upon adjustment, the treatment group HbA\(_{1c}\) level decrease by 1.23 percentage points was still significantly higher than the decrease of 0.28 in the control group. Therefore, the authors suggest that full-mouth tooth extraction could result in an improvement in glycemic control among people suffering from type 2 diabetes.

**Antibiotics in Periodontal Management in Diabetes**

To date, no clear-cut evidence supports a requirement for the use of antibiotics in combination with nonsurgical periodontal treatment in order to observe an improvement in glycemic control associated with nonsurgical periodontal therapy in those with type 2 diabetes. In some studies, it actually was the comparison group who did not receive antibiotics who had the greatest improvement in glycemic control,\(^92\) although other studies conclude that such adjunct local or systemic antibiotics enhance the clinical outcome.

It is important to note that evidence is emerging that contradicts the dogma that people with diabetes are more prone to infections and heal more slowly. This long-time belief seems to be unsupported by scientific evidence, which is a very important realization. For instance, Huang et al.\(^13\) compared the healing time upon tooth extraction in 224 persons with type 2 diabetes who took oral anti-diabetes medications with 232 diabetes-free individuals with no other conditions known to delay wound healing.
Observing more delayed healing in the younger control group, the authors concluded that persons with well controlled type 2 diabetes taking oral hypoglycemic medication should be treated as persons without diabetes in conjunction with dental extractions. Others reported normal socket healing without antibiotics in both nondiabetes and type 2 diabetes participants, despite poor glucose control in the latter.\textsuperscript{11,12} In a letter to the editor of the \textit{British Journal of Oral and Maxillofacial Surgery},\textsuperscript{93} the authors suggest, “the use of perioperative prophylactic antibiotics for routine extractions in controlled diabetic patients is not justified and not evidence-based in the same way as it is not indicated in non-diabetic patients. In today’s world of antibiotic-resistant infections, our responsibility to avoid unnecessary use of antibiotics has increased.” The problem of antibiotic resistance is addressed also in recent publications.\textsuperscript{94,95}

\textbf{SUMMARY: II. EVIDENCE FOR EFFECT OF PERIODONTAL INFECTION ON GLUCOSE LEVELS}

\textbf{B. INTERVENTION STUDIES}

In the body of literature consisting of both RCTs and non-RCTs, there is marked heterogeneity in the studies’ designs, geographic locations, source populations, conduct, length of follow-up for glycemic control assessment, types of participants and their baseline periodontal disease and glycemic control status, inclusion of control groups, periodontal treatment protocols, periodontal measures assessed, case definitions for periodontitis, sample size and power to detect differences in periodontal and metabolic response, and specific hypotheses tested. The details of the variation in this body of literature have been extensively described in several reviews, including those displayed in Table 2.

Despite such dissimilarities, intervention studies among people with type 2 diabetes report a positive effect on the blood glucose level. The magnitude of this improvement of HbA\textsubscript{1c} is similar to that expected by adding a second antidiabetic oral medication to metformin, thus representing an important clinical significance. Since the evidence also demonstrates that nonsurgical periodontal treatment is effective in improving periodontal health, it is recommended that people with diabetes or those who are at risk thereof, as well as individuals with no diabetes, attain and maintain a periodontium as healthy as possible as part of overall health and well-being. There is need, however, for well-controlled RCTs to determine the extent to which and in which patients’ resolution of periodontal disease affects glycemic control and, more importantly, complications of diabetes.

\textbf{III. ADVICE FOR PATIENTS WITH (OR AT RISK FOR) DIABETES AND THEIR HEALTHCARE PROVIDERS}

For some years, attention has focused on the importance of attaining and maintaining good oral health for persons with diabetes. Most recently, it has become apparent that controlling periodontal infection may play a role in management of blood glucose levels in health, prediabetes, and manifest diabetes. An increasingly loud call for interdisciplinary collaboration in a patient-centered, health-promoting setting is heard. Examples of professional advice and guidelines that are publicly available and free of charge are provided in the following text.

The group of experts who scrutinized the scientific evidence for links between periodontal disease and diabetes at the November 2012 EFP/AAP workshop agreed on advice or guidance for patients who have prediabetes, gestational, and manifest diabetes, or who are at risk thereof. Also, such guidance was agreed upon for the medical and dental care providers of these patients. All the guidelines are displayed in the publicly available consensus report that may be

An 11-page guideline booklet called *Oral Health for People with Diabetes* provided by the International Diabetes Federation (IDF) is freely available at http://www.idf.org/webdata/docs/OralHealth_EN_RTP.pdf.

Every year in January, the American Diabetes Association publishes in *Diabetes Care* an update of the diagnosis and classification of diabetes mellitus, along with updated Standards of Medical Care in Diabetes that may be freely viewed at http://care.diabetesjournals.org/content/37/Supplement_1/S14.full.pdf+html. Dental care has only been mentioned by listing in a table on components of the comprehensive diabetes evaluation as part of the Medical History (“Other: Psychosocial problems, dental disease”), along with “Dentist for comprehensive periodontal examination” under “Referrals.” For the first time, a brief passage in the body of the text is included in 2014, with its own subheading “Periodontal Disease” in section VII. Assessment of Common Comorbid Conditions. It reads: “Periodontal disease is more severe, but not necessarily more prevalent, in patients with diabetes than in those without.” Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits is currently lacking.”

Although the author of this chapter disagrees with the first and last statements, this is a welcome step toward acknowledgement by the American Diabetes Association that oral health is an important component of diabetes management.

“Gum disease can raise your blood sugar level” is the title of the “For the Dental Patient” page in the July 2013 issue of *JADA*. It briefly summarizes in plain language the aforementioned first systematic review of the effects of periodontal infection on blood glucose levels and is publically available for distribution at http://jada.ada.org/content/144/7/860.full.pdf+html.


Finally, the American Dental Association provides information and guidance via its Mouth Healthy™ program regarding diabetes and oral health at http://www.mouthhealthy.org/en/az-topics/d/diabetes.

**CHAPTER SUMMARY AND CONCLUSIONS**

The evidence reviewed in this chapter supports the mutually adverse effects of hyperglycemia/diabetes mellitus and periodontal infection:

1. Hyperglycemia/poorly controlled diabetes leads to greater development, extent, severity, and progression of periodontal breakdown. There is also some evidence that gestational diabetes may adversely affect periodontal health.

2. Periodontal infection, especially the severe form, with its subsequent inflammatory responses, elevates blood sugar levels in healthy persons as well as in those with prediabetes and type 2 diabetes. Such periodontal infection–initiated hyperglycemia contributes to poorer glycemic control in persons with diabetes and to the development of pre-diabetes and eventually manifest diabetes, and perhaps to the development of gestational diabetes, in individuals with no prior diabetes. Furthermore, evidence suggests that periodontal disease is associated with increased risk for diabetes complications.

3. Clinically successful nonsurgical, routine periodontal treatment in persons with type 2 diabetes has consistently been demonstrated in seven meta-analyses and in additional more recent individual studies to lead to a decrease in
HbA1c of about 0.4 percentage points 3 months after intervention. This is a magnitude similar to adding a second oral antidiabetes medication to metformin and hence is of clinical significance in managing type 2 diabetes. While treating periodontal infection in people with diabetes is clearly an important component in maintaining oral health, it may also play an important role in establishing and maintaining good glycemic control in those with type 2 diabetes and thereby possibly delaying the onset or progression of type 2 diabetes and complications of diabetes.

Consequently, dental health professionals may fulfill an important role when collaborating with other healthcare providers in a patient-centered approach to maintaining or improving the health of their mutual patients with diabetes or those at risk. This would ultimately improve the quality of life of individuals with diabetes or those at risk for type 2 or gestational diabetes, as well as aid in reducing the immense burden of diabetes and periodontal diseases on the individuals, their social network, and society in general.

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CHAPTER 7
Atherosclerosis: A Pervasive Disease Affecting Global Populations

Originally contributed by Stanley Wang and Sidney Smith
Updated and edited by Timothy C. Nichols

INTRODUCTION
Atherosclerotic disease results from the pathologic formation of plaques in arterial walls. Plaque development, or atherogenesis, is a complex process with many underlying inflammatory molecules participating in increasingly well-understood pathways. The consequences include a wide variety of clinical syndromes involving different organs with a common underlying deficiency—inadequate blood supply due to reduction of blood flow to the target organ.

This chapter reviews the clinical manifestations of atherosclerosis and explores its underlying molecular pathophysiology. Understanding the underpinnings of atherosclerosis is crucial to appreciating the potential interplay between atherosclerosis and periodontal disease, which is discussed in the next chapter.

TYPES OF ATHEROSEDEROUS DISEASE
Atherosclerosis may occur in any arterial bed; the most clinically relevant are the coronary, cerebrovascular, and peripheral arterial circulation. Atherosclerotic plaques may be stable or unstable, based on whether the plaque has ruptured. More recently, studies have shed additional light on “vulnerable” atherosclerotic plaques, which were most likely stable plaques that have developed a propensity for rupture.

Coronary heart disease is the most clinically evident form of atherosclerotic disease, affecting over 17 million Americans according to the American Heart Association’s 2013 statistical update.\(^1\) Manifestations of coronary atherosclerosis range from stable angina, resulting from myocardial ischemia caused by stable coronary arterial plaques that reduce luminal cross-sectional area and restrict blood flow, to acute coronary syndrome (ACS) characterized by unstable, ruptured coronary atherosclerotic plaques with superimposed occlusive or nearly occlusive thrombosis. ACS can be further subdivided into non-ST elevation ACS—such as unstable angina—or ST elevation and non-ST elevation myocardial infarction, depending on the degree of luminal occlusion following plaque rupture and intracoronary thrombosis.

Another location for atherosclerotic disease is the cerebrovascular bed. As with coronary atherosclerosis, clinical manifestations of cerebrovascular atherosclerosis vary, depending on the stability of the arterial plaques. Stable disease may lead to chronic symptoms of dementia, whereas unstable atherosclerosis may lead to transient ischemic attacks (sometimes called ministrokes) or a larger stroke with major neurologic sequelae.

Atherosclerotic disease also occurs in the aorta or the peripheral arteries, manifesting as obstructive disease or dilating aneurysms. In addition, atherosclerosis is thought to contribute to valvular heart diseases such as aortic stenosis.\(^2,3\)

MECHANISMS OF ATHEROMA FORMATION
Atherosclerotic disease is thought to progress from microscopic endothelial events, which eventually lead to plaque development, growth, and rupture. Many complex mechanisms appear to contribute to the formation
of atheromatous plaques. The initiating process involves endothelial injury, which may occur as a result of mechanical, biochemical, or immunologic factors. At the cellular level, the process begins with the recruitment of monocytes into the arterial wall through the effect of specific molecules, including the chemoattractants interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α). Selectins and antigens on the leukocyte surface mediate cell attachment and movement. Endothelial cell adhesion molecules (especially vascular cell adhesion molecule 1 and intercellular adhesion molecule 1) interact with leukocyte integrins, causing the monocytes to adhere to the endothelium and subsequently migrate across it. After these cells move into a subendothelial position, monocytes transform into macrophages and begin to secrete many inflammatory cytokines, proteases, and metalloproteinases.

Subsequently, the macrophages both accumulate and oxidize low-density-lipoprotein cholesterol (LDLC), becoming the foam cells that are a characteristic feature of atherosclerotic plaques. C-reactive protein (CRP) appears to stimulate the process of LDLC uptake by macrophages, which may explain why statin treatment of patients with elevated CRP levels appears to be clinically beneficial. Ongoing LDLC deposition and chronic inflammation lead to plaque growth, and hemodynamic mechanisms appear to play an important role as well.

Plaque rupture may occur at any point in the process and can be clinically silent or overt, producing significant clinical events. In an estimated two-thirds of patients with acute coronary syndromes, the inciting event is rupture of a previously stable coronary plaque that had been less than 50% to 70% occlusive. Ruptured plaques have distinctive histopathologic features: a relatively thin fibrous cap that has ruptured with superimposed thrombosis and hemorrhage into the plaque that contains a rich lipid core, macrophages, and other inflammatory cells. Recently, myocardial infarction and stroke in mice were shown to accelerate atherosclerosis progression by a mechanism that liberates hematopoietic stem and progenitor cells from bone marrow niches via sympathetic nervous system signaling. Thus, in animal models, atherogenesis appears to have a positive feedback loop.

**Role of Inflammation in Atherosclerotic Disease**

Although the precise mechanisms of atherogenesis are not completely understood, at the molecular level, atherosclerotic plaques appear to arise from an inflammatory reaction to cardiovascular risk factors. Chronic inflammation underlies the processes of plaque formation and progression, and although the mechanism(s) causing plaque rupture is not completely understood, acute inflammatory processes are likely involved.

On a molecular level, many mediators of inflammation have been identified, and more than 50 have been classified by structure and function. Some of these cytokines or “protein cell regulators” are proinflammatory, including IL-1, IL-12, IL-18, interferon gamma, and TNF-α. Others are anti-inflammatory, including IL-4, IL-10, IL-13, and transforming growth factor-beta.

These inflammatory cytokines stimulate the nuclear factor-kappa-B (NF-κB) pathway in macrophages and endothelium, leading to the increased production of a myriad of proteins, including cellular adhesion molecules, chemokines, growth factors, and nitric oxide synthase. Enhanced activity of the NF-κB pathway appears to correlate with an increased risk of developing atherosclerotic plaques.

**RISK FACTORS FOR CARDIOVASCULAR AND CEREBROVASCULAR DISEASES**

Traditional risk factors for cardiovascular...
disease include dyslipidemia, hypertension, obesity, insulin resistance, diabetes mellitus, tobacco use, and cocaine use. A common denominator among these seemingly varied risk factors is inflammation.

Dyslipidemia
Dyslipidemia appears to contribute directly to atherosclerotic disease, with the risk of cardiac events rising in direct proportion to plasma cholesterol levels, especially cholesterol particles containing apolipoprotein B (including LDL-C). These data are used to establish guidelines for recommending target cholesterol levels. The primacy of cholesterol in initiating atherosclerosis has been shown in many molecular studies, but may be most evident in studies of fetal aortas, in which quantitative and qualitative analyses of fatty streaks have shown that native LDL uptake in the intima precedes LDL oxidation and subsequent endothelial activation and monocyte recruitment. Oxidized LDL appears to increase endothelial expression of cellular adhesion molecules, attracting monocytes and promoting their differentiation into macrophages. LDL also stimulates the release of proinflammatory cytokines from macrophages. Apolipoprotein B particles containing the lipoprotein(a) moiety appear to be particularly atherogenic. In addition, the ratio of apolipoprotein B to apolipoprotein A holds promise in the prognostication of cardiovascular disease across multiple populations.

Hypertension
Systemic hypertension contributes by enhancing monocyte preactivation, increasing production of IL-1 and TNF-α, and raising circulating levels of cellular adhesion molecules. Studies have shown a clear relation between elevated high-sensitivity CRP levels in normotensive patients and the risk of developing incident hypertension, underscoring its inflammatory nature.

Obesity
Obesity with visceral adiposity is another emerging atherosclerotic risk factor. Adipose tissue acts as a metabolically active and dynamic endocrine organ with proinflammatory actions. Adipocytes secrete many inflammatory cytokines, including IL-6 and TNF-α. Although cytokine levels vary in proportion to overall adiposity, visceral adipose tissue appears to contribute to inflammation to a greater degree than does subcutaneous fat. There is an inverse relation between visceral adiposity and plasma levels of the anti-inflammatory adipocyte-derived protein, adiponectin. Lower adiponectin levels correlate with reduced insulin sensitivity and a higher risk of diabetes mellitus, as well as endothelial dysfunction, increased inflammation, and clinically significant atherosclerotic events such as myocardial infarction.

Insulin Resistance
Almost two-thirds of the population in the United States is overweight or obese, and more than one-fourth of the population meets diagnostic criteria for insulin resistance, a multiplex cardiovascular risk factor that arises from the interplay between adiposity and inflammation. Insulin resistance (IR) is defined as a decreased biologic response to normal concentration of serum insulin, which over time leads to compensatory hyperinsulinemia and often presages development of type 2 diabetes mellitus. Although fully manifested diabetes mellitus is a greater risk for cardiovascular disease than isolated IR without hyperglycemia, the presence of IR is a major independent risk factor with relative risk ratios between 2.2 and 2.7 when multifactorial linear regression analysis is used to assess risk.

Diabetes Mellitus
Diabetes mellitus appears to be associated with inflammation, which may explain its
close relation to atherosclerosis. Studies have shown that adipose tissue and macrophages recruited into adipose tissue release cytokines, including IL-1, IL-6, and TNF-α. These cytokines act on (1) the liver to promote dyslipidemia and dysfibrinogenemia, (2) adipose tissue to stimulate leptin secretion, and (3) the pituitary gland to increase secretion of adrenocorticotropic hormone. Moreover, serum levels of various inflammatory markers and mediators (CRP, fibrinogen, IL-6, plasminogen activator inhibitor 1, and serum amyloid A) correlate with the degree of hyperglycemia. Evidence is accruing to suggest that the formation and accumulation of advanced glycation end products (AGEs) may be a pathophysiologic link between diabetes and cardiovascular disease, mediated in part by the receptor for AGEs (RAGE).

RAGE, an immunoglobulin that binds multiple ligands and spurs production of toxic reactive oxygen species, is emerging as a potential therapeutic target for antagonists designed to reduce atherosclerosis and ischemia-reperfusion injury. Another potential therapeutic target that is attracting interest is protein kinase C (PKC) beta, an intracellular signaling molecule that plays a key role in the development of diabetic complications. Experimental PKC inhibitors have been shown to delay or even stop the progression of microvascular complications. One such agent has been submitted for regulatory clearance for the treatment of diabetic retinopathy.

**Cocaine Use**

Cocaine use causes hemodynamic effects as well as significant inflammation and is likely proatherogenic. Studies in mice suggest that cocaine increases the expression of cellular adhesion molecules and promotes greater neutrophil adhesion to the coronary endothelium. In human cells, cocaine exposure appears to increase the expression of gene coding for numerous inflammatory markers, such as IL-1, IL-6, and TNF-α.

**EPIDEMIOLOGY OF HEART DISEASE AND STROKE**

Although the overall death rate from cardiovascular diseases declined by 32.7% between 1999 and 2009, cardiovascular diseases remain the number one cause of mortality in the United States, accounting for 32.3% of all deaths in the United States in 2009. Based on 2004 International Classification of Disease-10 data from the Centers for Disease Control and Prevention, cerebrovascular diseases (including stroke) account for ~1 in every 19 deaths.

The prevalence and suboptimal control of traditional risk factors remain issues for many Americans. Data from the 2005–2006 National Health and Nutrition Examination Survey suggest that 30% or more of adults failed to undergo cholesterol screening in the previous 5 years, and an estimated 31.9 million adults had total cholesterol levels of 240 mg/dL or greater (goal < 200). Similarly, achieving adequate blood pressure control has proved to be challenging. In 2003 and 2004, only 44% of blood pressure recordings in approximately 176 million individuals

**Tobacco Use**

Cigarette smoking contributes to coronary heart disease through at least four pathophysiologic pathways, including induction of a hypercoagulable state through increased plasma levels of factor VII and thromboxane A2, reduction in oxygen delivery as a result of carbon monoxide generation, vasoconstriction of the coronary arteries (which is at least partially mediated by alpha adrenergic stimulation), and direct hemodynamic effects of nicotine. Cigarette use has gradually declined in the United States in the last 40 years, but remains a public health problem with approximately 20% of the population continuing to smoke.
demonstrated readings lower than the goal of 140/90 mm Hg. An estimated 154.7 million US adults are overweight or obese. Among children between ages of 2 and 19, 23.9 million are overweight or obese and 12.7 million meet the criteria for obesity. While smoking rates have declined over the past 40 years in the United States, it was estimated in 2012 that 21.6% of men and 16.5% of women over 18 years of age smoke, and 18% of students between grades 9 through 12 report current cigarette use. Control of cholesterol levels, blood pressure, obesity, and tobacco use are among the greatest clinical challenges and opportunities for prevention of cardiovascular disease.

**TRENDS IN DISEASE PATTERNS IN DEVELOPED AND DEVELOPING WORLDS**

Globally, cardiovascular disease (predominantly heart disease and stroke) is the leading chronic disease, accounting for 17 million deaths. More than one billion individuals meet the medical criteria for being overweight or obese, but the rates of atherosclerotic disease and risk factors vary among countries. Studies have confirmed the consistent impact of established cardiovascular risk factors (hypertension, dyslipidemia, obesity, smoking) on the risk of atherosclerotic disease across multiple populations. The INTERHEART study found that incremental changes in these risk factors, such as a 5 mm Hg elevation of blood pressure or a 10 mg/dL increase in LDL, raise the risk of atherosclerotic disease by a similar amount across people of different nationalities and ethnicities. The central implication is that variations in cardiovascular risk between populations likely reflect differences in total exposure to risk factors rather than biologic differences in sensitivity to these risk factors. When comparing developed with developing worlds, data indicate that low-income countries have the highest burden of high blood pressure and related sequelae, including stroke mortality and morbidity.

**CONCLUSION**

It is clear that more study is needed regarding the development, progression, treatment, and expression of atherosclerotic diseases at all levels—from molecular to global perspectives. Great opportunity remains to reduce the impact of atherosclerosis—a largely preventable disease. Moving forward, international coalitions such as that initiated by the World Heart Federation are likely to play a crucial role in promoting improvements in global cardiovascular health.

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CHAPTER 8
Association Between Periodontal Disease and Atheromatous Diseases

David W. Paquette, Robert J. Genco

INTRODUCTION
Atheromatous diseases constitute a broad set of chronic vascular conditions, including cardiovascular disease (CVD), which encompasses coronary artery disease (CAD), cerebrovascular disease (i.e., stroke), and peripheral arterial disease (PAD). These diseases are major causes of morbidity and mortality in human populations worldwide. For example, in the United States, atherosclerosis affects one in four persons and contributes to 39% of deaths annually.\(^1\) CVD accounts for 29% of deaths worldwide and ranks as the second leading cause of death after infectious and parasitic diseases.\(^2\)

In atherosclerosis, large- to medium-sized muscular arteries and large elastic arteries become occluded with fibrolipid lesions or “atheromas.” End-stage complications or events associated with atherosclerosis include coronary thrombosis, acute myocardial infarction (MI), and cerebral vascular accident or stroke. As presented in the preceding chapter, traditional risk factors related to behaviors, diet, lifestyle, and family history do not appear to fully account for the development of atherosclerosis. Furthermore, despite continued preventive efforts addressing modifiable risk factors, mortality rates from CVD have remained virtually unchanged over the last decade in developed countries.

Role of Inflammation
Currently, clinicians and investigators appreciate that inflammation appears to play a pivotal role in the pathogenesis of atherosclerosis—from the development of the “fatty streak” to plaque rupture. This appreciation has intensified the search for chronic exposures or infections that potentially cause inflammation in vessels. Putative infections that may at least exacerbate atherosclerosis include cytomegalovirus, herpes simplex virus, *Chlamydia pneumoniae*, *Helicobacter pylori*, and periodontal disease.\(^3\) Over the last two decades, observational studies in human populations have consistently shown a modest but significant association between periodontal disease and atheromatous diseases. In addition, animal models chronically exposed to periodontal infective agents have demonstrated more rapid progression of atherosclerosis. Finally, early intervention studies in human subjects suggest that periodontal disease treatment may improve surrogate markers associated with atherosclerosis and CVD. The objective of this chapter is to provide the reader with a strong understanding of the evidence implicating a relation between periodontal disease and atheromatous diseases.

EVIDENCE FROM HUMAN OBSERVATIONAL STUDIES
Patients with periodontal disease share many of the same risk factors as patients with atheromatous diseases, including age, gender (predominantly male), lower socioeconomic status, stress, and smoking.\(^4\) In addition, a large percentage of patients with periodontal disease also exhibit atherosclerosis or CVD.\(^5\) These observations suggest that periodontal disease and atherosclerosis share similar or common etiologic pathways. Several recent systematic reviews of the available evidence support an association between periodontal disease and atheromatous diseases. A 2012 systematic review conducted by the American Heart Association’s Committee on Rheumatic Fever, Endocarditis and
Kawasaki Disease and published in Circulation, concluded that the observational studies to date support a consistent association between periodontal disease and atheromatous diseases independent of known confounders. Although the authors acknowledged that the contribution of periodontal disease to atheromatous diseases is biologically plausible, they cautioned that the cumulative evidence does not currently support a causative relationship. Despite the paucity of definitive evidence on causation, an Editors’ Consensus Report published in the American Journal of Cardiology and the Journal of Periodontology makes recommendations for patient information, medical and dental evaluations, and risk factor treatment for patients with periodontitis who are at risk for atherosclerotic disease.

Meta-Analyses
A number of meta-analyses on the atherosclerosis-periodontal disease association have been conducted in an attempt to pool the available evidence and apply statistical methods to estimate an overall effect and any significance. Meurman and colleagues reported a 20% increase in the risk for CVD among patients with periodontal disease (95% CI: 1.08–1.32) and an even higher risk ratio for cerebrovascular disease or stroke, varying from 2.85 (95% CI: 1.78–4.56) to 1.74 (95% CI: 1.08–2.81). Similarly, Khader and colleagues and Vettore reported relative risk estimates of 1.19 (95% CI: 1.08–1.32) and 1.15 (95% CI: 1.06–1.25), respectively. These meta-analyses of the available observational human data lend credence to the hypothesis that periodontal and atheromatous diseases are associated with one another in various populations.

Case-Control Studies
Case-control studies, which select subjects with the dependent disease and assess exposure (risk), have consistently supported a positive association between periodontal disease and atheromatous diseases (Table 1). Mattila and coworkers first reported that poor oral health (including periodontal disease) was a predictor of MI among a Finnish population of 100 case patients and 102 control subjects. Using a Dental Severity Index score as a measure of periodontal and endodontic infections as well as dental caries, the investigators found that individuals with evidence of oral infections were 30% more likely to present with MI compared with subjects with no oral infections. This association was significant after adjusting for known risk factors such as age, total cholesterol levels, hypertension, body mass index, and cigarette smoking. In a follow-up publication in the same population, these investigators documented a significant and specific association between dental infections and severe coronary atheromatosis in males.

More recently, Arbes and others evaluated available cross-sectional data from the Third National Health and Nutrition Survey (NHANES III). Accordingly, for cases with severe clinical attachment loss and periodontitis, the odds ratio for MI was 3.8 (95% CI: 1.5–9.7) compared with that of periodontally healthy controls. In addition, the probability of a coronary event rose with increasing periodontitis severity. Although the discussed case-control studies do not provide information on the chronicity of exposure and disease, they do indicate that the association has relative strength, is specific, and follows an exposure-response relationship.

Cohort Studies
Longitudinal cohort studies, in contrast, provide a higher level of evidence since they properly document that periodontitis exposure precedes the CVD (Table 2). Beck and colleagues evaluated 1,147 males ages 21 to 80 who were participants in the Normative Aging Study and who were free of CAD at baseline. The periodontal status of this population was
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<td>100 cases</td>
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ABI = ankle-brachial pressure index; CAL = clinical attachment loss; EKG = electrocardiogram; IMT = intima-media wall thickness; MI = myocardial infarction; NHANES = National Health and Nutrition Survey; OR = odds ratio; PAD = peripheral arterial disease; PD = probing depth.
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assessed using the percent alveolar bone loss observed in dental radiographs. Over an 18-year follow-up period, 207 men developed CAD, 59 died from CAD, and 40 experienced strokes. Odds ratios adjusted for age and established cardiovascular risk factors were 1.5 (95% CI: 1.04–2.14), 1.9 (95% CI: 1.10–3.43), and 2.8 (95% CI: 1.45–5.48) for periodontal bone loss and total coronary heart disease, fatal coronary heart disease, and stroke, respectively. When Beck and colleagues graphed the cumulative incidence of coronary heart disease or events versus baseline mean alveolar bone loss, they noted a linear relation such that increasing severities of periodontitis were accompanied by increasing occurrences of CVD (Figure 1).

Another cohort study conducted by DeStefano and colleagues assessed this risk relationship among 9,760 adults followed up for 14 years in NHANES I. Several potentially confounding variables were also examined, including age, gender, race, education, marital status, systolic blood pressure, total cholesterol levels, body mass index, diabetes, physical activity, alcohol consumption, poverty, and cigarette smoking. Accordingly, those with preexisting clinical signs of periodontitis were 25% more likely to develop CAD compared to those with minimal periodontal disease, after adjusting for other known risk factors or confounders. Males younger than 50 with periodontitis in this study were 72% more likely to develop CAD compared with their periodontally healthy counterparts. Similarly, Wu and colleagues evaluated the potential contribution of periodontitis to stroke risk within this same NHANES I population (n = 9,962 adults). The investigators reported that the presence of clinical periodontitis significantly increased the risk for fatal and nonfatal strokes twofold. Increased relative risks (RR) for total and nonhemorrhagic strokes were observed for both genders, whites, and African Americans with periodontitis.

### Table 2. Cont’d Summary of Evidence from Cohort Studies Investigating an Association Between Periodontal and Atheromatous Diseases in Human Populations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Periodontal Outcome or Exposure</th>
<th>Cardiovascular Outcome</th>
<th>Findings and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvarieux et al. 20052</td>
<td>1,056 subjects from INVEST</td>
<td>Subgingival bacterial burden</td>
<td>Carotid artery IMT ≥1mm</td>
<td>Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR=3.64)</td>
</tr>
<tr>
<td>Pussinen et al. 20049</td>
<td>6,950 Finnish subjects in the Mobile Clinic Health Survey</td>
<td>Serum antibodies to <em>P. gingivalis or A. actinomyctemcomitans</em></td>
<td>Incident fatal or nonfatal stroke</td>
<td>Seropositive subjects had an OR of 2.6 for stroke</td>
</tr>
<tr>
<td>Pussinen et al. 200510</td>
<td>1,023 males in the Kuopio Ischemic Heart Disease Study</td>
<td>Serum antibodies to <em>A. actinomyctemcomitans</em></td>
<td>Incident MI or CAD death</td>
<td>Subjects with the highest tertile of <em>A. actinomyctemcomitans</em> antibodies were two times more likely to suffer MI or CAD death (RR=2.0) compared with those with lowest tertile of antibodies levels</td>
</tr>
<tr>
<td>Abnet et al. 200511</td>
<td>29,584 rural Chinese subjects</td>
<td>Tooth loss</td>
<td>Incidence of fatal MI or stroke</td>
<td>Tooth loss was associated with increased odds for death from MI (RR=1.29) and stroke (RR=1.12)</td>
</tr>
</tbody>
</table>

ARIC = Atherosclerosis Risk in Communities; CAD = coronary artery disease; CRP = C-reactive protein; CVD = cardiovascular disease; HPS = Health Professional Follow-up Study; IMI = intima-media wall thickness; INVEST = Oral Infections and Vascular Disease Epidemiology Study; LDL = low density lipoprotein; MI = myocardial infarction; NHANES = National Health and Nutrition Survey; NHS = Nurses Health Study; OR = odds ratio; RR = relative risk; tPA: tissue plasminogen activator.
In contrast, two prominent cohort studies failed to detect any significant association between periodontitis and atheromatous diseases in primary or secondary analyses. Hujoel and cohorts\textsuperscript{17} reexamined data from the NHANES I population over a longer, 21-year follow-up period and reported a nonsignificant hazard ratio of 1.14 (95% CI: 0.96–1.36) for periodontitis and CAD. In addition, Howell and colleagues found no association between self-reported periodontal disease and CVD events for 22,037 participants in the Physicians’ Health Study I.\textsuperscript{18} Accordingly, the relative risk for physicians with self-reported periodontal disease and subsequent CVD events over a mean 12.3 years was 1.13 (95% CI: 0.99–1.28). These studies suffer from their overadjustment of confounders or misclassification of exposures with the long follow-up or with self-reporting methods.

Population Studies
Different findings from several large, worldwide population studies provide supportive and positive evidence for an association. These studies include Atherosclerosis Risk in Communities Study (ARIC), the Health Professional Follow-up Study (HPFS), the Nurses Health Study (NHS), the Oral Infections and Vascular Disease Epidemiology Study (INVEST), and the Western New York MI/Perio Studies conducted in the United States. Other studies have involved populations from Sweden, Finland, and China.

Elter et al.\textsuperscript{19} and Beck and colleagues\textsuperscript{20,21} collected periodontal clinical data on 6,017 persons ages 52 through 75 years, who participated in the ARIC study. The investigators assessed both the presence of clinical CAD (as manifested by MI or revascularization procedure) and subclinical atherosclerosis (carotid artery intima-media wall thickness [IMT] using B-mode ultrasound) as dependent variables in the population. Individuals with both high attachment loss (≥ 10% of sites with attachment loss > 3 mm) and high tooth loss (< 17 remaining teeth) exhibited elevated odds of prevalent CAD compared with individuals with low attachment loss and low tooth loss (OR = 1.5, 95% CI: 1.1–2.0 and OR = 1.8, CI: 1.24–2.4, respectively).\textsuperscript{19}

A second logistic regression analysis indicated a significant association between
severe periodontitis and thickened carotid arteries after adjusting for covariates such as age, gender, diabetes, lipids, hypertension, and smoking (Figure 2). Accordingly, the odds ratio for severe periodontitis (i.e., 30% or more of sites with ≥ 3-mm clinical attachment loss) and subclinical carotid atherosclerosis was 1.31 (95% CI: 1.06–1.66). In a third report, these investigators quantified serum IgG antibody levels specific for 17 periodontal organisms using a whole bacterial checkerboard immunoblotting technique. Analyzing mean carotid IMT (≥ 1 mm) as the outcome and serum antibody levels as exposures for this same population, the investigators noted that the presence of antibody to *Campylobacter rectus* increased the risk for subclinical atherosclerosis twofold (OR = 2.3, 95% CI: 1.83, 2.84). In particular, individuals with both high *C. rectus* and *Peptostreptococcus micros* antibody titers had almost twice the incidence of carotid atherosclerosis than did those with only a high *C. rectus* antibody (8.3% versus 16.3%). Stratification by smoking indicated that all microbial models significant for smokers were also significant for subjects who had never smoked, except for *Porphyromonas gingivalis*. Thus, clinical signs of periodontitis are associated with CAD and subclinical atherosclerosis in the ARIC population, and exposures to specific periodontal pathogens significantly increase the risk for atherosclerosis in smoking and nonsmoking subjects.

Hung and colleagues assessed self-reported periodontal disease outcomes and incident CVD in two extant databases, HPFS (n = 41,407 males followed up for 12 years) and NHS (n = 58,974 females followed up for 6 years). After controlling for important cardiovascular risk factors, males with a low number of reported teeth (≤ 10 at baseline) had a significantly higher risk of CAD (RR = 1.36, 95% CI: 1.11–1.67) compared with males with a high number of teeth (25 or more). For females with the same reported extent of tooth loss, the relative risk for CAD was 1.64 (95% CI: 1.31–
2.05) compared with women with at least 25 teeth. The relative risks for fatal CAD events increased to 1.79 (95% CI: 1.34, 2.40) for males and 1.65 (95% CI: 1.11–2.46) for females with tooth loss, respectively. In a second report, the investigators evaluated the association between self-reported periodontal disease and serum elevations in CVD biomarkers cross-sectionally in a subset of HPFS participants (n = 468 males). Serum biomarkers included C-reactive protein (CRP), fibrinogen, factor VII, tissue plasminogen activator (tPA), low-density lipoprotein cholesterol (LDLC), von Willebrand factor, and soluble tumor necrosis factor receptors 1 and 2. In multivariate regression models controlling for age, cigarette smoking, alcohol intake, physical activity, and aspirin intake, self-reported periodontal disease was associated with significantly higher levels of CRP (30% higher among periodontal cases compared with nonperiodontal cases), tPA (11% higher), and LDLC (11% higher). These analyses reveal significant associations between self-reported number of teeth at baseline and risk of CAD, and between self-reported periodontal disease and serum biomarkers of endothelial dysfunction and dyslipidemia.

The INVEST Study
The INVEST population study was planned a priori and conducted exclusively to evaluate the association between CVD and periodontal outcomes in a cohort population. Engeretson and colleagues reported that for a group of 203 stroke-free subjects (ages 54–94) at baseline, mean carotid plaque thickness (measured with B-mode ultrasound) was significantly greater among dentate subjects with severe periodontal bone loss (≥ 50% measured radiographically) than among those with less bone loss (< 50%). Indeed, the group noted a clear dose-response relation when they graphed subject tertiles of periodontal bone loss versus carotid plaque thickness. The investigators next collected subgingival plaque from 1,056 subjects and tested for the presence of 11 known periodontal bacteria using DNA techniques. The investigators found that cumulative periodontal bacterial burden was significantly related to carotid IMT after adjusting for CVD risk factors. Whereas mean IMT values were similar across burden tertiles for putative and health-associated bacteria, IMT values rose with each tertile of etiologic bacterial burden (Aggregatibacter actinomycetemcomitans, P. gingivalis, Treponema denticola, and Tannerella forsythia; Figure 3). Similarly, white blood cell values (but not serum CRP) increased across these burden tertiles. These data from INVEST provide evidence of a direct relation between periodontal microbiology and subclinical atherosclerosis independent of CRP.

Western New York Population Study
A population-based, case-control study of MI and periodontal disease was conducted in Western New York that included approximately 1,485 subjects ages 35 to 69 years. Cases were survivors of incident MI, and matched controls were randomly selected from residents in the same region. The observed association between periodontal disease and incident MI was consistent across different measurements and/or case definitions of periodontal disease, including attachment loss, pocket depth, alveolar crestal height, and number of missing teeth, respectively. Odds ratios ranged from 2.19 to 1.04, the lowest associated with missing teeth. All associations were statistically significant at the P < 0.05 level. In a second study from the same group, the association between periodontal disease and incident MI was found in both genders, with an odds ratio of 2.08 (95% CI: 1.47–2.94) in women and 1.34 (95% CI: 1.15–1.57) in men. An important finding from this study is that the association between periodontal disease and
incident MI was independent of the possible confounding effects of smoking, since it was found in both cigarette smokers (OR = 1.49, 95% CI: 1.26–1.77) and nonsmokers (OR = 1.40, 95% CI: 1.06–1.86) after adjusting for age, gender, body mass index, physical activity, hypertension, cholesterol, diabetes, and total pack-years of smoking. This is an important finding because there is an active debate among authors suggesting that smoking is a causal confounding factor between periodontal disease and CVD. The positive association of periodontal disease and MI in nonsmokers provides strong evidence that periodontal disease can affect coronary heart disease independent of smoking.

Population Studies in Europe and Asia
Consistent associations between periodontal outcomes and atherosclerosis have been demonstrated among populations in Europe and Asia. For 131 adult Swedes, mean carotid IMT values were significantly higher in subjects with clinical and/or radiographic evidence of periodontal disease compared with values in periodontally healthy controls. Multiple logistic regression analyses identified periodontal disease as a principal independent predictor of carotid atherosclerosis with an odds ratio of 4.64 (95% CI: 1.64–13.10). Pussinen and associates monitored antibody responses for *A. actinomycetemcomitans* and *P. gingivalis* among 6,950 Finnish subjects for whom CVD outcomes over 13 years were available (Mobile Clinic Health Survey). Compared with the subjects who were seronegative for these pathogens, seropositive subjects had an odds ratio of 2.6 (95% CI: 1.0–7.0) for a secondary stroke. In another report on 1,023 males (Kuopio Ischemic Heart Disease Study), Pussinen and colleagues observed that patients with MI or CAD death were more often seropositive for *A. actinomycetemcomitans* than the control subjects who remained healthy (15.5% versus 10.2%). In the highest tertile of *A. actinomycetemcomitans* antibodies, the relative risk for MI or CAD death was 2.0 (95% CI: 1.2–3.3) compared with the lowest tertile. For *P. gingivalis* antibody responses, the relative risk was 2.1 (95% CI: 1.3–3.4).
Abnet and colleagues have published findings from a cohort study of 29,584 healthy, rural Chinese adults monitored for up to 15 years. Tooth loss (evaluated as an exposure outcome for periodontal disease) and mortality from heart disease or stroke were modeled as independent variables. Individuals with greater than the age-specific median number of teeth lost exhibited a significantly increased risk of death from MI (RR = 1.28, 95% CI: 1.17–1.40) and from stroke (RR = 1.12, 95% CI: 1.02–1.23). These elevated risks were present in men and women regardless of smoking status. Collectively, these findings indicate consistent associations for periodontal disease and pathogenic exposures with CVD.

**Observational Studies on Peripheral Artery Disease**

Three recent observational studies have focused on the relation between periodontal disease and PAD. The study population for the first of these reports consisted of 3,585 participants who were 40 or older in NHANES III during 1999 to 2002. PAD was defined as an ankle-brachial pressure index of < 0.9, and the presence of periodontal disease was based on clinical attachment severity scores (i.e., 0%, 1–15%, 16–33%, and more than 33% of sites with clinical attachment loss ≥ 3 mm). Although 4.8% of subjects were recognized as having PAD, multiple logistic regression analyses indicated that periodontal disease was significantly associated with PAD (OR = 2.25, 95% CI: 1.20–4.22) after adjusting for age, gender, race, poverty, traditional risk factors of PAD, and other potential confounding factors. Systemic markers of inflammation (CRP, white blood cell count, fibrinogen) were also associated with clinical attachment loss or periodontitis.

A second case-control study included 25 patients diagnosed with PAD (aortoiliac and/or femoropopliteal occlusive disease) and 32 generally healthy control subjects. Polymerase chain reaction was used to identify *P. gingivalis, T. denticola, A. actinomycetemcomitans, Prevotella intermedia,* Cytomegalovirus (CMV), *Chlamydia pneumoniae,* and *H. pylori* in tissue specimens obtained at the time of bypass grafting. After adjusting for age, gender, diabetes, and smoking, periodontitis increased five-fold the risk of having PAD (OR = 5.45, 95% CI: 1.57–18.89). In addition, periodontopathic bacteria were detected in approximately half of the atherosclerotic specimens. In contrast, CMV or *C. pneumoniae* was detected in only 4% of specimens, and *H. pylori* was detected in none of the specimens.

In the third study involving an Asian Indian cohort, 532 with gingivitis and 282 with periodontitis were assessed for early peripheral vascular changes including pulse wave velocity, arterial stiffness, and ankle-brachial index using computed oscilometry methods. Accordingly, periodontitis patients exhibited significantly higher degrees of peripheral atherosclerosis as measured by brachial pulse wave velocity and the ankle-brachial index. Collectively, these early observational data suggest a higher likelihood of PAD among subjects with periodontal disease and suggest that DNA sequences specific to periodontal pathogens may be present in some PAD lesions.

**BIOLOGIC PLAUSIBILITY AND EVIDENCE FROM ANIMAL MODELS**

Since periodontal infections result in low-grade bacteremias and endotoxemias in affected patients, systemic effects on vascular physiology via these exposures appear biologically plausible. Four specific pathways have been proposed to explain the plausibility of a link between CVD and periodontal infection. These pathways (acting independently or collectively) include (1) direct bacterial effects on platelets; (2) autoimmune responses; (3) invasion and/or uptake of
bacteria in endothelial cells and macrophages; and (4) endocrine-like effects of proinflammatory mediators. In support of the first pathway, two oral bacteria, *P. gingivalis* and *Streptococcus sanguis* express virulence factors called “collagen-like platelet aggregation-associated proteins,” which induce platelet aggregation in vitro and in vivo. Second, autoimmune mechanisms may play a role since antibodies that cross-react with periodontal bacteria and human heat shock proteins have been identified (Figure 4). In one recent study, CVD patients with extensive periodontal pocketing (≥ 4 sites with pocket depth ≥ 4 mm) had not only higher levels of subgingival pathogens such as *P. gingivalis* and *T. forsythia* but also significantly increased antibody responses to heat shock protein 50 relative to those CVD subjects with limited pocketing (≤ 1 site with pocket depth ≥ 4 mm). Third, Deshpande and colleagues have demonstrated that *P. gingivalis* can invade aortic and heart endothelial cells via fimbriae (Figure 5). Several investigative groups have independently identified specific oral pathogens in atheromatous tissues. In addition, macrophages incubated in vitro with *P. gingivalis* and low-density lipoprotein uptake the bacteria intracellularly and transform into foam cells. In the last potential pathway, systemic proinflammatory mediators are upregulated for endocrine-like effects in vascular tissues, and studies consistently demonstrate elevations in CRP and fibrinogen among periodontally diseased subjects (Figure 6).

**Murine Model**

Experiments with animal models demonstrate that specific infections with periodontal pathogens can actually accelerate atherogenesis. For example, inbred heterozygous and homozygous apolipoprotein E (apoE)-deficient mice exhibit increased aortic atherosclerosis when challenged orally or intravenously with invasive strains of *P. gingivalis*. In one of these experiments, Lalla and colleagues randomized 50 male homozygous apoE-null mice to either topical inoculation with *P. gingivalis* (strain 381 orally and anally because of the coprophagia

**Figure 4. Infection-Induced Stimulation of Accelerated Atherosclerosis by Autoimmune Responses or “Molecular Mimicry”**

**Note:** Specific antibodies directed toward bacterial heat shock proteins cross-react with human heat shock proteins, leading to endothelial cell damage, monocyte recruitment, elevated circulating lipids such as oxidized LDL (ox-LDL), and atherogenesis. *Source: J Dent Res 2006;85:106-21.* Reproduced with permission.
**Figure 5.** Invasion of the Vascular Endothelium by Pathogenic Bacteria Resulting in Induction of Local Inflammatory Responses

Note: This includes expression of cell adhesion molecules (CAMs), toll-like receptors (TLRs), chemokines, and cytokines. These events culminate in monocyte recruitment, elevations in oxidized LDL (ox-LDL), and accelerated atherogenesis. Source: *J Dent Res* 2006;85:106-21. Reproduced with permission.

nature of the animals) over 3 weeks or antibiotics plus vehicle (sterile phosphate-buffered saline) on the same schedule. Accordingly, *P. gingivalis*-infected animals displayed evidence of local periodontal infection and marked alveolar bone loss. Infected animals also exhibited serum IgG responses to *P. gingivalis*, elevated serum levels of interleukin 6, and increased aortic expression of vascular cell adhesion molecule 1 and tissue factor. *P. gingivalis* DNA was localized in the aortic tissue from a limited number of infected mice, but not in any noninfected controls. Most important, morphometric analyses revealed a statistically significant 40% increase in mean atherosclerotic lesion
area for \textit{P. gingivalis}-infected animals compared with controls.

In another study involving apoE-deficient mice with spontaneous hyperlipidemia, injections with live or heat-killed \textit{A. actinomyctetemcomitans} or \textit{A. actinomycetemcomitans} lipopolysaccharide accelerated atherosclerosis relative to mice injected with vehicle.\textsuperscript{53} In addition, \textit{A. actinomyctetemcomitans} challenge also promoted mRNA expression of innate immune signaling molecules such as Toll-like receptors and NOD-like receptors while enhancing low-density lipoprotein oxidation, events implicated in atheroma formation.

**Porcine Model**

Similarly, Brodala and colleagues\textsuperscript{54} have demonstrated accelerated atherogenesis in a pig bacteremia model. Accordingly, the investigators allocated pigs (\textit{N} = 36) to either low- or high-fat diets. They sensitized some animals with heat-killed \textit{P. gingivalis} (10\textsuperscript{9} organisms) and then challenged them with live \textit{P. gingivalis} (10\textsuperscript{6}–10\textsuperscript{7} organisms) injected intravenously three times weekly over a 5-month period. Other animals that were sensitized with \textit{P. gingivalis} (no live challenge) or that were treated with saline served as controls. Results indicated that \textit{P. gingivalis}-challenged pigs

\textbf{Figure 6.} Persistent Periodontal Infection May Promote Atherosclerosis via Chronic Upregulation of Inflammatory Cascades

\textit{Note:} These include tumor necrosis factor-alpha (TNF-\textalpha{}), interleukin-1 (IL-1), interferon (IFN), IL-8, monocyte chemo-attractant protein-1 (MCP-1), and C-reactive protein (CRP). \textit{Source: J Dent Res} 2006/85:106–21.\textsuperscript{7} Reproduced with permission.
developed significantly more coronary and aortic atherosclerosis than controls in the low-fat (normcholesterolomic) group and nearly as significant in the high-fat (hypercholesterolemic) group (Figure 7). P. gingivalis was detected by polymerase chain reaction in arteries from most (94%) of the challenged pigs, but not from controls. This finding suggests that P. gingivalis bacteremia may exert an atherogenic stimulus independent of high cholesterol levels in pigs.

Figure 7. Histology of Right Coronary Artery Atherosclerosis from Study Pigs

A: Coronary artery from a P. gingivalis-sensitized and challenged pig (Group 1) fed low-fat diet (immunohistochemical staining); smooth muscle cells comprise the majority of cells in the lesion. B: Higher magnification of rectangle in A. C: Coronary artery from a pig fed a high-fat diet and injected with saline control (Group 6). D: Coronary artery from a P. gingivalis-challenged pig fed a high-fat diet (Group 5). E: Coronary artery from a P. gingivalis-sensitized pig fed low-fat diet (Group 3). AP indicates atherosclerotic plaque; L, lumen. Source: Arterioscler Thromb Vasc Biol 2005;25:1446-51.54 Reproduced with permission.

Summary of Animal Studies
It is worth noting that a wide range of P. gingivalis doses was used in these murine and porcine studies. Even though the clinically relevant dose for human subjects is unknown at present, it probably varies greatly.55-57 The reader should note that P. gingivalis challenges enhanced atherosclerosis despite different routes of administration and dosing regimens in both species. Although P. gingivalis’ 16 ribosomal DNA could be detected in atherosomas from some but not all of the animals, these experiments suggest that both the host response and the virulence of specific P. gingivalis strains appear to be important variables in these infection-atherogenesis models.

EVIDENCE FROM HUMAN INTERVENTION STUDIES
Human evidence demonstrating beneficial effects of periodontal therapy on atheromatous disease outcomes is limited and indirect at present.58 In an initial intervention trial, D’Aiuto and colleagues59 demonstrated that periodontitis patients treated with scaling and root planing exhibited significant serum reductions in the CVD biomarkers, CRP and interleukin 6. In particular, patients who clinically responded to periodontal therapy in terms of pocket depth reductions were four times more likely to exhibit serum decreases in CRP compared with patients with a poor clinical periodontal response.

A recent retrospective cohort study using national health insurance data and
involving over 700,000 Taiwanese subjects investigated whether dental prophylaxis or periodontal treatment was associated with reduced incidence of ischemic stroke. Subjects were first stratified as either periodontitis cases versus non-cases. Periodontitis cases were further divided into a dental prophylaxis group, an intensive periodontal treatment group (subgingival curettage, root planing, flap surgery and/or extraction), and a no-treatment group based on insurance coding. Incident stroke rates were then assessed over a 10-year follow-up period. The incidence of stroke among periodontitis non-cases was 0.32%/year. In contrast, periodontitis cases who received dental prophylaxis had the lowest stroke rate (0.14%/year). Periodontitis patients with intensive treatment or tooth extraction had a higher stroke rate (0.39%/year), and subjects with no treatment had the highest stroke rate (0.48%/year). After adjusting for confounders, the dental prophylaxis group and the intensive treatment case group had significantly lower hazard ratios (HR) for stroke than the non-case group (HR 0.78 and 0.95, 95% CI: 0.75–0.81 and 0.91–0.99, respectively), whereas the no-treatment group had a significantly higher hazard ratio for stroke (HR 1.15, 95% CI: 1.07–1.24), especially among the youngest (20–44) age group (HR 2.17, 95% CI: 1.64–2.87). These retrospective cohort data suggest that preventive and active interventions for periodontal disease are associated with lowered stroke rates at least among Taiwanese subjects.

The PAVE Study
In 2009, Offenbacher and collaborators published results from the Periodontitis and Vascular Events (PAVE) pilot study, which was conducted to investigate the feasibility of a randomized secondary-prevention trial. Accordingly, five clinical centers recruited participants who had documented CAD (≥ 50% blockage of one coronary artery or previous coronary event including MI, coronary artery bypass graft surgery, or coronary transluminal angioplasty 3 to 36 months before enrollment) and who met study criteria for periodontal disease (≥ 3 teeth with probing depths ≥ 4 mm, ≥ 2 teeth with interproximal clinical attachment loss ≥ 2 mm, and ≥ 10% of sites with bleeding on probing). Three-hundred-three eligible participants were enrolled, and all subjects received extractions for hopeless teeth. Thereafter, subjects were randomized to receive either periodontal therapy (intensive treatment group consisting of scaling and root planing at baseline) or community-based dental care (control group). Serum samples obtained at baseline (before randomization) and at 6 months were analyzed for levels of high-sensitivity (hs) CRP. The intensive treatment protocol significantly improved periodontal probing parameters over 6 months, but the treatment did not significantly improve mean serum hsCRP levels in the overall population. In secondary analyses, it was noted that 48% of the community care control group received some form of preventive or periodontal therapy over the 6-month study period (e.g., dental prophylaxis, scaling and root planing, and/or periodontal surgery).

When the investigators stratified for any treatment and obesity, they detected a treatment effect on hsCRP levels clustered among the non-obese subjects (Figure 8). Among non-obese individuals in the community who received no treatment, 43.5% had elevated hsCRP (≥ 3 mg/L) at 6 months. In contrast, 18% of subjects receiving any treatment exhibited elevated hsCRP values. Logistical regression modeling indicated that any treatment among all subjects resulted in a statistically significant reduced odds ratio for high hsCRP (OR = 0.42, 95% CI: 0.18–0.99). The effects were even stronger among the non-obese subjects, with an even lower odds ratio for having high hsCRP at 6 months with any treatment (OR = 0.26, 95% CI: 0.09–0.72).
Figure 8. Percent of Subjects with Elevated Serum High Sensitivity C-Reactive Protein (hsCRP) > 3 mg/L at 6 Months by Treatment Group and Stratified by Obesity for the Periodontitis and Vascular Events (PAVE) Pilot Study

These data suggest that crossover from the control arm may be high within intervention studies and that any periodontal disease treatment effect on hsCRP levels may be exaggerated among non-obese patients.

The data summarized in Figure 8 also suggest that even a dental prophylaxis, which includes supragingival removal of plaque and oral hygiene instruction, has an effect on systemic inflammation. From Figure 8 it can be seen that those in the Community Screening Group receiving prophylaxis who were non-obese had a significant reduction in serum CRP levels ($P = .009$). It is reasonable, therefore, to recommend good oral hygiene practices in cardiovascular patients, including tooth brushing with a toothpaste containing active ingredients that have antigingivitis, as well as antiplaque effects.

Studies of Endothelial Function

At least three other human intervention trials have evaluated the effects of periodontal disease interventions on endothelial function, another surrogate outcome for atherosclerosis. Elter and colleagues treated 22 periodontitis patients with “complete mouth disinfection” (scaling and root planing, periodontal flap surgery, and extraction of hopeless teeth within a 2-week interval) and observed significant improvements in endothelial function (flow-mediated dilation of the brachial artery) and serum biomarkers such as interleukin 6. Similarly, Seinost and colleagues tested endothelial function in 30 patients with severe periodontitis versus 31 periodontally healthy control subjects. Before interventions, flow-mediated dilation was significantly lower in patients with periodontitis than in control subjects. Periodontitis patients with favorable clinical responses to nonsurgical periodontal therapy (i.e., scaling and root planing, topical and peroral antimicrobials plus mechanical retreatment) exhibited concomitant improvements in flow-mediated dilation of the brachial artery and serum hsCRP concentrations.

In a larger third trial, Tonetti and colleagues documented endothelial responses for 120 medically healthy patients with severe periodontitis. Subjects in this trial were randomized to either community-based
periodontal care (control) or intensive periodontal treatment (extraction of hopeless teeth, scaling and root planing, plus locally administered minocycline microspheres). At 24 hours post-treatment, intensive flow-mediated dilation was significantly lower in the intensive treatment group than in the control treatment group (Figure 9), and levels of hsCRP, interleukin 6, E-selectin, and von Willebrand factor were significantly higher. However, by 60 and 180 days, subjects receiving the intensive treatment exhibited significantly improved flow-mediated dilation and improved plasma levels of soluble E-selectin compared with such factors in control subjects.

**Figure 9.** Flow-Mediated Dilation and Nitroglycerin-Mediated Dilation Over 6 Months for Periodontitis Subjects Treated with Intensive Therapy versus Community Controls

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The effects of periodontal therapy on end-stage events in patients with atheromatous diseases have yet to be determined in controlled clinical trials; however, the available evidence suggests that periodontal interventions may be associated with 3- to 6-month improvements in serum inflammatory biomarkers and endothelial function that are predictive of atheromatous diseases.

A recent study has shown that statins, a common treatment for CVD, can affect periodontal disease. The investigators compared high-dose (80 mg) versus low-dose (10 mg) atorvastatin in a randomized controlled trial. They found that periodontal inflammation as assessed by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) was significantly reduced in the high-dose atorvastatin group. Furthermore, they found that changes in periodontal inflammation correlated with changes in carotid inflammation. These data raise the possibility that a portion of the beneficial impact of statins on atherosclerosis relates to reduced inflammation in extracardiac tissues as, for example, the periodontium. This is the first randomized controlled trial to report beneficial effects of cardiovascular treatment on those with periodontitis, and it is further evidence of a close association of the two.

CONCLUSION
Evidence from human observational studies that periodontal disease imparts an increased risk for future atheromatous disease is both strong and consistent. Meanwhile, in vitro and experimental animal models continue to support an interaction between the diseases that is biologically plausible. Although treatments aimed at decreasing periodontal infection can reduce serum inflammatory biomarkers predictive of atheromatous diseases and improve vascular responses, the clinical relevance of these surrogate changes to reduced risk for MI or stroke is not known at this time. Nevertheless, clinicians and patients should be knowledgeable about this consistent association and the potential preventive benefits of periodontal interventions.

Supplemental Readings


REFERENCES


CHAPTER 9
Adverse Pregnancy Effects
Silvana P. Barros, Steven Offenbacher

PREGNANCY COMPLICATIONS: OVERVIEW
Despite much research and healthcare effort, preterm birth (PTB, < 37 weeks’ gestation) remains a major public health problem, and children born preterm have a higher risk of morbidity and mortality. This contributes to over one third of all US infant mortalities and is linked to major, long-term morbidities. Although pregnancy complications are clearly multifactorial in nature and involve a complex molecular and biologic interplay of mother and fetus, many studies suggest that periodontal infections may be potentially one of the causes of adverse pregnancy outcomes. Furthermore, in women who have preterm delivery, direct biologic evidence shows that periodontal organisms are associated with amniotic fluid inflammation, intrauterine fetal exposure, and fetal inflammation.

More recently, epigenetics has been postulated as another mechanism linking the early developmental environment to adult diseases. Differences in fetal DNA methylation are evident in fetuses born preterm versus full term, and altered methylation has been associated with infection status (chorioamnionitis). It has been suggested that patterns established at birth may provide insight into long-term consequences associated with PTB. Thus, since the first publication in 1996 linking infection by periodontal pathogens with pregnancy complications, numerous studies have explored the association. These studies include case-control, longitudinal, and intervention studies in humans as well as models of experimental periodontal infections in pregnant rodents, rabbits, and monkeys. In the last decade, evidence has continued to support the concept that periodontal infections can serve as a distant site of infection, affecting prematurity and fetal growth. Despite the evidence supporting an association and the biologic data suggestive of causality, the evidence supporting the ability of maternal periodontal treatment to prevent prematurity is still equivocal. The association remains strong between the two conditions, but not all treatment studies show significant reduction in preterm deliveries. In other words, the findings suggest that managing periodontal disease in pregnancy is difficult and that treatment to control periodontal disease may not disrupt the biologic basis of oral infection-mediated pregnancy complications.

Some studies suggest that the treatments are ineffective in reducing prematurity, depending on the nature and timing of the treatment provided. These findings suggest that if periodontal disease is a cause of prematurity, it may be a nonmodifiable cause of disease, or at least our treatment protocols are not optimized to yield potential benefits. As we understand the associations between periodontal infection and systemic health and we begin to examine intervention studies, the concept has emerged that the treatments that we use to control oral manifestations of periodontal disease may not be sufficient to control the systemic effects of oral infection. In spite of the tremendous amount of association data gathered from studies around the world, as well as the biologic plausibility and mechanistic incrimination of causality, we have not yet identified how to treat or prevent periodontal infection from having deleterious effects on the fetal-placental unit.

In this chapter, we discuss the evidence linking periodontal diseases to pregnancy
and neonatal development abnormalities. We highlight the animal models data as well as the population studies in humans. Recently published meta-analyses and reviews are cited as background information to focus the discussion on recent trials and the interpretation of findings that bear on clinical practice and healthcare policy. The key learning objectives include the following:

1. To understand the types of obstetric complications that have been associated with periodontal disease.
2. To learn the evidence linking periodontal disease to obstetric complications, as it relates to other risk factors for adverse pregnancy outcomes.
3. To gain insight into the current models of pathogenesis that establish biologic plausibility and the evidence from human and animal models that support these mechanisms, including new findings on the role of epigenetics associated with bacterial infection.
4. To appreciate how this information impacts our thinking regarding the clinical management of the pregnant mother and the potential implications for maternal-child health.
5. To underscore the importance of oral hygiene and periodontal health in women prior to conception to increase the likelihood of healthy birth outcomes, given our current inability to mitigate adverse outcomes during pregnancy.

ASSOCIATION OF PREGNANCY WITH PERIODONTAL DISEASE

Epidemiologic and longitudinal studies have clearly shown that pregnancy is associated with an increase in gingival inflammation and a worsening of periodontal status. Periodontal diseases, including gingivitis and periodontitis, affect approximately three out of four pregnant women. This increased susceptibility during pregnancy is thought to be attributable to changes in gingival tissue structure, the nature and quality of the host response, and alterations in the oral biofilm composition. Pregnancy provides a special opportunity for the emergence of the biofilm pathogens. Increases in serum progesterone serve to increase the gingival crevicular fluid flow rate, altering conditions within the subgingival sulcus and leading to increased levels of Porphyromonas species. Moreover, an overgrowth of the Socransky red and orange complexes contributes to an increased prevalence of gingivitis and severity of periodontal disease during pregnancy.

The gingival tissues themselves are affected by the hormonal increases that lead to increased synthesis of hyaluronic acid and to glycosaminoglycan aggregates, which osmotically induce tissue edema and gingival enlargement. These changes lead to greater clinical inflammation. The typical inflammatory appearance demonstrating the changes in gingival tissue architecture has been well described and emphasizes that neovascularization within the gingival tissues increases during pregnancy, since the gingival changes almost mirror those of the uterus during this hormonal barrage. Finally, the maternal immune response changes during pregnancy and can be best characterized as a relative state of immunotolerance (discussed further in the text that follows), which serves to protect the fetus from host-versus-graft immunorejection. Thus, alterations in the maternal immune response likely contribute to the increase in gingival inflammation that occurs during pregnancy.

TYPES OF OBSTETRIC ADVERSE EVENTS ASSOCIATED WITH PERIODONTAL DISEASE

Maternal infections have long been recognized as increasing risk for pregnancy complications such as PTB, fetal growth restriction, preeclampsia, fetal loss (spontaneous
abortions and fetal demise), and stillbirth. Although these obstetric complications differ in clinical presentation and outcomes, there are similarities in terms of pathogenesis, reflecting common inflammatory effector pathways that result in disease. Oral infection in the mother appears to be one potential stimulus for this inflammatory effector mechanism, but it is not the only cause. Rather, oral infection appears to be just one factor triggering inflammatory events that result in a variety of obstetric complications. Furthermore, there is not sufficient evidence to suggest that the effects of periodontal infection are limited to one particular obstetric complication. Thus, the lack of specificity is likely attributable to a commonality of pathologic signals or to the presence of an unknown, underlying inflammatory trait that places the mother at risk for both periodontal disease and obstetric complications.

It is possible that mothers with obstetric complications have a genetic trait that creates an abnormal hyperinflammatory response that can result in pregnancy complications and can simultaneously be associated with more severe periodontal disease. Indeed, obstetric complications exhibit familial aggregation, suggesting a genetic component. However, such hyperinflammatory traits may create the genomic structure that enables infectious agents to disseminate and cause pathology of the fetal–placental unit. An underlying inflammatory factor that places a mother at risk for both conditions would create the possibility of oral infections—or any other infection—to increase the risk of obstetric complications. Thus, the importance of oral infection is even more relevant to obstetric risk in the presence of a hyperinflammatory trait. One might consider that the presence of a genetic predisposition might diminish the importance of oral infection as a mitigating factor in abnormal pregnancy outcomes, but in fact it increases the relevance of oral infection in the management of maternal–child health outcomes, since the effects of oral infection would be exaggerated in a person with this trait. More specifically, preeclampsia has been conceptually characterized as a hyperinflammatory state, which is linked to the fact that more than 30% of the leukocytic cells in the placental decidual layer in normal pregnancy are macrophages. Macrophages in the placental tissue are important cytokine producers and may be “pivotal regulatory cells” for controlling trophoblast cell invasion in the maternal vascular system. Macrophages may have cytolytic effects, presumably by the production of cytotoxic cytokines, and hyperactivation may be linked to placentaion defects and pregnancy complications.

In the following text, we discuss prematurity and fetal growth obstetric complications and summarize the evidence linking these obstetric outcomes to periodontal disease. The condition of preeclampsia is different in clinical presentation and pathogenesis and is discussed separately. The data linking periodontal disease to fetal demise and stillbirth are limited and are included under both human and animal discussions.

**PRETERM BIRTH AND FETAL GROWTH RESTRICTION**

In the United States, preterm birth (PTB), defined as birth of an infant born before 37 weeks of completed gestation or before 259 days of gestational age, is occurring at an increasing rate in the population, with a rise of 13% for the period of 1981–1989 and 16% for 1990–2002. Furthermore, in 2004, low birth weight (LBW; < 2,500 g) affected 8.1% of live births, an increase from 7.6% in 1998. Although weight at birth and gestational age are highly correlated, in many countries the determination of gestational age by date of last menstrual period and
ultrasound are not routinely performed; therefore, LBW becomes a worldwide reporting standard. The increased rate of prematurity is due to three factors: our inability to identify all causal risk factors, our inability to adequately control known risk factors, and our improved ability to support survival of the smallest and most premature babies. As a result, the incidence of PTB and LBW deliveries has actually increased in most industrialized nations.\(^7\)\(^9\) With prematurity remaining the leading cause of perinatal morbidity and mortality worldwide and with widespread recognition that inflammation is responsible for a substantial percentage of PTBs,\(^10\)\(^12\) maternal periodontal disease has gained prominence as a potentially modifiable risk factor for adverse pregnancy outcomes.

Systemic dissemination of oral pathogens with subsequent maternal, fetal, and/or placental inflammatory responses has been associated with pregnancy complications.\(^13\)\(^14\) Furthermore, periodontal disease and the systemic bacteremias caused by periodontal pathogens are significant contributors to a systemic maternal inflammatory response during pregnancy, which involves cytokinemia and the release of acute-phase proteins by the liver, such as C-reactive protein (CRP). Inflammation in turn can serve as an independent biochemical threat to the fetal-placental unit by inducing labor, rupture of membranes, and early parturition. These inflammatory processes can extend to the developing fetus to also threaten the health of the neonate, an effect that may persist into childhood and even into adulthood by early intrauterine exposures that permanently affect neurologic and metabolic systems. Most of these concepts have been demonstrated in animal models and reflected in human data.\(^15\)\(^17\)

Normal term deliveries occur at 40 weeks; PTB is defined by delivery at less than 37 weeks’ gestation. Very PTB means birth at less than 32 weeks of completed gestation. The risk of serious postnatal complications, disability, and mortality increases significantly at earlier gestational ages. In Figure 1, representative statistics from the state of North Carolina demonstrate the national trend. About 50% of the preterm deliveries occur near-term between 35 and 37 weeks of gestation, and the rate of morbidity and mortality in this group is relatively low, compared with earlier gestations. One can see (Figure 1) that the rate of mortality increases rather steeply at earlier gestations, with about 16% mortality at 32 weeks.

Understanding the potential causes of prematurity is important because it is the leading cause of death in the first month—up to 70% of all perinatal deaths.\(^18\) Even late premature infants, those born between 34 and 37 weeks, have a greater risk of feeding difficulties, thermal instability, respiratory distress syndrome, jaundice, and delayed brain development.\(^13\) Prematurity is responsible for almost 50% of all neurologic complications in newborns and leads to lifelong complications in health that include but are not limited to visual problems, developmental delays, gross and fine motor delays, deafness, and poor coping skills. The increase in morbidity among survivors also increases markedly at an earlier gestational age.

In many ways, the fetus physiologically functions as a foreign body with parasitic properties. The placenta is an invasive fetal-derived tissue and is efficient in its ability to take nutrients from the mother. If the mother is nutritionally deprived, the mother’s reservoirs are depleted first. All the placental nutrient exchange molecules have higher binding affinities than those of the mother to favor a unidirectional nutrient and vitamin exchange from mother to fetus. For example, if the mother is starving, the maternal liver shrinks to one third of its normal size during pregnancy and the fetus continues to grow. Thus, any impairment in fetal
growth is believed to be attributable to impairments in nutrient exchange or impaired growth factor secretion via placental damage rather than to maternal-based nutrient impairments. Prematurity, on the other hand, is due to maternal responses that involve uterine smooth muscle contraction and rupture of the membranes. This is a maternal tissue response triggered by an inflammatory biochemical cascade. Infection can be one important source of inflammation, but fetal stress can be another source of inflammation that targets the maternal uterine smooth muscle and/or the membrane integrity. Either or both can be involved in pregnancy complications.

About one third of preterm delivery occurs as a consequence of preterm premature rupture of membranes (PPROM), one third as a consequence of preterm labor, and one third everything else, including preeclampsia and medical and fetal indications for delivery. Inflammation can extend beyond the maternal membranes and uterus to promote prematurity but can also reach the placenta and fetus to impair growth and damage fetal tissues. Impaired growth or growth restriction can occur at any gestational age, even full-term babies can be small for gestational age (SGA, typically defined as birth weight lower than the tenth percentile of weight for gestational age). Many of the molecular and cellular inflammatory effector pathways that underlie the pathogenesis of PTB are also involved in growth restriction and developmental problems ranging from

Figure 1. Percent Infant Death Rate and Births by Gestational Age
respiratory distress to cognitive and learning disabilities. For example, fetal neurologic tissues are especially susceptible to damage through cytokines, such as interferon gamma (IFN-γ), which induce apoptosis and impair development of synapse connections among embryologic neurons.19

Although advances in technology help to save infants who are born premature or LBW, the lifelong problems associated with these conditions have not declined.

Potential risks to a baby born with fetal growth restriction include the following:

• Increased risk for motor and neurologic disabilities
• Chromosomal abnormality
• Hypoglycemia
• Increased risk for hypoxia
• Decreased oxygen levels

Selected neonatal complications after PTB include the following:

• Chronic lung disease
• Developmental delay
• Growth impairment
• Periventricular leukomalacia
• Respiratory distress syndrome
• Hearing impairment
• Intraventricular hemorrhage

ASSOCIATION OF PRETERM BIRTH AND FETAL GROWTH RESTRICTION WITH PERIODONTAL DISEASE

The human data supporting an association between maternal periodontal disease and PTB have been recently reviewed by Ide and Papapanou.20 In this systematic review, the high degree of heterogeneity of the study populations, as well as differences in methodology, are highlighted. The authors found 18 publications suitable for qualitative analysis, including five case-control, three cross-sectional, and 10 prospective studies. This systematic review revealed a positive, independent association between maternal periodontitis and PTB and LBW emerging from cross-sectional and case-control studies with a more attenuated association demonstrated by the prospective studies. However, the optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes is still a subject for future investigation.21

Thus, the consensus of the available data support the concept that maternal periodontal disease is associated with prematurity. The specifics of maternal infection have been studied in a few publications, and some trends appear. First, antenatal maternal disease status or periodontal progression during pregnancy is most strongly associated with earlier deliveries. That is, periodontal infection as an exposure appears to confer greater risk to the pregnancy early in gestation, as illustrated in Figure 2. As the exposure occurs closer to term, the risk diminishes, but remains statistically significant at greater than 1.0. For example, the hazards ratio of delivery at 32 weeks of gestational age for moderate to severe periodontal disease is about 3.7, but less than 2.0 by 35 weeks (see Figure 2). A similar relation can be seen with bacterial vaginosis, a vaginal infection that increases risk of prematurity. Thus, as the fetal–placental unit nears delivery, it appears less susceptible to infectious and inflammatory challenge.

Another more direct assessment that periodontal pathogens may translocate to the fetal–placental unit derives from data generated by other laboratory techniques such as polymerase chain reaction (PCR) and immunochemistry. Specifically, León and colleagues22 found that from the nine bacteria tested only Porphyromonas gingivalis seemed to invade the amniotic cavity, since it was detected in the amniotic fluid of women with threatened preterm labor. P. gingivalis and Actinobacillus actinomycetemcomitans have also been found in the placentas of women with PTB or preeclampsia.23-25 Moreover, in a case of PTB the oral species Bergeyella was identified in the amniotic fluid.26 Fusobacterium nucleatum is also one
of the most common isolates from the amniotic fluid of patients with preterm low birth weight and intact membranes, but has also been detected in the chorionic tissues of high-risk pregnant women. Finally, *P. gingivalis, F. nucleatum,* and *Capnocytophaga* have been found in neonatal gastric aspirates obtained from complicated pregnancies, indicating a possible bacterial translocation to fetal organs.

Note that periodontal pathogens have also been detected in the amniotic/fetal-placental tissues of women with normal pregnancies. Moreover, studies have shown that it is possible to isolate bacteria considered as periodontal pathogens from periodontally healthy subjects. On this basis, it is unknown (1) what factors determine whether the translocation of these pathogens to the fetal-placental unit will contribute to pregnancy complications and (2) whether the clinical parameters of periodontal disease are always good indicators of the risk for pregnancy complications. This point is best illustrated by a secondary analysis of the Oral Conditions and Pregnancy (OCAP) study, which tries to examine the role of these various maternal-fetal compartments simultaneously.

Figures 3 through 5 represent secondary analyses of previously published findings that are reorganized to reflect the adverse outcome based on the timeline of pregnancy complication, that is, gestational age deliveries of less than 37 weeks, less than 35 weeks, and less than 32 weeks. We include as potential exposure variables all the available maternal clinical findings:

- Antenatal status: periodontal health, mild and moderate/severe disease
- Incident disease: progression during pregnancy
- Microbiologic status: (subgingival counts of orange complex organisms antena-
tally (red and other complexes not significant)

- Antenatal maternal antibody (maternal IgG to oral complex organisms)
- Fetal exposure, as indexed by fetal cord blood IgM seropositivity to oral organisms at delivery (red plus orange)
- Traditional maternal risk factors such as age, first pregnancy, and smoking

By including all these variables in a single model, our original OCAP sample size of 1,020 decreases to 439 for this analysis, largely because of the lack of cord blood data for measuring fetal exposure, bacterial counts, and serum antibody levels. Nonetheless, we have statistically significant logistic models for each adverse outcome, and it is informative to appreciate how these different exposures relate to the gestational age at delivery. The data are displayed using receiver operator curves (ROC) showing the area under the curve for each exposure variable, which reflects the magnitude of the effect and the area for the overall model. In these three models, we include all variables and highlight those in red that are statistically significant (i.e., 95% Wald confidence limits do not include 0.5).

In Figure 3, the association with preterm delivery, as defined by gestational age of less than 37 weeks indicates that there are three variables significantly associated with preterm delivery. In decreasing order of effect, they are race, progression of periodontal disease, and severity (moderate/severe) of periodontal disease. It is significant that incident disease (increase of pocket depth by more than 2 mm with a pocket depth of at least 4 mm at postpartum in more than four sites) is the most important periodontal predictor of gestational age if less than 37 weeks. This includes even periodontally healthy mothers who developed incident periodontal disease during pregnancy. Mild periodontal disease had no effect on the rate of prematurity, nor did any microbial or antibody markers. However, the overall area under the curve (AUC) for this model is only 0.65, so the effects of periodontal disease parameters are statistically significant, but are weak predictors. For this reason, measuring only maternal periodontal status antenatally without measuring periodontal progression might easily result in null findings of association with PTB.

Figure 4 illustrates the model for gestational age of less than 35 weeks, which is associated with much greater neonatal mor-
bidity. Approximately 50% of all preterm deliveries occur between 35 and 37 weeks’ gestation, but most of the newborns have lower morbidity or mortality than those at gestational age of less than 35 weeks, whereas those at gestational age of less than 32 have the highest morbidity and mortality rates. For gestational age of less than 35 weeks, again race is the major explanatory variable. However, the antenatal periodontal status is no longer significant in the model, only progression is. Furthermore, the maternal microbial load (orange complex) and the interaction with maternal serum IgG levels to the orange complex are both significant contributors. There is a significant interaction term here between the maternal antenatal IgG to orange complex and the level of the organisms in the plaque. The risk occurs when the maternal serum levels are low and the microbe levels are high. This suggests a lack of protective antibody. Recently, Singer and colleagues linked high oxidative stress to poor IgG response to the commensal biofilm in a community-based study. This is interesting in the context of the reports of high oxidative stress as a risk factor for abnormal pregnancy outcomes and the potential protective role of the maternal antibody response. Most important, in Figure 5 fetal exposure now occurs in this model. This is consistent with the previous discussions of periodontal progression with high bacterial load in the absence of protective maternal antibody leading to increased fetal challenge and adverse outcomes.

In Figure 5, we are examining the highest risk outcome group for those deliveries at less than 32 weeks. In this model only three variables are predictive—race (non-Caucasians = African Americans and Hispanics), periodontal disease progression, and fetal exposure. Other variables contribute to the overall model as the overall AUC is 0.935. Thus, for this highest risk group and earliest event, maternal progression and fetal exposure are the most important oral components of risk.

Although the key periodontal pathogens possess specific virulence factors that enable them to colonize, evade host defenses, and invade host tissues, in the case that periodontal pathogens reach, while alive, the fetal–placental unit, it is unclear whether they will remain in a planktonic form or will develop a biofilm, as in the case of dental plaque.32
Figure 5. Secondary Analysis of Highest Risk Outcome Group (> 32 Weeks’ Gestation)

Recently, the presence of a particulate matter in the amniotic fluid, recognized as “amniotic fluid sludge,” was associated with the presence of bacteria and intra-amniotic inflammation. Electron microscopy provided evidence that this sludge was indeed a biofilm. Whether several different periodontal pathogens are necessary to translocate to the fetal–placental unit and form a biofilm or whether periodontal pathogens could colonize a biofilm formed by other extraoral bacteria remains a mystery.33

Since evidence indicates that periodontal pathogens, dead or alive, may reach the fetal–placental unit, the question arises as to the origin of these pathogens. The current paradigm indicates that most intrauterine infections originate in the lower genital tract, with the infectious agents ascending into the otherwise sterile womb. Usually, the amniotic membranes and the placenta are the first to be infected, followed by the fetus via the blood vessels of the umbilical cord or the aspiration of the infected amniotic fluid.10 Hence, it is reasonable to suggest that periodontal pathogens may enter the amniotic space as a result of ascending infection following oral–genital transfer. However, because not all women who experience pregnancy complications have genital infections and because periodontal pathogens and/or their byproducts may enter the blood circulation, these pathogens very likely may translocate to the fetal–placental unit by hematogenous spread. It is possible that disease progression may potentially facilitate dissemination. It is interesting that Campylobacter rectus is associated with the clinical sign of bleeding on probing and has been implicated as a key fetal pathogen.34 To date, two studies in humans provide evidence of this route of infection. In one case, the same clonal type of uncultivated oral Bergeyella was identified in the subgingival plaque and the amniotic fluid of a woman with PTB, whereas no Bergeyella cells were detected in the mother’s vaginal tract.26 In the second case, oral F. nucleatum was identified as the cause of a term stillbirth and was isolated from the lung and stomach of the infant. The same clonal type of F. nucleatum was present in the subgingival plaque of the mother, but not in her vaginal or rectal microflora.35
Besides periodontal pathogens, the adverse effects on pregnancy could be mediated by the release of major components of the bacterial cell wall (i.e., lipopolysaccharides [LPS] or other virulence factors). LPS in the systemic circulation can bind either to serum proteins or to LPS-binding proteins and reach the maternal–fetal interface. As described later, local host cells may interact with these byproducts and produce inflammatory cytokines (tumor necrosis factor alpha [TNF-α], interleukin 1 [IL-1], and IL-6) and mediators (prostaglandin E2 [PGE2]). Since, during pregnancy, the innate proinflammatory immune response is strictly regulated within the uterus to prevent immunologic rejection of the fetal allograft, this local increase in proinflammatory mediators may disrupt this delicate balance and elicit an inflammatory burden that may contribute to preterm rupture of the membranes and uterine contraction, which may, in turn, lead to miscarriage or preterm delivery.

Patients with periodontitis also experience an increase in the production of proinflammatory cytokines and mediators from periodontal tissues. Once released, they may diffuse in the gingival crevicular fluid or enter the blood circulation and reach the placenta–fetus interface. IL-1, IL-6, and TNF-α could stimulate the production of prostaglandins in the chorion and, in conjunction with the maternally derived PGE2 generated at the gingival level and released in the circulation, may exacerbate cervical ripening and uterine contraction, leading to an increased risk for PTB. However, although elevated serum and amniotic fluid levels of these cytokines and mediators have been associated with various adverse pregnancy outcomes, evidence is limited and mostly negative that the elevation of these mediators in either the gingival crevicular fluid, the serum, or the amniotic fluid are associated with pregnancy complications in periodontitis patients. Proinflammatory cytokines released in the maternal circulation along with the transient bacteremia from periodontal tissues may also induce a low-grade systemic inflammation by stimulating the production by the liver of acute-phase reactants such as CRP and fibrinogen. Elevated levels of plasma CRP could amplify the inflammatory response at the fetal–placental interface through complement activation, tissue damage, and induction of proinflammatory cytokines. Thus, CRP has been associated not only with periodontal disease, but also with pregnancy complications such as PTB, intrauterine growth restriction (IUGR), preeclampsia, and gestational diabetes mellitus.44-47

Although pregnant women with moderate to severe periodontal disease have elevated levels of serum CRP, to date, only a few studies have evaluated the association between pregnancy complications and CRP levels in patients with periodontitis. Thus, several reports indicate that elevated CRP levels in pregnant women with periodontitis appear to mediate PTB and preeclampsia, whereas others found no such association. Perhaps periodontal disease and CRP share a common risk factor predisposing certain persons to a hyperinflammatory response.

Other, less common, adverse pregnancy outcomes (e.g., diabetes, small-for-gestational-age birth weight, miscarriage) may also be associated with maternal periodontal infection. Infants who are small for gestational age (less than the 10th percentile for birth weight) have significantly higher neonatal mortality rates when compared with appropriate- and large-for-gestational-age infants.4

PREECLAMPSIA

Risk Factors and Complications

Preeclampsia is a pregnancy complication recognized by new-onset gestational hypertension and proteinuria. It is considered one of the most significant health problems in
human pregnancy, and it complicates 8% to 10% of all pregnancies. The disorder affects both mothers and their infants with considerable fetal mortality and morbidity owing to the effects of the disease on the fetus as well as to prematurity. The induced delivery in women, to prevent the progression of preeclampsia, is responsible for 15% of all PTBs.\textsuperscript{53} In the last two decades, appreciation that preeclampsia is a multisystem syndrome characterized by vasoconstriction, metabolic changes, endothelial dysfunction, activation of the coagulation cascade, and increased inflammatory response has redirected research. Intravascular inflammation and endothelial cell dysfunction, with altered placental vascular development, is believed to be central to the pathogenesis of preeclampsia.\textsuperscript{54} Cardiovascular, central nervous, renal, respiratory, hepatic and coagulation systems are affected to variable extents, increasing maternal blood pressure with proteinuria during pregnancy. Risk factors for preeclampsia include obesity, diabetes, and inflammation.\textsuperscript{55}

Women with preeclampsia are three to four times more likely to deliver a small-for-gestational-age infant than are women without preeclampsia. Conservatively estimated, 20,000 PTBs at less than 34 weeks occur annually in the United States as a result of complications of preeclampsia. Potential mechanisms associated with preeclampsia include direct local effects of infectious agents on endothelium (on vascular smooth muscle cells and/or on macrophages within the atherosclerotic lesion) or amplification of the systemic inflammatory response.\textsuperscript{56} There are epidemiologic data supporting the premise that chronic infection could link preeclampsia to later atherosclerosis, especially given the increased susceptibility to chronic infection due to reduced cell-mediated immunity in pregnancy (helper T cell type I [Th1]), which is the outcome of the trophoblastic activity in the placenta protecting the fetus from maternal immune attack by reducing cell-mediated immunity.\textsuperscript{57} Fetal cells contribute to the process by producing immunosuppressive cytokines, chemokines, and prostaglandins that dampen T-lymphocyte proliferation and export high levels of immune suppressive hormones such as progesterone. Case reports have linked gastrointestinal, urinary, and lower genital tract infections to the development of preeclampsia.\textsuperscript{58}

Maternal clinical periodontal disease at delivery has been associated with an increased risk of preeclampsia, independent of the effects of maternal age, race, smoking, gestational age at delivery, and insurance status. In addition, clinically active disease, as measured by periodontal disease progression, was also associated with an increased risk of preeclampsia.\textsuperscript{59}

**Association of Preeclampsia with Periodontal Disease**

Bogges and colleagues\textsuperscript{59} were the first investigators to report an association between maternal clinical periodontal infection and the development of preeclampsia. In a longitudinal study of over 1,000 women, the presence of periodontal infection at delivery, or disease worsening during the course of pregnancy, was associated with a twofold increased risk for preeclampsia compared with that of women without periodontal infection or progression. Since that report, several other investigators have demonstrated an association between maternal periodontal infection and preeclampsia. Canakci and colleagues\textsuperscript{58} reported that women with preeclampsia were three times more likely to have periodontal infection than healthy normotensive women and that periodontal disease also affects the severity of preeclampsia. In another case-control study, Barak and associates\textsuperscript{24} also found that women with preeclampsia had more severe periodontal disease compared with healthy controls, with
significant elevation in gingival crevicular fluid levels of PGE$_2$, IL-1, and TNF-α. In another study, women with preeclampsia were found to have worse periodontal infection compared with healthy women. In addition, two “red complex” microorganisms, *P. gingivalis* and *Tannerella forsythensis*, were more prevalent in the oral plaque among preeclamptic women compared with controls. All these studies raise the question as to whether periodontal treatment may be a potential preventive intervention therapy for preeclampsia through periodontal infection control.

**ASSOCIATION OF PERIODONTAL DISEASE AND ADVERSE PREGNANCY EVENTS**

**Human Studies**

Several studies suggest a significant association between maternal periodontal disease and pregnancy complications such as premature delivery and preeclampsia. $^{24,60}$

Since the first reported case-control study in humans, published in 1996 and showing that mothers with premature, LBW babies have more severe periodontal disease independent of other traditional obstetric risk factors, many other studies have explored the potential association between maternal periodontal disease and prematurity and LBW. These studies have been generally, but not universally, supportive of an association.

Moderate to severe periodontal disease (defined as 15 or more sites with 5 or more mm of probing depth) is highly prevalent among pregnant women, with about 15% affected during the first trimester and overall about 25% showing worsening periodontal progression during pregnancy. $^{14,32,62}$ Both antenatal periodontal disease and progression during pregnancy appear to confer risk for preterm delivery, and the strength of the association increases at earlier gestational deliveries. Periodontal disease is twice as prevalent among African Americans; it has been suggested that this difference in prevalence may partly explain the observed increased risk in preterm delivery and fetal growth restriction among African Americans. $^{23}$ Studies exploring the connection between maternal infection with specific periodontal pathogenic organisms and periodontal disease progression in relation to fetal immune response to oral pathogens have generally supported the notion that periodontitis is independently associated with PTB and LBW.

In 2001, Madianos and colleagues $^{32}$ analyzing clinical data from the first 812 deliveries from OCAP, a cohort study of pregnant mothers, demonstrated that both antepartum maternal periodontal disease and incidence/progression of periodontal disease are associated with PTB and growth restriction after adjusting for traditional obstetric risk factors. The high prevalence of elevated fetal IgM to *C. rectus* among premature infants raised the possibility that this specific maternal oral pathogen contributed as a primary fetal infectious agent eliciting prematurity.

With the objective to determine whether oral bacteria can be found in the amniotic cavity, Bearfield and associates $^{62}$ collected samples, including dental plaque and amniotic fluid from 48 women attending for elective cesarean section delivery. Data analysis indicated that *Streptococcus* spp. and *F. nucleatum* in the amniotic fluid may have an oral origin. Han and colleagues $^{36}$ have also demonstrated that the exact same maternal clonal type of oral organism can be isolated from the amniotic fluid in cases of PTB.

More recently, Lin and colleagues $^{63}$ exploring the underlying microbial and antibody responses associated with bacterial complexes most often linked with periodontitis, conventionally termed “orange” and “red” microbial clusters, have found that high levels of periodontal pathogens and low maternal IgG antibody response to peri-
odontal bacteria during pregnancy are associated with an increased risk for preterm delivery, with higher levels of periodontal pathogens measured antepartum in the preterm deliveries compared with the term deliveries. Overall, the data from meta-analyses that combine data from several studies continue to demonstrate a significant association between periodontal disease severity and abnormal pregnancy outcomes.

**Animal Studies**

The studies that tried to evaluate the biologic mechanisms behind the possible association between periodontal disease and adverse pregnancy outcomes used hamsters, mice, and rabbits. Several experimental models have been used to simulate in a simplified and reproducible manner a periodontal infection in these pregnant animals. Thus, periodontal bacteria or their pathogenic products (LPS) have been injected in the blood circulation mimicking bacteremia. In other experiments, a metal chamber/cylinder was placed subcutaneously and periodontal bacteria were injected in the chamber creating a distant site of infection. Because of the open ends of the chamber, bacteria and/or their released byproducts could leave the chamber and enter the systemic circulation, mimicking a periodontal infection that takes place at a distance from the fetal-placental interface.

The first experiments occurred in golden hamsters. When *P. gingivalis* LPS was injected intravenously before and during pregnancy, there was an increase in fetal malformation, IUGR, and resorptions. The frequency and severity of these adverse pregnancy outcomes were dose-dependent and similar to those occurring after IV injection with *E. coli* LPS.64 This was the first proof of principle experiment to suggest a possible association of periodontal disease with adverse pregnancy outcomes. Specifically, it demonstrated that when periopathogenic byproducts enter the systemic circulation, they may induce pregnancy complications. Similar results occurred when various periodontal microorganisms were injected into the pregnant animals. Hence, in the chamber model, *P. gingivalis* has been shown to induce IUGR and elevated numbers of resorptions in golden hamsters. Note that the severity of these complications depended on the extent of the inflammatory response in the chamber as evaluated by the increased levels of TNF-α and PGE₂.64 IUGR, and increased resorptions (analogous to miscarriages) have also been demonstrated after intrachamber injection of *P. gingivalis* or *C. rectus* in mice.65-67 It is worth noting that besides oral *C. rectus*, other *Campylobacter* species have been shown to be implicated in the induction of pregnancy complications, especially in abortions of sheep and cattle.68 Moreover, in humans, *C. fetus*, *C. jejuni*, and *C. coli* have been associated with abortion, PTB, and perinatal sepsis, whereas in mice intravenous injection of these campylobacters results in IUGR, impaired fetal development, and increase in resorptions.69,70 Finally, IV injection of *F. nucleatum* in mice resulted in premature delivery, stillbirths, and nonsustained live births.71

Since, in these animal models, infection with periodontal pathogens/byproducts could cause pregnancy complications, investigators tried to elucidate whether these microorganisms disseminate systemically and translocate to the fetal-placental unit. In the chamber model in mice, *C. rectus* DNA was found in the maternal liver and placenta of infected dams.66 Similarly, *P. gingivalis* DNA was detected in maternal liver, uterus, and placenta of the IUGR fetuses. Furthermore, infected dams with IUGR fetuses presented with elevated levels of serum TNF-α and *P. gingivalis*-specific IgG antibodies and reduced levels of IL-10.65 However, IV infection of mice with *F. nucleatum* was restricted inside the uterus, without spreading systemically. In studies by Arce and colleagues,72 C.
rectus was able to effectively invade human trophoblasts (BeWo) in culture but not murine trophoblasts (SM9-1) and showed a trend for more invasiveness than C. jejuni. C. rectus challenge significantly upregulated both mRNA and protein levels of IL-6 and TNF-α in a dose-dependent manner in human trophoblasts, but did not increase cytokine expression in murine cells, suggesting a correlation between invasion and cytokine activation.

Both the chamber and the IV infection models indicate that periodontal pathogens may translocate to the fetal-placental compartment; however, there is a controversy concerning the activation of the systemic inflammatory/immune response and the dissemination of pathogens to other maternal organs. It has been suggested that the chamber model represents a chronic infection, since P. gingivalis is repeatedly inoculated systemically through the chamber, whereas the IV infection more closely resembles an acute infection that mimics predominantly bacteremia. In the case of the acute infection, bacterial translocation is organ-specific (i.e., only in the placenta), and this is likely due to the immune suppression in the placenta, which allows the bacteria to proliferate freely, whereas the bacteria are killed by the immune cells in the liver.3 Periodontitis is usually a chronic infection in which transient bacteremias occur; hence, both models may coexist and explain the somewhat diverse results in systemic inflammation elicited by pregnant women. In addition, both models support the hematogenous dissemination of the periodontal pathogens without however, excluding the possibility of an ascending infection from the lower genital tract that may also occur in humans.

It is also clear that both models present with a serious limitation, since they simulate more a mono-infection rather than an infection organized in biofilms, in which the presence and collaboration of different types of microorganisms are necessary. Recent reports by Arce and colleagues74 indicate that oral infection with the human periodontal pathogens C. rectus and P. gingivalis is able to induce fetal growth restriction and placental inflammation and enhance Toll-like receptors 4 (TLR4) expression in a murine pregnancy model. Pregnant mice were sacrificed at embryonic day (E) 16.5, and placenta were collected and analyzed for TLR4 mRNA levels and qualitative protein expression by real-time PCR and immunofluorescence. TLR4 mRNA expression was found to be increased in the C. rectus-infected group (1.98 +/- 0.886-fold difference, P < .01, ANOVA) compared with controls. Microscopic analysis of murine placentas showed enhanced immunofluorescence of TLR4 in trophoblasts, mainly in the placental labyrinth layer. Also, combined oral infection with C. rectus and P. gingivalis significantly reduced the overall fecundity compared with controls (16.7% vs 75%, infected vs noninfected mice, respectively, P = .03, Kaplan-Meier). The results supported an enhanced placental TLR4 expression after oral infection with periodontal pathogens, consistent with the known TLR4 activation in human placental inflammation and preterm pathogenesis.

Periodontal pathogens and/or their byproducts may not need to be part of biofilms to have a deleterious effect on pregnancy. In a recent study, a diverse group of oral bacteria were found to translocate to the mouse placenta following IV injection with pooled human saliva or subgingival plaque from the deep pockets of periodontitis patients. Many of these bacteria have been associated with pregnancy complications in humans, and the majority of them are oral commensal organisms.75 This is consistent with studies in humans in whom the fetus may be exposed to various periodontal pathogens.32 Also, it demonstrates the possibility that these pathogens may organize in
biofilms, as indicated by the recent finding of bacterial biofilms formed in the amniotic fluid from complicated pregnancies in humans.33 The tropism of oral organisms to the nutrient-rich fetal–placental unit may be analogous to the concept of anachoresis first described by Ascoli in the early 1900s, which describes the fact that organisms disseminate systemically to seek out nutrient-rich environments, such as those associated with inflammation.

In mice, the pattern of fetal–placental interface infection by *F. nucleatum* parallels that in humans. First, *F. nucleatum* is detected in placental blood vessels. Maybe because of the slow blood flow in the venous sinuses, the bacteria have the opportunity to invade the endothelial cells lining the vessels, cross the endothelium, proliferate in the surrounding tissues, and finally spread to the amniotic fluid.71 These data suggest that bacteria can survive in the oxygen-rich blood circulation and reach the placenta. Moreover, they demonstrate that invasion may be an important virulence mechanism for placental infection. In fact, it has been shown, that FadA adhesin of *F. nucleatum* plays a critical role in this process.69 IV injection of *P. gingivalis* into pregnant rats also caused strain-dependent colonization in the placenta, whereas *C. rectus* is able to invade human trophoblast cells in vitro.72,77 Placental colonization by all three bacteria has been associated with intrauterine infections in humans, but perhaps other invasive periodontal pathogens may have similar properties as well.33,32

Colonization of periodontal pathogens in the placenta results in the induction of local inflammatory responses. Specifically, in IUGR placenta infected with *P. gingivalis* there is an increase in IL-2 and IFN-γ, whereas IL-10 is reduced, indicating a shift in Th1/Th2 cytokine balance. IL-6 and TNF-α are also elevated after stimulation of human decidual cells with *F. nucleatum*, *A. actinomyctemcomitans* and *P. gingivalis*. This is consistent with intrauterine infections in humans that lead to adverse pregnancy outcomes.78 In murine placenta, inflammatory responses induced by *F. nucleatum* and *C. rectus* seem to be mediated via TLR-4.74,79

Histologically, this inflammatory response is accompanied by an increase in the inflammatory infiltrate, predominantly by neutrophils, in the decidua, whereas *F. nucleatum* also stimulates decidual necrosis.79 It is interesting that *C. rectus* infection induces major alterations in the structure of the placenta as indicated by the decrease in the size of the labyrinth.67 The labyrinth is the area of the placenta in which the exchange of nutrients and waste between mother and fetus takes place. Hence, its diminished volume may imply insufficient nutrition of the fetus and consequently impaired growth and LBW. Furthermore, structural damage in the placenta may disrupt the normal blood flow between fetus and mother, affecting the maternal blood pressure and leading to preeclampsia.

Using mRNA expression microarray technology, *C. rectus* infection in mice has been demonstrated to attenuate the expression of genes related to placental and fetal growth, such as platelet-derived growth factor (PDGF) which is the main placental angiogenic factor, and insulin-like growth factor-2 (IGF-2).80 The question that arose is whether infection reduced the size of the labyrinth that led to a decreased expression of these genes or whether infection induced the attenuation in gene expression that resulted in impaired placental development. The question was partially answered by the examination of the expression of the murine *IGF-2* gene. This gene belongs to the group of “imprinted genes” whose expression is dictated mainly by the methylation status of their promoter. *C. rectus* infection induced hypermethylation of the promoter of *IGF-2*, which was associated with the attenuation of
its expression.\textsuperscript{81} Since these epigenetic changes are inherited in somatic cells, infection of the fetus could alter the expression of imprinted genes and possibly affect the offspring throughout life.

Finally, \textit{C. rectus} infection elevated the rates of neonatal mortality in mice. In the surviving pups, \textit{C. rectus} was detected in the brain and induced a local inflammatory response, which was accompanied by an increase in apoptosis and defects in nerve myelination.\textsuperscript{67} Similarly, human neonates exposed to both \textit{C. rectus} and \textit{P. gingivalis} are found to be twice as likely to be admitted to the neonatal intensive care unit (NICU), whereas preterm infants have an increased risk in developing neurodevelopmental, behavioral, and learning problems.\textsuperscript{82}

Early studies in animal models using oral organisms as a challenge in the 1980s demonstrated a dose response that is related to obstetric outcomes. At low microbial challenges, there is a mild systemic inflammatory response, which is associated with transient increases in circulating cytokines, like TNF-\(\alpha\) and increases in activation of the hepatic acute-phase response as evidenced, for example, in mice by increases in serum amyloid A (SAA). In rodents, the major acute-phase reactant is SAA, compared with CRP in humans. Not only is there a mild systemic inflammatory response at low levels of challenge, there is also mild inflammation of maternal amniotic membranes, increase of inflammatory mediators within the amniotic fluid, and uterine smooth muscle irritability. The membranes and the uterus are maternal tissues that become inflamed at low levels of microbial challenge. In humans, this inflammation would be associated with earlier rupture of membranes and uterine contraction leading to preterm delivery. However, there are no animal models of preterm delivery. For example, in rodents there are changes in inflammatory mediators and histologic evidence of inflammation, but only primates and humans have preterm deliveries. At moderate dosages of bacterial challenge, there are enhanced maternal membrane and uterine inflammatory changes compared with those seen at lower dosages, but now there are also exposures that reach the fetal tissues, beginning with the placenta. Placental inflammation is associated with alterations in placental architecture that cause the incomplete development of the labyrinth zone of the placenta. This is the portion of the placenta that exchanges nutrients from the maternal side to the fetal side, and its incomplete development is associated with impaired fetal growth. In rodents, one can see a clear linkage between placental exposure of the organisms and fetal outcomes. For example, a pregnant mouse would typically have seven to eight fetal pups, each with their own placenta and membranes. A maternal challenge of \(10^7\) colony-forming units (CFU)/mL of \textit{P. gingivalis} during pregnancy, as an example, would cause three of the eight fetuses to have impaired growth, and these would be runted. Analysis of placentas from all eight fetuses shows that when \textit{P. gingivalis} is found within the placenta, the fetus is runted, whereas \textit{P. gingivalis}-negative placentas would have normal-sized fetuses. Increasing the concentration to \(3\times10^7\), one sees three normal fetuses, four runts, and two that have been resorbed (fetus is nonviable). At even higher bacterial concentrations, there are more resorptions and more runts, with some runts having congenital anomalies. Thus, the higher the dose of microbial challenge, the more severe the effect on fetal development and the possibility of birth defects among survivors. This suggests that many of these infection-mediated complications appear as part of a continuum beginning with prematurity to very preterm to growth restriction to fetal loss and anomalies. Thus, when considering the human condition, the level and the timing of the exposure likely have a
major influence on the type of obstetric complication observed.

Early work with pregnant rodent models exploring the role of maternal periodontitis as a potential maternal–fetal stressor demonstrated that low-grade challenges with oral organisms during pregnancy resulted in impaired fetal growth that was demonstrated using a chronic subcutaneous infection model and challenge with *P. gingivalis*. Later, using the same distant chronic infection model in mice and challenging with *P. gingivalis* and *C. rectus*, it was also demonstrated that low-grade infections with oral organisms were associated with dissemination to the fetal unit. These studies have shown the ability of the oral organisms to translocate hematogenously to the placental tissues and cause growth restriction. The importance of placental dissemination was convincingly demonstrated when it was shown that those placentas that harbored oral organisms had growth-restricted fetuses, whereas placentas from normal-sized littermates from the same mother had noninfected placentas. Thus, once at the site of the placenta, *P. gingivalis* has been shown to modulate both fetal growth and the local Th1/Th2 immune response. Evidence from pregnant murine infection models indicates that maternal challenge with *P. gingivalis* that resulted in growth restriction was also associated with increases in maternal TNF-α and a suppression of IL-10 within the serum. This was accompanied by an increase in placental mRNA expression of IFN-γ and IL-2 as well as a decrease in IL-10, IL-4 and TGF-α. Thus, *P. gingivalis* challenge was associated with an overall increase in the placental Th1/Th2 ratio, consistent with the observed shifts seen in human growth restriction.

In rodents and humans, there is no blood-brain barrier early in gestation, and organisms that cross the placenta can also reach the brain. In rodent models, a distant maternal challenge with *C. rectus* resulted in *C. rectus* infecting the fetal brain. This brain tropism is analogous to that seen during a maternal syphilis infection in humans. In the rodent, this challenge was associated with increasing fetal brain levels of TNF-α mRNA and attendant growth restriction. This was accompanied by alterations in neurodevelopment with altered myelination and white matter damage in the hippocampus.

In 2007, Bobetsis and colleagues reported that, in addition to the inflammatory placental response triggered by maternal infections, there were also structural abnormalities in placental development with impaired formation of the placental labyrinth zone. This zone is the point of maternal–fetal vascular anastomoses that regulate nutrient and oxygen exchange and is rich in spongiosotrophoblasts, which secrete growth factors such as IGF that stimulate fetal growth and development. In humans, impairment of placental IGF-2 expression is associated with intrauterine growth restriction. Therefore, we examined whether the alterations in placental structure seen in our pregnant mouse infection model were related to IGF-2 suppression in murine IUGR. Not only did Bobetsis and collaborators demonstrate that IUGR was associated with low IGF-2 placental expression, but that this suppression was due to alterations in the placental chromatin structure. This alteration in chromatin structure specifically involved altered DNA methylation of the IGF-2 promoter, which is termed an epigenetic modification, since it does not involve a sequence change but does result in a change in gene expression, which can persist even following gene replication. These investigators reported that the bacterial infection induced epigenetic modification of placental tissues represented by hypermethylation of the *IGF-2* gene, with consequent downregulation of this gene, which plays a critical role in fetal growth and development programming.
With these findings, investigators proposed a new mechanism linking an environmental infectious and inflammatory insult to now include epigenetic modifications. Epigenetic modifications carry important consequences for development, since they can be permanently retained in the genome. These potentially permanent alterations may in part explain the poor prognosis of the infant born small for gestational age (SGA), because the modifications that occur in utero due to alterations in methylation patterns may persist for the entire life of the offspring. This was proposed as a new hypothesis underlying the linkages found between preterm delivery and diseases of the offspring that account for a wide spectrum of adult-onset diseases that include neurologic impairments and adult-onset conditions, such as diabetes and cardiovascular disease.556 This concept raises the possibility that intrauterine exposure to oral organisms of maternal origin may have more permanent effects that extend beyond the prenatal period.

INTERVENTION TRIALS

Early clinical trials that have provided periodontal treatments with scaling and root planing have shown promise for preventing PTB. A landmark study by Lopez and collaborators87 suggested that periodontal treatment may reduce the rate of preterm deliveries fivefold. However, many additional clinical trials are still in progress. The data are encouraging, but not conclusive. A recent meta-analysis conducted by Polyzos and colleagues88 summarized the available data from seven randomized trials and reported that overall treatment reduced prematurity. The overall reported odds ratio was 0.48; 95% CI, 0.23-1.00; \( P = .049 \). Thus, there is marked consistency between the two meta-analyses in that periodontal disease increases the risk 2.8-fold and treatment potentially decreases the risk twofold. Furthermore, the treatment provided does not appear to increase the rate of adverse events, suggesting that periodontal treatment during pregnancy may be safe. Nonetheless, one large multicentered study conducted by Michalowicz and colleagues89 that was included in this treatment meta-analysis failed to show any obstetric benefits, suggesting that additional treatment studies need to be conducted to better understand the potential risks and benefits of periodontal care. Also, Offenbacher and colleagues89 reported data from a multicenter, randomized, controlled clinical trial investigating pregnant women with periodontal disease who received periodontal therapy and standard obstetric care to reduce obstetric risk; the results indicated that periodontal therapy during pregnancy did not alter the rates of PTB, or fetal growth restriction. However, it was also reported that the progression of periodontal disease could not be controlled by the treatment rendered between baseline and delivery in 40.7% of the treatment group, and only a small proportion of the women treated for periodontal disease achieved what would be considered periodontal health.

Thus, it remains to be proven whether periodontal disease is a reversible cause of PTB or pregnancy complications. Furthermore, the linkage with neonatal health and the recent discovery of intrauterine epigenetic influences raise important questions for future studies to determine the impact of maternal infection on the health of the baby from birth through adulthood.

FUTURE STUDIES

Clearly, additional research is needed to understand the effects of periodontal treatment on pregnancy outcomes. Many clinicians and scientists continue to debate when the findings from association studies and treatment studies enable us to infer causality. Some suggest that the Bradford Hill criteria of causality (strength, consistency, specificity,
temporality, biologic gradient, biologic plausibility) need to be applied before we consider public health consequences. However, not all causes of disease are modifiable. For example, bacterial vaginosis is generally believed to be a cause of prematurity, and yet most intervention trial studies fail to show any benefits of treatment. This suggests that the treatments either confer additional risk unto themselves or fail to modify the components of the vaginal infection that confer risk. Note that maternal periodontal health is in itself an extremely important outcome regardless of the potential influence on pregnancy. Thus, as long as periodontal care can be provided safely, it is difficult to imagine a downside to improving maternal oral health. Ideally, prevention would be the public health measure of choice. Additional studies to understand the biologic processes that underlie the association between maternal periodontal disease and pregnancy complications, as well as the effects of treatments will provide insight into pathogenesis. In other words we need to understand the cellular and molecular events that underlie the association between periodontal progression and fetal exposure and how treatments—successful or not—modify these biologic components. For example, Lin and colleagues reported that although periodontal treatments reduced the risk of PTB, among treated mothers who experienced prematurity, there was a significant persistence of high levels of oral P. gingivalis infection. This suggested that the treatment provided did not adequately control infection in all mothers and was therefore insufficient to improve obstetric outcomes.

The need for more research is highlighted by the fact that research has been focused, primarily, on few selected oral pathogens, whereas it is known that periodontal pockets may harbor more than 700 microbial species and each one may have various strains with virulence factors of different potencies. Furthermore, the emphasis has been artificially placed on periodontal disease and the importance of clinical signs and responses to treatment rather than on understanding the role of these commensal organisms in pregnancy. Hence, how all these organisms interact with each other or act separately to induce pregnancy complications is still far from understood. In addition, the host’s susceptibility with regard to its ability to control the infection and whether an underlying genetic predisposition due to a hyperinflammatory trait places women at risk for both periodontal disease and pregnancy complications remain important missing pieces of the puzzle.

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CHAPTER 10
Oral Health and Diseases of the Respiratory Tract

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INTRODUCTION
Because the surfaces of the oral cavity are contiguous with those of the trachea and lower airway, pathogenic bacteria that colonize the oral cavity can be aspirated into the lower airway to cause infection. These bacteria can be exogenous pathogens, which are not normal members of the oral flora, or endogenous, opportunistic commensal organisms. In addition, oral inflammation, for example in the form of periodontal disease, results in release of biologically active inflammatory mediators and hydrolytic enzymes into the oral fluids, which may also be aspirated into the airway to incite inflammation and increase susceptibility to infection. Recent evidence suggests that oral bacteria and oral inflammation are associated with respiratory diseases and conditions with significant morbidity and mortality. Furthermore, some respiratory illnesses (such as asthma) may have an effect on orofacial morphology or even on the dentition. This chapter discusses several important respiratory diseases that may be influenced by the oral microflora or oral inflammation. Much of the material presented has been previously reviewed and discussed.1-5

PNEUMONIA
Pneumonia is an infection of the lungs caused by bacteria, mycoplasma, viruses, fungi, or parasites. Bacterial pneumonia is a common and significant cause of mortality and morbidity in human populations. Pneumonia, together with influenza, is an important cause of death throughout the world. Pneumonia also contributes to morbidity and decline in quality of life as well as in increased medical care costs. Formerly, bacterial pneumonia was categorized into several subtypes: community-acquired pneumonia, aspiration pneumonia, hospital-acquired (nosocomial) pneumonia, ventilator-associated pneumonia, and nursing home-associated pneumonia. In all cases, connections have been made with oral health status. However, in 2005, a new category was created called healthcare-associated pneumonia or HCAP. HCAP was defined as pneumonia occurring in a diverse group of patients, including those undergoing home infusion therapy or wound care or chronic dialysis, recently hospitalized patients, or nursing home residents. The common denominator for this diverse group was the supposed high risk for pneumonia caused by multidrug-resistant organisms such as methicillin-resistant Staphylococcus aureus or resistant gram-negative bacilli. As a result, treatment guidelines for HCAP include broad-spectrum antibiotic therapy. Since the publication of the ATS/IDSA (American Thoracic Society/Infection Diseases Society of America) guideline describing HCAP, there has been considerable concern that this group is too diverse, and nursing home-associated pneumonia (NHAP) is clearly the most important infection in this category. The authors also note that although NHAP tends to be associated with a higher mortality rate than community-acquired pneumonia, recent studies have found that the prevalence of multidrug-resistant organisms as an etiologic agent in this group is low. Therefore, in this chapter NHAP is reviewed as a distinct entity rather than being grouped together as part of HCAP. In addition, an increasing number of studies have evaluated methods for improving oral hygiene in
nursing home residents as a method of reducing rates of pneumonia.

**Community-Acquired Pneumonia**

Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality. Bacterial pneumonia is often preceded by viral infection or *Mycoplasma pneumoniae* infections, which diminish the cough reflex, interrupt mucociliary clearance, and enhance pathogenic bacterial adherence to the respiratory mucosa to foster the chain of events that may eventually lead to CAP.\(^8\)

The major etiologic agents of CAP are viruses, such as respiratory syncytial virus and rhinovirus. Bacterial causes of CAP include group B streptococci or gram-negative enteric bacteria early in life, as well as *Streptococcus pneumoniae*. *S. pneumoniae* and *Haemophilus influenzae* are often the cause of CAP in adults.

**Epidemiology**

About 4 million CAP cases occur in the United States each year.\(^9\) Most of these patients are treated outside the hospital. For example, a recent large, population-based cohort study of 46,237 seniors aged 65 and older were observed over a 3-year period.\(^10\) The overall rate of CAP ranged from 18.2 cases per 1,000 person-years among persons aged 65 to 69 years to 52.3 cases per 1,000 person-years among those 85 and older. In this population, 59.3% of all pneumonia episodes were treated on an outpatient basis. Overall, CAP results in more than 600,000 hospitalizations, 64 million days of restricted activity, and 45,000 deaths annually.

**Risk Factors**

Risk factors for CAP are age, male gender, chronic obstructive pulmonary disease, asthma, diabetes mellitus, congestive heart failure, and smoking.\(^10\) In a study of 1,336 patients with CAP and 1,326 controls for risk factors,\(^11\) multivariate analysis found cig-
arette smoking, usual contact with children, sudden changes of temperature at work, inhalation therapy (particularly containing steroids), oxygen therapy, asthma, and chronic bronchitis all to be independent risk factors for CAP. It is interesting to note that a visit to a dentist in the previous month was an independent protective factor for CAP, presumably by encouraging improvements in oral hygiene, which can limit colonization by respiratory pathogens. A recent case-control study assessed the association between periodontal infections and CAP in a group of patients admitted to a hospital.\(^12\) A total of 140 patients were enrolled, with 70 patients having CAP (case group) and the other 70 patients being diagnosed with other systemic diseases (control group). Chronic periodontitis was more common in patients with CAP (case: 61.4%; control: 41.4%), and the presence of moderate or severe chronic periodontitis increased the risk for CAP over fourfold, even after adjusted for age, ethnicity, gender, and smoking.

**Symptoms and Diagnosis**

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigors, and pleuritic chest pain.\(^9\) Depending on the pathogen, a patient’s cough may be persistent and dry, or it may produce sputum. Other presentations may include headache and myalgia. Certain bacteria, such as *Legionella*, may induce gastrointestinal symptoms.

Chest radiography is a critical tool for the diagnosis of pneumonia. A typical positive chest radiograph shows consolidation within the lung lobe, or a more diffuse infiltration.\(^9\) However, chest radiography performed early in the course of the disease may be found to be negative.

A worrisome recent development is the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections, including CAP.\(^13\) Although it is still a rare infection, it has been found in one
study that the median age of MRSA patients, four of whom died, was 21 years, and usually a short interval occurred between the development of respiratory symptoms and the detection of disease.\textsuperscript{13}

**Treatment**
Antibiotics are the cornerstone of treatment for CAP. Guidelines for the treatment of CAP were originally published in 1993 and have been revised several times. The most recent guideline was published in 2007 by the American Thoracic Society in collaboration with the Infectious Diseases Society of America.\textsuperscript{14} The reader is referred to this guideline for specific treatment recommendations.

The focus for CAP is typically on short-term outcomes; however, it is becoming more apparent that sometimes there are long-term negative consequences of CAP, particularly in the elderly.\textsuperscript{15} For example, a large study of the Medicare database used a matched case-control design to evaluate 1-year mortality rate of 158,960 older CAP patients compared with that of 794,333 control subjects hospitalized for reasons other than CAP.\textsuperscript{16} The 1-year mortality rate for CAP patients exceeded that of control subjects (40.9\% vs 29.1\%, respectively); the differences could not be explained by the types of underlying diseases. These findings suggest that the consequences of CAP in the elderly are important to long-term survival and thus should be prevented.\textsuperscript{15}

**Aspiration Pneumonia**
Aspiration pneumonia is an infectious process caused by the inhalation of oropharyngeal secretions colonized by pathogenic bacteria.\textsuperscript{17} Aspiration pneumonia is differentiated from aspiration pneumonitis, which is typically caused by chemical injury after inhalation of sterile gastric contents. Aspiration pneumonia is often caused by anaerobic organisms derived from the oral cavity (gingival crevice), and often develops in patients with an elevated risk of aspiration of oral contents into the lung, such as those with dysphagia or depressed consciousness, and is very common in the nursing home setting. Aspiration pneumonia may also occur in the community.

Most adults inhale small amounts of oropharyngeal secretions during sleep. However, the small number and typically avirulent nature of the commensal microflora, as well as defense mechanisms such as coughing, ciliary action, and normal immune mechanisms all work together to prevent onset of infection. However, circumstances that increase the volume of aspirate, especially the number of organisms in the aspirate, increase the risk of pneumonia. The risk of aspiration pneumonia is lower in patients without teeth as well as in patients who receive aggressive oral care\textsuperscript{18} (explained in further detail below). However, little information is available regarding the effect of periodontal therapy in the prevention of aspiration pneumonia in vulnerable populations.

**Nosocomial Pneumonia (Hospital-Acquired Pneumonia)**
Hospital-acquired pneumonia (HAP), defined as pneumonia occurring with onset over 48 hours after admission to the hospital, is a common infection in the hospital, often causing considerable morbidity and mortality, as well as extending the length of stay and increasing the cost of hospital care. HAP can be further divided into two subtypes: ventilator-associated pneumonia (VAP) and nonventilator-associated pneumonia. Pneumonia is the most common infection in the intensive care unit (ICU) setting, accounting for 10\% of infections in the ICU.\textsuperscript{19}

VAP is the second most common hospital-acquired infection.\textsuperscript{20,21} It is a leading cause of death in critically ill patients in the ICU, with estimated prevalence rates of 10\% to 65\% and mortality rates of 25\% to 60\%, depending on the study, patient populations,
and medical/surgical conditions involved.\textsuperscript{19,22-27} VAP and other forms of HAP are independent risk factors for mortality in hospitalized patients regardless of the severity and type of underlying illness.\textsuperscript{26} An episode of HAP adds approximately 5 to 6 days to the length of hospital stay and thousands of dollars in cost to medical care.\textsuperscript{22-27} Patients with VAP typically have a significantly longer stay in the ICU, with a longer ventilation dependency.\textsuperscript{29} The onset of pneumonia can easily double the length of the patient’s hospital stay, and the cost of VAP treatment has been estimated to average as high as $40,000 per patient.\textsuperscript{30,31}

**Nursing Home-Associated Pneumonia**

NHAP is the most important common infection affecting nursing home residents because of the high morbidity and mortality associated with this infection.\textsuperscript{32} Pneumonia is also a common reason for transfer of residents from a nursing home to a hospital.\textsuperscript{33} Incidence of NHAP in a published series has varied from 0.3 to 2.5 episodes per 1000 resident care days.\textsuperscript{34} Independent predictors of NHAP that have been identified in multiple studies include poor functional status, use of a nasogastric tube or feeding tube, chronic lung disease, tracheostomy, increasing age, male gender, and inadequate oral care.\textsuperscript{34}

The importance of oral hygiene as a risk factor for NHAP was particularly emphasized in a study by Quagliarello et al.,\textsuperscript{35} who found that among 613 residents in five nursing homes in New Haven, Connecticut, followed up prospectively for radiologically confirmed pneumonia, only inadequate oral care and dysphagia were independently associated with pneumonia. A more recent study from this group described a prospective observational cohort study of 3,075 well-functioning community-dwelling adults aged 70 to 79 enrolled in the Health, Aging, and Body Composition Study from 1997 to 1998, with 1,441 subjects having complete data.\textsuperscript{36} The investigators found that the incident mobility limitation and higher mean dental plaque score were the only modifiable risk factors for pneumonia. Another study found that in 89 cases of 138 (64.5%), the dental plaques of dependent elderly were colonized by potential respiratory pathogens.\textsuperscript{37} Therefore, dental plaque must be considered a specific reservoir of colonization and subsequent aspiration pneumonia in dependent elderly.

**The Oral Cavity as a Reservoir of Respiratory Infection**

The oral cavity may be an important source of bacteria that cause infections of the lungs. Dental plaque, a tooth-borne biofilm that initiates periodontal disease and dental caries, may host bacterial species as part of the normal flora that are capable of causing respiratory infection or may become colonized by exogenous respiratory pathogens. Oral pathogens may then be shed from the oral biofilm and released into the oral secretions, which then are aspirated into the respiratory tract.

**Mechanics Causing Pulmonary Infection**

Bacteria causing community-acquired pneumonia are typically species that normally colonize the oropharynx such as *S. pneumoniae*, *H. influenzae*, and *M. pneumo*niae. Nosocomial pneumonia is, in contrast, often caused by bacteria that are not common members of the oropharyngeal flora such as *Pseudomonas aeruginosa*, *S. aureus*, and enteric gram-negative bacteria. These organisms colonize the oral cavity in certain settings, for example, among institutionalized subjects and people living in areas served by unsanitary water supplies. Respiratory pathogens, such as *S. aureus*, *P. aeruginosa*, and *Escherichia coli*, are found in substantial numbers on the teeth in both institutionalized elders\textsuperscript{38} and intensive care patients.\textsuperscript{39}
One cubic millimeter of dental plaque contains about 100 million bacteria and may serve as a persistent reservoir for potential pathogens, both oral and respiratory bacteria. Oral and respiratory bacteria in the dental plaque are likely shed into the saliva and then aspirated into the lower respiratory tract and lungs to cause infection. Indeed, the commensal, or normal, microflora of the oral cavity, especially periodontal disease-associated anaerobic bacteria that reside in the subgingival space, often cause aspiration pneumonia in patients who have a high risk for aspiration, such as those with dysphagia or neurologic impairment affecting the swallowing apparatus.

Cytokines and enzymes induced from the periodontally inflamed tissues by the oral biofilm may also be aspirated into the lungs where they may stimulate local inflammatory processes preceding colonization of pathogens and the actual lung infection. Other possible mechanisms that may explain pulmonary infection are inhalation of airborne pathogens and translocation of bacteria from local infections via bacteremia.

**Patients at Risk**

In a healthy subject, the respiratory tract is able to defend itself against aspirated bacteria. However, patients with diminished salivary flow, decreased cough reflex, swallowing disorders, poor ability to perform good oral hygiene, or other physical disabilities have a high risk for pulmonary infections. Mechanically ventilated patients in an ICU with no ability to clear oral secretions by swallowing or coughing, have a particularly high risk for developing VAP, especially when the ventilation lasts for more than 48 hours. Oral bacterial load increases during intubation, and higher dental plaque scores predict risk of pneumonia. Anaerobic bacteria are frequently found to colonize the lower respiratory tract in mechanically ventilated patients. Colonization of bacteria in the digestive tract has been suggested as a source of nosocomial pneumonia, but recently oral and dental bacterial colonization has been proposed as being the major source of bacteria implicated in the etiology of VAP. It is likely that bacteria that first colonize the dental plaque can be shed and attach to the tubing that passes through the oral cavity into the lung (Figure 1). In the institutionalized elderly, aspiration of saliva seems to be the main route by which bacteria enter the lungs to cause aspiration pneumonia. Dysphagia seems to be an important risk factor, even a predictor, of aspiration pneumonia. For example, the major oral and dental risk factors for aspiration pneumonia in veteran residents of nursing homes were number of decayed teeth, periodontitis, oral S. aureus colonization, and requirement of help with feeding. In another study of 613 elderly nursing home patients, inadequate oral care and swallowing difficulties were also associated with pneumonia.

Dentate status may constitute a risk for pneumonia and respiratory tract infections: patients with natural teeth develop aspiration pneumonia more often than edentulous subjects. Cariogenic bacteria and periodontal pathogens in saliva or dental plaque have also been shown to be risk factors for aspiration pneumonia in nursing home patients. It is well known that the teeth and gingival margin are places that favor bacterial colonization, and periodontal pockets may serve as reservoirs for potential respiratory pathogens. Previous studies have shown that enteric bacteria colonize periodontal pockets. Periodontitis, along with abundant dental plaque, together may facilitate colonization of dental plaque by respiratory pathogens and therefore promote pneumonia.

**Identification of Bacterial Strains**

Several recent published studies have clearly demonstrated the genetic identity of bacterial
strains from dental plaques with isolates from the lower airway from mechanically ventilated patients with suspected pneumonia. For example, strains of potential respiratory pathogens recovered from lung fluid were compared by pulsed-field gel electrophoresis with isolates of the same species from the dental plaque of critically ill residents of long-term care facilities transferred to an intensive care unit.\textsuperscript{50} Of 13 isolates recovered from bronchoalveolar lavage fluid, nine respiratory pathogens appeared genetically identical to isolates of the same species recovered from the corresponding dental plaque. A subsequent study also assessed the genetic relation between strains of respiratory pathogens first isolated from the oral cavity and those later isolated from bronchoalveolar lavage fluid from patients admitted to a trauma critical care unit undergoing mechanical ventilation with suspected VAP.\textsuperscript{51}

Pulse-field gel electrophoresis and multilocus sequence typing were used to determine the genetic relatedness of strains obtained from oral, tracheal, and bronchoalveolar lavage samples. Isolates of

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**Figure 1. Bacteria Associated with Dental Plaque**
S. aureus, P. aeruginosa, Acinetobacter species, and enteric species recovered from plaque from most patients were indistinguishable from isolates recovered from bronchoalveolar lavage fluid (Figure 2). These studies suggest that respiratory pathogens isolated from the lung are often genetically indistinguishable from strains of the same species isolated from the oral cavity in patients who receive mechanical ventilation and who are admitted to the hospital from both nursing homes and the community. Thus, dental plaque is an important reservoir for VAP infection.

**Figure 2.** Pulse-Field Gel Electrophoresis Patterns with Dendrogram for Pseudomonas aeruginosa Isolates

These results demonstrate that the bacterial isolates from the supragingival dental plaque (SG), tracheal secretions (TS), and bronchoalveolar lavage (BAL) from the same subject with suspected pneumonia are genetically identical. **Source:** Heo et al. Clin Infect Dis 2008;47:1562-70.

**Oral Intervention to Reduce Pulmonary Infections**

Recent systematic reviews of the literature have substantiated the link between poor oral health and pneumonia. Oral interventions to reduce pulmonary infections have been examined in both mechanically ventilated ICU patients and nonventilated elderly patients. These studies have mostly included chemical intervention using topical antimicrobial agents such as CHX and betadine. Fewer studies have evaluated the effectiveness of traditional oral mechanical hygiene. Oral topical CHX reduces pneumonia in mechanically ventilated patients and may even decrease the need for systemic IV antibiotics or shorten the duration of mechanical ventilation in the ICU. Also, oral application of CHX in the early post-

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**Pseudomonas aeruginosa**

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These results demonstrate that the bacterial isolates from the supragingival dental plaque (SG), tracheal secretions (TS), and bronchoalveolar lavage (BAL) from the same subject with suspected pneumonia are genetically identical. **Source:** Heo et al. Clin Infect Dis 2008;47:1562-70.
example, gingival decontamination with CHX gel significantly decreased the prevalence of oropharyngeal colonization by pathogenic bacteria in ventilated patients, but this was not sufficient to reduce the incidence of respiratory infections. Another study reported that a significant reduction in pneumonia using CHX rinse in ICU patients was achieved only after 24 hours of intubation. Other studies demonstrated no benefit from CHX rinsing with regard to pneumonia reduction in critically ill patients. In our own randomized trial, the application of CHX once or twice a day was found not to have great impact on the quantity of potential respiratory pathogens in the oral cavity of mechanically ventilated subjects, with the exception of *S. aureus*, which was significantly reduced in numbers after exposure to CHX.

The efficacy of oral CHX decontamination to reduce VAP needs further investigation, since no clear reduction in mortality rate has been demonstrated. In addition to CHX, other antiplaque agents have been investigated. Antimicrobial gels including polymyxin B sulfate, neomycin sulfate, and vancomycin hydrochloride or gentamicin/colistin/vancomycin also reduce VAP. Several studies have demonstrated that mechanical oral care, in some cases in combination with povidone iodine, significantly decreases pneumonia in ventilated ICU patients. Although the electric toothbrush can reduce the amount of dental plaque in ventilated subjects, it appears that tooth brushing alone was not an effective addition to an oral care protocol either to reduce the number of oral potential respiratory pathogens or to reduce pneumonia.

Institutionalized but nonventilated patients, mainly elders living in nursing homes, appear to also benefit from improved oral care by showing lower levels of oral bacteria and fewer pneumonia episodes and febrile days. Daily tooth brushing and topical oral swabbing with povidone iodine significantly decreased pneumonia in residents in long-term care facilities. However, in an earlier study by the same research group, oral care with both brushing and antimicrobial gargling had an effect only on febrile days but not on incidence of pneumonia. Professional cleaning by a dental hygienist once a week significantly reduced the prevalence of fever and fatal pneumonia in 141 elderly patients in nursing homes. Similar once-a-week professional oral cleaning significantly reduced influenza infections in an elderly population.

Dental plaque is known to form clearly visible masses in the teeth in a few days, but these studies suggest that improved oral care even without chemical agents and even if not performed daily not only reduces the oral bacterial, viral, and fungal load, but also may have an effect on reducing the risk of pneumonia. Therefore, more studies are needed to find the simplest oral decontamination method to reduce pulmonary infections in elderly nursing home patients.

Oral cleansing reduces pneumonia in both edentulous and dentate persons, suggesting that oral colonization of bacteria contributes to nosocomial pneumonia to a greater extent than periodontitis does. However, intervention studies of the treatment of periodontitis on the incidence of pneumonia have not been performed because of the complexities required in investigating ICU or bed-bound nursing home patients. In edentulous people, dentures may easily serve as a similar reservoir as teeth for oral and respiratory bacterial colonization if not cleaned properly and daily.

**Suggestions for Oral Care of Hospitalized and Nursing Home Residents to Prevent Respiratory Infection**

Many studies demonstrate that improved oral hygiene can reduce the risk of pneumonia in vulnerable patients. This raises the question as to what is the present status of
oral hygiene practice in hospitals and nursing homes. In light of the recent findings just described, routine nursing practice needs to include more rigorous oral care procedures.

A survey assessed the type and frequency of oral care provided in ICUs in the United States, as well as the attitudes, beliefs, and knowledge of health care personnel. The findings showed that although 512 (92%) of 556 respondents perceived oral care to be a high priority, the primary oral care procedures involved the use of foam swabs, moisturizers, and mouthwash. Interventions thought to reduce oral colonization by respiratory pathogens, such as tooth brushing and antiseptic rinses such as CHX, appear to be used infrequently in critical care settings.

No official guidelines promulgated by professional societies or regulatory agencies have been published to date. However, a recent paper described clinical practice guidelines for oral hygiene in critically ill patients based on a systematic literature review followed by prospective consideration of the evidence during a consensus development conference. From this, several recommendations were offered to guide clinicians in the care of vulnerable patients:

1. Provision of effective oral care is an important strategy in reducing nosocomial pneumonia.
2. A designated oral care protocol should be used.
3. Systematic clinical assessment of the oral cavity using standardized methods (to include the condition of the teeth, gums, tongue, mucous membranes, and lips).
4. The use of a soft-bristled brush removes debris and subsequent plaque.
5. Mouth swabs (foam and cotton) should be used when there is a contraindication to brushing (e.g., because of bleeding gums associated with thrombocytopenia).
6. Use of one oral rinse over another is considered questionable (with the exception of CHX 0.12% in cardiac surgical patients).
7. Tap water should not be used for oral hygiene in the critically ill (it is often contaminated with potential respiratory pathogens).
8. Subglottic suctioning in mechanically ventilated patients limits aspiration of contaminated secretions.
9. Although the optimal frequency for oral hygiene has never been evaluated, brushing at least twice a day is suggested.
10. Although the optimal duration for oral care has never been evaluated, brushing, i.e., oral cleansing for 3 to 4 minutes using a brush that allows access to all areas of the mouth, is suggested.
11. No evidence supports the use of individual, clean storage devices for oral hygiene tools, but the guideline committee recommends the use of designated containers.

Other measures to consider for intubated patients may include removal of all dental appliances on admission to the critical care unit, periodic repositioning of the tube, and deflation of the cuff. Removal of hard deposits (e.g., tartar/calculus) from the teeth should be considered if possible before admission (as in the case of elective surgery). Placement of the patient’s head to the side or place in semi-Fowler’s position (semireclined body position) also minimizes inadvertent aspiration.

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

Patients with chronic obstructive pulmonary disease (COPD) have chronic airflow obstruction due to narrowing of the airways, with excess production of sputum resulting from chronic bronchitis and/or emphysema.
**Chronic bronchitis** is defined as the result of irritation to the bronchial airway and excessive secretion of mucus sufficient to cause cough with expectoration for at least 3 months of the year over 2 consecutive years.\(^2\) Emphysema results from distention of the air spaces distal to the terminal bronchiole with destruction of the alveolar septa. Although this condition is associated with certain symptoms, the definitive diagnosis of emphysema can only be made histologically.

**Epidemiology**

Chronic bronchitis is quite prevalent, with 20% to 30% of all adults over the age of 45 years having some history of this condition,\(^3\) typically as a sequela of smoking. The incidence of emphysema is less well known because the main tool for noninvasive diagnosis (CT scanning) cannot be practically applied in population studies. Although it is rare to find lungs completely free of emphysema postmortem, most individuals do not show well-defined histologic evidence of emphysema and do not have clinical symptoms of the disease.

The most significant risk factor for COPD is prolonged cigarette smoking. Other environmental risk factors include chronic exposure to toxic atmospheric pollutants (e.g., second-hand smoke). Possible genetic risk factors include a defective alpha\(_1\)-antitrypsin gene, variant alpha\(_1\)-antichymotrypsin, alpha\(_2\)-macroglobulin, vitamin D-binding protein, and blood group antigen genes.\(^4\) These genetic defects are found in only a small percentage of individuals with COPD.

Worldwide, the prevalence of physiologically defined COPD in adults aged 40 years or older is approximately 9% to 10%.\(^5\) In 2001, about 12.1 million adults older than 25 years of age were diagnosed with COPD in the United States, and another 24 million showed impaired lung function.\(^6\) It is likely that the estimated COPD in the community remains underreported because of the difficulties in the diagnosis of COPD. COPD is the fourth leading cause of morbidity and mortality in the United States and is projected to become the fifth most common cause of morbidity and the third most common cause of mortality worldwide by the year 2020. After adjusting for sociodemographic factors and smoking status, estimated mean excess cost of COPD is $4,932 per patient.\(^7\) Direct medical costs in the United States were estimated to be $18 billion in 2002. Inpatient costs are greater than outpatient costs, and emergency costs ($8.3 vs $7.8 billion) and hospital and medication costs account for most resources spent.\(^8\)

**Pathogenesis**

COPD is the result of chronic airflow limitation resulting from an inflammatory response to inhaled particles and gases in the lung, in most cases delivered from tobacco smoking.\(^9\) Smoking is related to macrophage-predominant inflammation and airspace enlargement. High concentrations of reactive oxygen species (ROS) in tobacco smoke results in oxidative stress. Resulting recruitment of macrophages leads to release of proteases such as macrophage elastase (matrix metalloproteinase (MMP)-12), which seems to be a key pathogenic factor in emphysema. For example, a MMP-inhibitor, AZ11557272, prevented smoke-induced increases in lung inflammatory cells, lavage desmosine (a marker of elastin breakdown) and serum tumor necrosis factor (TNF)-alpha in a guinea pig model of cigarette smoke-induced COPD.\(^10\)

COPD is a complex disease that is influenced by a variety of environmental and genetic factors. Several environmental factors, such as cigarette smoking and air pollution, have been strongly associated with the initiation and progression of the disease. Clearly, not all smokers get the disease. Thus, other factors—likely genetic—may help
explain why some persons develop COPD and others do not.\textsuperscript{91,92} It is well known that COPD is related to alpha-1-antitrypsin deficiency,\textsuperscript{93,94} although severity of disease is affected by other risk factors such as gender, history of asthma, chronic bronchitis, and pneumonia. Some evidence has been presented demonstrating that COPD sometimes clusters in families. Genetic factors may also influence susceptibility to respiratory infections leading to acute COPD exacerbations, that is, episodes of worsening COPD symptoms (shortness of breath, quantity and color of phlegm) often triggered by an infection with bacteria or viruses that may last for several days. It appears that, to date, attempts to associate COPD experience with specific genetic polymorphisms, for example, targeting cytokine or global promoter genes, have proved to be inconclusive.\textsuperscript{92}

A major complication of COPD is the occurrence of periodic disease exacerbations, which have recently been associated with bacterial infection,\textsuperscript{95,96} typically by nontypeable \textit{H. influenzae}, \textit{S. pneumoniae}, and \textit{Moraxella catarrhalis}. Viral infection has also been implicated in initiating this process.\textsuperscript{97} Acute exacerbations of COPD are thus often treated using empiric antibiotic therapy. The cost of therapy for affected patients is extraordinarily high. Treatment failure from routine antimicrobial therapy can lead to hospitalization, respiratory failure, and death. Antibiotic therapy for exacerbations of COPD can also lead to emergence of bacterial antibiotic resistance and increased costs.

\textbf{Treatment}

A mainstay of therapy for COPD is inhaled drug therapy. In severe cases, lung volume reduction surgery has been shown to reduce mortality, increase exercise capacity, and improve quality of life. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxemic patient. Noninvasive ventilation has been used as a palliative treatment to reduce dyspnea.

A recent systematic review of the literature concluded that antibiotics effectively reduce treatment failure and mortality rates in COPD patients with severe exacerbations.\textsuperscript{98} However, antibiotics may not be generally indicated for patients with mild to moderate exacerbations.

\textbf{COPD and Oral Health}

Associations between respiratory diseases and oral health in community-dwelling populations were initially assessed by analysis of the National Health and Nutrition Examination Survey I (NHANES I) data.\textsuperscript{99} This database contains information on the general health status of 23,808 persons. Of these, 365 individuals reported a respiratory condition, categorized as confirmed chronic respiratory disease (chronic bronchitis or emphysema) or acute respiratory disease (influenza, pneumonia, acute bronchitis). After controlling for gender, age, and race, subjects with confirmed chronic respiratory disease had a significantly greater oral hygiene index than those without respiratory disease. Furthermore, subjects with acute disease tended to have more decayed teeth than those without disease. No other statistical associations were noted between any of the other measures of oral health and acute respiratory disease. Also, no associations were noted between the periodontal index and either acute or chronic diseases.

Another study found periodontal disease, measured as alveolar bone loss that occurred between baseline and later measurements from periapical radiographs, to be an independent risk factor for COPD in adult males enrolled in the VA Normative Aging study.\textsuperscript{100} These results were supported by a subsequent study that measured associations between poor oral health and chronic lung
disease, and this study was able to carefully control for a number of potentially confounding variables. Data from NHANES III, which documented the general health and nutritional status of randomly selected United States subjects from 1988 to 1994, were analyzed. This cross-sectional, retrospective study of the NHANES III database included a study population of 13,792 subjects 20 years of age and older having at least six natural teeth. A history of bronchitis and/or emphysema was recorded from the medical questionnaire. Lung function was estimated by calculation of the ratio of forced expiratory volume after 1 sec (FEV$_1$)/forced vital capacity (FVC). Oral health status was deduced from the Decayed Missing Filled System (DMFS/T) index (summary of cumulative caries experience), gingival bleeding, gingival recession, gingival pocket depth, and periodontal attachment level.

Subjects with COPD had, on average, more periodontal attachment loss (CAL 1.48 ± 1.35 mean ± SD) than those without COPD (mean CAL 1.17 ± 1.09). To simultaneously control for multiple variables that may confound statistical analysis, gender, age, race, education, income, dental treatment history, alcohol consumption, diabetes status, and smoking status were considered in a logistic regression model against history of COPD. The risk for COPD appeared to be significantly elevated when mean attachment loss (MAL) was found to be severe (mean attachment loss; MAL ≥2.0 mm) compared with periodontal health (<2.0 mm MAL: odds ratio 1.35, 95% CI: 1.07–1.71). Furthermore, the odds ratio was 1.45 (95% CI: 1.02–2.05) for those who had ≥3.0 mm MAL. A trend was also noted in that lung function appeared to diminish as the amount of attachment loss increased. No such trend was apparent when gingival bleeding was considered. No other statistical associations were noted among any of the measures of oral health and acute respiratory diseases, such as influenza or pneumonia.

Another study examined the relation between airway obstruction and periodontal disease in a cohort of 860 community-dwelling elders enrolled in the Health, Aging, and Body Composition Study (Health ABC). Results showed that, after stratification by smoking status and adjustment for age, race, gender, center, and number of pack-years, those with normal pulmonary function had significantly better gingival index (P = .036) and loss of attachment (P = .0003) scores than those with airway obstruction. Thus, a significant association between periodontal disease and airway obstruction was noted, especially in former smokers.

Also, an association between chronic periodontitis and severe COPD was supported by a recent study that demonstrated a greater prevalence of chronic periodontitis in 130 patients with very severe COPD than that in 50 patients with other very severe respiratory diseases. The prevalence of periodontitis was found to be 44% in the COPD group compared with 7.3% in the non-COPD group. This difference was significant after adjustment for age, gender, and number of pack-years smoked.

Several parameters related to periodontal health have been associated with the COPD exacerbation, including the amount of plaque on the teeth, number of teeth, and infrequent toothbrushing. Moreover, a recent meta-analysis was performed that evaluated data from 14 studies involving 3,988 COPD patients. A significant association between pulmonary disease and COPD was identified.

**Chronic Lung Disease in Hospitalized Patients**

Dental plaque may serve as a reservoir of respiratory pathogen colonization in hospitalized patients with chronic lung diseases. Using a checkerboard DNA-DNA hybridization technique to determine prev-
alence of eight respiratory pathogens and eight oral pathogens, species such as S. aureus, P. aeruginosa, Acinetobacter baumannii, and Enterobacter cloacae were detected in plaque from 29 of the 34 (85.3%) hospitalized patients, whereas only 12 of 31 (38.7%) nonhospitalized subjects had colonizations. These results indicate that dental plaque may serve as a reservoir of infection in hospitalized patients with chronic lung diseases.

CONCLUSION
Ample research now supports associations between oral health, especially dental plaque and periodontal disease, and respiratory diseases such as nosocomial pneumonia and COPD. Further research may allow development and routine implementation of simple and effective strategies to prevent respiratory disease in vulnerable populations.

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CHAPTER 11

Osteoporosis

Hector F. Rios, William V. Giannobile

INTRODUCTION

Bone as a tissue represents a highly dynamic biologic system that comprises a series of tightly regulated and synergistic anabolic and catabolic events that lead to proper metabolic and skeletal structural homeostasis. Multiple factors may negatively influence these processes leading to decreased bone mass, decreased density, altered microarchitecture, and increased bone fragility. The term osteoporosis has been collectively used to refer to conditions in which the ability of the skeletal tissue to respond and adapt to environmental and physiologic challenges is compromised. Because of the above-mentioned factors, microdamage accumulation and increased fracture susceptibility can occur. Within this context, numerous proinflammatory cytokines have been identified as important determinants of bone loss.1-7 A significant increased production of proinflammatory cytokines occurs in conditions such as periodontitis, a disease initiated by bacterial plaque biofilms. The impact of osteoporosis on host susceptibility to periodontal breakdown is clinically relevant.8-11 This chapter reviews and evaluates the available literature regarding the association between these two complex multifactorial conditions, their effect on disease extent and severity, and the coexisting mechanisms by which they may affect the overall bone structural integrity and homeostasis.

OSTEOPOROSIS AND BONE REMODELING

Bone is a highly dynamic tissue with the capacity to adapt based on physiologic needs. Hence, bone adjusts its mechanical properties according to metabolic and mechanical requirements.12-14 The skeletal adaptation mechanism is primarily executed by processes of bone resorption and bone formation and referred to collectively as bone remodeling (Figure 1). Bone is resorbed by osteoclasts, after which new bone is deposited by osteoblastic cells.15 From the perspective of bone remodeling, it has been proposed that osteoclasts recognize and are targeted to skeletal sites of compromised mechanical integrity and initiate the bone-remodeling process for the purpose of inducing the generation of mechanically competent new bone.16

The remodeling process takes place in bone multicellular units (BMUs) (Figure 2). A BMU comprises (1) a front of osteoclasts residing on a surface of newly resorbed bone referred to as the resorption front, (2) a compartment containing vessels and pericytes, and (3) a layer of osteoblasts on a newly formed organic matrix known as the deposition front. In Figure 2, the resorption front is clearly visualized by the cells stained for tartrate-resistant acid phosphatase (TRAP). The number of new and active BMUs is regulated by a variety of hormones and cytokines, which dictate the spatiotemporal synchronization and coupling of the anabolic and catabolic remodeling events.

The molecular and cellular pathogenesis of osteoporosis has been an area of significant research for more than a decade. Proteins that serve as “master switches” have been identified (Figure 3). These key molecules serve as signals that coordinate activities of osteoblasts and osteoclasts during bone remodeling. This new molecular biology frontier has trig-
Figure 1. 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 formation. Finally, successive waves of mesenchymal cells differentiate into functional osteoblasts, which lay down matrix in the formation phase. **Source:** Mediators of periodontal osseous destruction and remodeling: principles and implications for diagnosis and therapy. *J Periodontol* 2002;73:1377–91. Reproduced with the permission of the American Academy of Periodontology.

Figure 2. Bone Multicellular Units (BMUs)

Bone remodeling occurs in local groups of osteoblasts and osteoclasts called BMUs; each unit is organized into a reabsorbing front of osteoclasts, followed by a trail of osteoblasts reforming the bone to fill the defect left by osteoclasts. The red staining (tartrate resistant acid phosphatase) highlights the resorption front. Note the increased number of multinucleated osteoclasts in this area.
Figure 3. Bone Formation/Resorption Coupling

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

Triggered significant innovation in the field and further develops our understanding of the principles of bone pathophysiology. Differentiation from osteoclast precursor cells to fully activated multinucleated osteoclasts depends critically on the presence of receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the tumor necrosis factor (TNF) family. RANKL is abundantly expressed by bone-forming osteoblasts as well as bone marrow stromal cells and activates its receptor, RANK, expressed on osteoclasts. Parathyroid hormone (PTH) and vitamin D3 have receptors in osteoblasts and stromal cells, where they promote the transcription of RANKL and limit the production of osteoprotegerin (OPG), a naturally occurring antagonist of RANKL.

After RANKL-induced RANK stimulation, activated RANKL couples to an adaptor protein, TNF receptor-associated factor 6 (TRAF6), which enhances the activity of important osteoclast intracellular protein kinases. The Src kinase is highly expressed in osteoclasts and acts as a mediator of multiple pathways regulating osteoclast activity. Several key regulatory transcription factors and enzymes are enhanced to promote the differentiation, proliferation, multinucleation, activation, and survival of osteoclasts. T cells also stimulate osteoclast activation by this same pathway. In this case, besides OPG, a second mechanism slows down the activation. Interferon gamma (IFN-γ) stimulates the degradation of TRAF6 and blocks the signal arriving from RANK.

When osteoclasts are fully differentiated and attached to bone, this synchronizes the release of H+ and Cl− into the resorption lacunae via the v-ATPase proton pump and the voltage-gated chloride channel CLC-7. As a result, acidification of this space occurs and profoundly in-
roduces mineral degradation. In addition, the osteoclasts deliver cathepsin K (CatK), a key proteinase, into this space. This results in increased collagen degradation and breaks down bone. CatK is a critical determinant of resorptive activity by osteoclasts that remove bone of poor quality, where microcracks have accumulated over time.

In addition, hormonal factors 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. Osteocyte apoptosis occurs in states of 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 (Figure 4). It is also well known that the parathyroid glands react to low calcium levels by secreting parathyroid hormone (PTH), which increases bone resorption to ensure sufficient calcium in the blood.

In postmenopausal osteoporosis, a lack of estrogen leads to increased BMUs and altered remodeling due to uncoupling of bone formation and bone resorption. This process results in too little bone being laid down by osteoblasts compared with the amount of bone resorbed by osteoclasts. Such disruption in the normal remodeling events compromises the ability to adapt to external and internal demands. Without an efficient coupling mechanism, each remodeling event results in net loss of bone, which ultimately com-

**Figure 4. Calcium and Bone Metabolism**

[Diagram of calcium balance and bone metabolism]

Calcium homeostasis is of major importance for many physiologic processes necessary to 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, whereas 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.
promises the bone strength owing to resulting altered architecture (Figure 5). The affected skeletal integrity in osteoporosis is characterized by cortical and trabecular thinning as well as loss of trabecular connectivity. In addition, the number of osteons per unit volume of bone decreases, offering less resistance to crack initiation and propagation owing to a larger interstitial bone between osteons. The reduced bone quality in osteoporosis is also reflected by a decrease in cell density. The reduced osteocytic density in interstitial bone reduces the ability to detect damage and thus to remove it. If bone formation is decreased in the BMU as a result of reduced osteoblast numbers, then reduced synthesis of osteocytes may also contribute to the deficit in this cell type, which is considered the orchestrator of bone remodeling. Reduced periosteal bone formation in adulthood contributes to fragility because endocortical resorption is not compensated for, so there is both failure to offset cortical thinning and failure to shift the cortical bone outward from the neutral axis—a change that increases resistance to bending.

In summation, the interaction of genetic and environmental factors on bone loss underlies the development of fragile bone tissue, decreasing the inherent capacity of the skeleton to adapt and respond adequately to structural needs.

**OSTEOPOROSIS AND BONE MINERAL DENSITY**

Osteoporosis severely compromises the skeletal integrity. However, fractures tend to occur late in the disease process. Today, it is generally accepted that the bone mineral density (BMD) measurement is the most valuable parameter to identify patients who are more susceptible or at greater risk for fractures. The widespread availability and popularity of bone densitometry have led to a widely accepted definition proposed by the World Health Organization (WHO) in 1994, based on BMD measurements in standard devia-

**Figure 5.** Altered Cortical and Trabecular Architecture in Osteoporosis

In osteoporosis, there is a 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.
tion units called T-scores\textsuperscript{25} (Figure 6).

Essentially, the T-score indicates the difference between an individual’s BMD and the normal BMD achieved by a young adult. As illustrated in Figure 7, the WHO defines four main levels of osteoporosis risk assessment based on T-scores:

- Normal bone mineral density is found when the T-score is $\geq -1$.
- Osteopenia refers to a low BMD T-score between $-1.0$ and $-2.5$.
- Osteoporosis is diagnosed when an individual has a T-score $\leq -2.5$.
- Osteoporosis is considered to be established when an individual has one or more fragility fractures in addition to a T-score $\leq -2.5$.

**Types of Osteoporosis**

The clinical presentation of osteoporosis includes several characteristics that facilitate the diagnosis. However, the primary etiology that leads to the appearance of the condition may vary considerably. Our ability to recognize and classify etiologic differences among conditions that may appear clinically similar have an impact on our ability to successfully treat these patients. Primary osteoporosis is simply the form seen in older persons and women after menopause in which bone loss is accelerated over that predicted for age and sex. Secondary osteoporosis results from a variety of identifiable conditions.

**Primary Osteoporosis**

There are two forms of primary osteoporosis: type I and type II. The determining factor for the actual existence of osteoporosis, either type I or type II, is the amount of calcium remaining in the skeleton and whether it places a person at risk

*Figure 6. Bone Mineral Density (BMD)*

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

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 (WHO) 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.
of fracture. Someone who has exceptionally dense bones to begin with will probably never lose enough calcium to reach the point at which osteoporosis occurs, whereas a person with low bone density could easily develop osteoporosis despite losing only a relatively small amount of calcium.

Type I osteoporosis (postmenopausal osteoporosis) generally develops in women after menopause when the amount of estrogen in the body greatly decreases. This process leads to an increase in the resorption of bone (the bones lose substance). Type I osteoporosis occurs in 5% to 20% of women, most often between the ages of 50 and 75 because of the sudden postmenopausal decrease in estrogen levels, which results in a rapid depletion of calcium from the skeleton. It is associated with fractures that occur when the vertebrae compress together causing a collapse of the spine, and with fractures of the hip, wrist, or forearm caused by falls or minor accidents. Type I accounts for the significantly greater risk of osteoporosis in women versus men.

Type II osteoporosis (senile osteoporosis) typically happens after the age of 70 and affects women twice as frequently as men. Type II osteoporosis results when the process of resorption and formation of bone are no longer coordinated, and bone breakdown overcomes bone building. This occurs with age in everyone to some degree. Type II affects trabecular and cortical bone, often resulting in fractures of the femoral neck, vertebrae, proximal humerus, proximal tibia, and pelvis. It may result from age-related reduction in vitamin D synthesis or resistance to vitamin D activity (possibly mediated by decreased or unresponsive vitamin D receptors in some patients). In older women, types I and II often occur together.

**Secondary Osteoporosis**

Secondary osteoporosis is caused by other conditions, such as hormonal imbalances, certain diseases, and medications (e.g., corticosteroids). Secondary osteoporosis accounts for less than 5% of cases of osteoporosis. Causes include endocrine disease (e.g., glucocorticoid excess,
hyperparathyroidism, hyperthyroidism, hypogonadism, hyperprolactinemia, diabetes mellitus), drugs (e.g., glucocorticosteroids, ethanol, dilantin, tobacco, barbiturates, heparin), and other conditions (e.g., immobilization, chronic renal failure, liver disease, malabsorption syndromes, chronic obstructive lung disease, rheumatoid arthritis, sarcoidosis, malignancy, prolonged weightlessness as found in space flight).

**OSTEOPOROSIS AND INFLAMMATION**

Emerging clinical and molecular evidence suggests that inflammation also exerts significant influence on bone turnover, inducing osteoporosis. Numerous pro-inflammatory cytokines have been implicated in the regulation of osteoblasts and osteoclasts, and a shift toward an activated immune profile has been hypothesized as an important risk factor. Chronic inflammation and the immune system remodeling characteristic of aging, as well as of other pathologic conditions commonly associated with osteoporosis, may be determinant pathogenic factors.

The cellular and molecular pathogenic mechanisms in inflammation-induced osteolysis and sclerosis have been explored extensively. There is substantial evidence that bone remodeling is a tightly regulated and finely balanced process influenced by subtle changes in proinflammatory and inhibitory cytokines as well as hormones and cellular components that act primarily but not exclusively through the RANK/RANKL/OPG system. Therefore, an acute or chronic imbalance in the system due to infection or inflammation could contribute to systemic (or local) bone loss and increase the risk of fracture.

Generalized osteoporosis and an increased risk of fracture are commonly observed in chronic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease. Current evidence suggests that osteoporosis that develops during chronic inflammation may result from the inhibition of bone formation and is associated with systemic overproduction of proinflammatory mediators, such as cytokines, nitric oxide (NO), and prostaglandins. In patients with periodontal disease and concomitant postmenopausal osteoporosis, the possibility exists that the lack of estrogen influences the activities of bone cells and immune cells in such a way that the progression of alveolar bone loss is enhanced.

**ALVEOLAR BMD VS SKELETAL BMD**

Systemic factors can lead to loss of BMD throughout the body, including bone loss in the maxilla and mandible. The resulting local reduction of BMD in the jaw bones can set the stage for more rapid loss of alveolar crestal height because a comparable challenge of bacteria-derived bone-resorbing factors can be expected to result in greater alveolar bone destruction than in an individual with normal bone mass. In addition, systemic risk factors such as smoking, diabetes, diet, and hormone levels affect systemic bone levels and may also affect periodontitis.

Oral bone loss has been shown to be associated with osteoporosis and low skeletal BMD. In their search for oral radiographic changes associated with osteoporosis, most investigators have focused on measures of jaw bone mass or morphology. The commonly used assessment of oral bone includes radiographic measures of loss of alveolar crestal height, measures of resorption of the residual ridge after tooth loss, and assessment of oral BMD. Tools used to measure bone mass include single and dual photon absorptiometry, dual-energy x-ray absorptiometry
(DEXA), quantitative computed tomography (QCT), and film densitometry.

Mandibular mineral content is reduced in subjects with osteoporotic fractures.\textsuperscript{26} Furthermore, the BMD of buccal (but not trabecular) mandibular bone correlates with osteoporosis (low skeletal BMD).\textsuperscript{27,28} Mandibular density (measured with a DEXA scan) also correlates with skeletal BMD.\textsuperscript{29}

Using film densitometry, most investigators have found that the optical density of the mandible is decreased in subjects with osteoporosis (low skeletal BMD) compared with that of controls. In addition, mandibular radiographic optical density correlates with vertebral BMD in osteoporotic women,\textsuperscript{30} control (nonosteoporotic) women,\textsuperscript{31} and women with a history of vertebral fracture.\textsuperscript{32,33} Reduction in cortical and subcortical alveolar bone density has also been reported to correlate with osteoporosis (low skeletal BMD) in longitudinal studies.\textsuperscript{34–36} As reported by Hildebolt in 1997, the preponderance of the evidence indicates that the jaws of subjects with osteoporosis show reduced bone mass.\textsuperscript{37} Table I summarizes the available data regarding the relation between systemic and oral bone loss.

**ASSOCIATION BETWEEN OSTEOGENIA AND INCREASED SEVERITY OF ALVEOLAR BONE LOSS AND TOOTH LOSS**

It is hypothesized that periodontitis results from bacteria that produce factors that cause loss of collagenous support of the teeth, as well as resorption of alveolar bone. Systemic factors can lead to loss of BMD throughout the body, including bone loss in the maxilla and mandible. The resulting local reduction of BMD in the jawbones could set the stage for more rapid marginal bone loss because a comparable challenge of bacterial bone-resorbing factors could be expected to result in greater alveolar crestal bone resorption than in a person with normal bone mass. In addition to this finding, systemic risk factors such as smoking, diabetes, diet, and hormone levels affect systemic bone level and may also affect periodontitis. Although periodontal disease has historically been thought to be the result of a local infectious process, others have suggested that periodontal disease may be an early manifestation of generalized osteopenia.\textsuperscript{38}

Several potential mechanisms have been proposed by which osteoporosis or systemic bone loss may be associated with periodontal attachment loss, reduction of alveolar bone height or density, and tooth loss. One of these mechanisms states that low BMD or loss of BMD may lead to more rapid resorption of alveolar bone after insult by periodontal bacteria. With less dense oral bone to start, loss of bone surrounding the teeth may occur more rapidly. Another mechanism proposes that systemic factors affecting bone remodeling may also modify the local tissue response to periodontal infection. Persons with generalized bone loss are known to have increased systemic production of cytokines (i.e., interleukin-1 [IL-1] and IL-6) that may have effects on bone throughout the body, including the bones of the oral cavity. Periodontal infection has been shown to increase local cytokine production that, in turn, increases local osteoclast activity resulting in increased bone resorption. A third potential mechanism is related to genetic factors that predispose an individual to systemic bone loss and that would also influence or predispose an individual to periodontal destruction. Also, certain lifestyle factors such as cigarette smoking and suboptimal calcium intake, among others, may put individuals at risk for development of both systemic osteopenia and oral bone loss.
### Table 1. Studies on the Relationship Between Systemic and Oral Bone Loss

<table>
<thead>
<tr>
<th>Studies</th>
<th>Oral</th>
<th>Systemic</th>
<th>Study Type</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earnshaw et al.(^a)</td>
<td>Tooth count</td>
<td>Lumbar BMD</td>
<td>√</td>
<td>NO</td>
</tr>
<tr>
<td>Elders et al.(^b)</td>
<td>Bone height/Tooth count</td>
<td>Lumbar BMD</td>
<td>√</td>
<td>NO</td>
</tr>
<tr>
<td>Klemetti et al.(^c)</td>
<td>Bone height/Tooth count</td>
<td>Skeletal BMD</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>Krall et al.(^d)</td>
<td>Tooth loss</td>
<td>Skeletal BMD</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>Jeffcoat et al.(^e)</td>
<td>Mandibular BMD</td>
<td>Femoral neck BMD</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>Hildebolt et al.(^f)</td>
<td>CAL</td>
<td>Lumbar/Femoral neck BMD</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>Kribbs(^g)</td>
<td>CAL</td>
<td>Normal osteoporosis</td>
<td>√</td>
<td>NO</td>
</tr>
<tr>
<td>Tezal et al.(^b)</td>
<td>CAL/Bone height</td>
<td>Skeletal BMD</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>von Wowern et al.(^i)</td>
<td>CAL</td>
<td>Forearm BMD</td>
<td>√</td>
<td>YES</td>
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<tr>
<td>Payne et al.(^j)</td>
<td>Bone height/Bone density</td>
<td>Normal Osteopenia</td>
<td>√</td>
<td>YES</td>
</tr>
<tr>
<td>Yoshihara et al.(^k)</td>
<td>CAL</td>
<td>Normal Osteopenia</td>
<td>√</td>
<td>YES</td>
</tr>
</tbody>
</table>

BMD = bone mineral density; CAL = clinical attachment loss.

ROLE OF CALCIUM IN MODERATING THE RELATIONSHIPS BETWEEN OSTEOPOROSIS AND PERIODONTAL DISEASE

Osteoporosis and osteopenia may influence periodontal disease and tooth loss. Although many studies suggest that in elderly men and women, maintenance of normal BMD is associated with improved tooth retention, the evidence is still inconclusive. Hormone replacement therapy and calcium and vitamin D supplements used to prevent or treat osteoporosis appear to have beneficial effects on tooth retention as well. Future prospective studies, including randomized clinical trials, are needed to confirm these findings.

PROPOSED MECHANISM

The integrity of the periodontium in patients with osteoporosis faces many coexisting challenges. Local and systemic factors have an impact on the host’s ability to maintain the homeostasis within these tissues. Hypothetically, three different challenges may be influencing the periodontal integrity in patients with osteoporosis, thereby increasing periodontal disease susceptibility and the aggravation of the local signs of disease (Figure 7).

In the context of systemic and local reduced bone mass due to systemic osteoporosis, it is possible that superimposed inflammation-induced bone resorption may lead to enhanced progression of bone loss. This is particularly true with respect to the roles of the proinflammatory cytokines (e.g., IL-1, TNF-α, and IL-6) and the osteoclastogenic cytokine RANKL. In primary osteoporosis, the modulatory effect of estrogen in the expression of the bone-resorbing cytokines IL-1, TNF-α, and IL-6, is absent. There are greater levels of these molecules produced in an inflammatory process in postmenopausal women with estrogen deficiency, compared with an inflammatory process in women with normal estrogen levels. In addition, in the presence of a mechanically challenging environment such as the oral cavity, the amount of microcracks accumulating in the alveolar bone may further signal osteoclasts in an attempt to repair the already compromised osseous architecture.

OSTEOPOROSIS AND ORAL IMPLANTS

The impact of osteoporosis in alveolar bone quality and its potential influence on the implant therapy outcome has been well studied. Several investigations have reported successful implant placement in osteoporotic individuals. No correlation between DEXA scores and implant failure has been found as shown by case-control studies. A retrospective study analyzing 16 patients with osteoporosis who received implant therapy showed an overall implant survival rate of 97% in the maxilla and 97.3% in the mandible with a follow-up time of 6 months to 11 years.

Implant success in patients with osteoporosis as it relates to the presence of marginal bone loss around implants has also been reported. von Wowern and collaborators reported no implant failures in any of the osteoporotic and healthy patients, although marginal bone loss increased around the implants placed in patients with osteoporosis.

Bone-to-implant contact (BIC) is altered in osteoporotic conditions. BIC is significantly decreased in osteoporosis. In a preclinical study by Cho and collaborators, the greatest decreases in BIC were noted when an osteoporotic state was induced after osseointegration had occurred. BIC in the osteoporosis group
was reported as 50% compared with 79% in the control group. The results of these studies imply that although osseointegration of implants in osteoporotic bone is possible, the long-term stability of implants may be compromised by disease.

The literature supports dental implants as a viable treatment option for patients with osteoporosis. However, it is important to understand that owing to the altered bone metabolism, less BIC may occur with a higher risk of marginal bone loss. However, more studies are needed to determine the long-term effects of osteoporosis in this patient population.

PHARMAcOLOGIC MECHANISMS OF THERAPEUTICS
Perhaps the most dynamic and prolific aspect in the field of osteopenia and osteoporosis research lies in the discovery and development of novel targets that lead to promising treatment options with potential adaptation for treatment of periodontal disease or for promotion of osseointegration.55 Two therapeutic approaches are currently available: (1) antiresorptive drugs, which slow down bone resorption; and (2) anabolic drugs, which stimulate bone formation (Figure 8).

Antiresorptive Drugs
Bisphosphonates
In confirmed osteoporosis, bisphosphonate drugs are considered first-line treatment in women. The most frequently prescribed bisphosphonates are presently sodium alendronate (Fosamax) 10 mg/day or 70 mg/once per week, risedronate (Actonel) 5 mg/day or 35 mg/once per week, and/or ibandronate (Boniva) once per month. A 2007 manufacturer-supported study suggested that in patients who had suffered a low-impact hip fracture, yearly infusion of 5 mg zoledronic acid reduced risk of any fracture by 35% (from 13.9% to 8.6%), vertebral fracture risk from 3.8% to 1.7%, and nonvertebral fracture risk from 10.7% to 7.6%. This study also found a mortality benefit of 28% (9.6% of

Figure 8. Chemotherapeutics to Treat Bone Loss

In general, two groups can be distinguished among all of the known chemotherapeutic agents: (1) antiresorptive agents and (2) anabolic agents. These exert beneficial effects in the treatment of the osteoporotic patient by targeting distinct cell populations or by modulating the interaction of certain cells.
the study group had died of any cause after 1.9 years compared with 13.3% of the control group).

Oral bisphosphonates are relatively poorly absorbed and must therefore be taken on an empty stomach with no food or drink to follow for the next 30 minutes. They are associated with esophagitis and therefore sometimes poorly tolerated; weekly or monthly administration (depending on the preparation) decreases the likelihood of esophagitis and is now the standard regimen. Although intermittent dosing with the intravenous formulations such as zolendronate prevents oral tolerance problems, these agents are implicated at higher rates in a rare but debilitating oral affliction called osteonecrosis of the jaw (ONJ).

**Estrogen**

Estrogen deficiency in menopause is a major cause of osteoporosis in women. It acts to maintain bone mass, and its withdrawal leads to accelerated bone resorption. Estrogen protects bone by inducing a paracrine signal originating in osteoblasts leading to the death of preosteoclasts, therefore establishing an appropriate ratio between bone-forming osteoblasts and bone-resorbing osteoclasts in part through the induction of osteoclast apoptosis. Estrogen replacement therapy remains a good treatment option for the prevention of osteoporosis and is being studied as a way of preventing oral bone loss. Hormone replacement therapy and calcium and vitamin D supplements appear to have beneficial effects on tooth retention.

**Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs) selectively bind to estrogen receptors and inhibit bone resorption and turnover. This is possible because they lack the steroid structure of estrogens but possess a tertiary structure that allows them to bind to the estrogen receptor.

Unlike estrogens, which are uniformly agonists, SERMs exert selective agonist or antagonist effects on various estrogen target tissues. The mechanism of mixed agonism/antagonism may differ depending on the chemical structure of the SERM, but in general, it appears to be related to the ratio of coactivator to corepressor proteins in different cell types and the conformation of the estrogen receptor induced by drug binding. This in turn determines how strongly the drug/receptor complex recruits coactivators relative to corepressors.

Clinically, the benefits of SERM therapy on bone are well established. In postmenopausal women with osteoporosis, SERM treatment decreases markers of bone turnover by 30% to 40% after 1 year and increases bone density 2% to 3% after 3 years. It also decreased the incidence of vertebral fractures by 30% to 50%.

Although control studies evaluating oral bone loss are needed, SERMs appear to have excellent therapeutic potential for minimizing local and systemic consequences of postmenopausal osteoporosis.

**Strontium Ranelate**

Oral strontium ranelate belongs to a class of drugs called dual action bone agents (DABAs). It stimulates the calcium sensing receptors and leads to the differentiation of preosteoblasts to osteoblasts, which increases bone formation. In addition, it enhances the secretion of osteoprotegerin by osteoblasts, thereby inhibiting osteoclast differentiation in relation to the RANKL system, which leads to the decrease in bone resorption.

Strontium ranelate is taken for the treatment of osteoporosis to prevent vertebral and hip fracture. In post-
menopausal women with osteoporosis, strontium ranelate 2 g/day increased BMD.\textsuperscript{64} In regard to vertebral fractures, strontium ranelate treatment was associated with reductions of vertebral fractures of 49\% compared with data from control groups.\textsuperscript{65} Strontium ranelate has also shown significant efficacy against peripheral fractures and hip fractures.\textsuperscript{66}

Although strontium ranelate appears to be protective against fractures in the patient with osteoporosis and increases BMD values, it is not yet FDA approved for therapeutic use in the United States.

\textbf{Denosumab}

Denosumab is a neutralizing human monoclonal antibody to RANKL, mimicking the biologic function of OPG.\textsuperscript{67} Clinical studies evaluating the clinical efficacy using an intermittent regimen either every 3 or every 6 months demonstrated a strong inhibition of bone resorption as observed by up to 88\% reduction in the levels of serum C-telopeptide, an indicator of bone remodeling, with a rapid onset of action 3 days after administration and with a sustained, but reversible, antiresorptive effect.\textsuperscript{68,69} At 1 year, denosumab treatment significantly increased bone mineral density, especially in the lumbar spine and to a minor extent in the total hip and the distal radius. The clinical benefits of denosumab were similar to or exceeded those induced by alendronate and revealed dose-dependency.\textsuperscript{69} Although not detected in the original pivotal clinical trial, in a seven-year open label extension two patients receiving Denosumab for osteoporosis treatment presented ONJ lesions which accounts for a prevalence of 0.061\%.\textsuperscript{70}

\textbf{Other Emerging Approaches}

\textbf{Odanacatib}

Based on the concept that the protease cathepsin K plays an important role in enzymatic bone degradation, the use of cathepsin K inhibitors has emerged as a novel therapeutic approach. Odanacatib is currently the only cathepsin K inhibitor under clinical investigation. In phase 1 studies, odanacatib at an oral dose of 50 mg and 100 mg once per week significantly reduced serum markers of bone turnover.\textsuperscript{71,72}

\textbf{Saracatinib}

Other promising agents are the Src kinase inhibitors. The effect of impaired osteoclastic functions in Src-deficient mice provided the rationale to explore the skeletal effects of this class of inhibitor. In a phase 1 trial, the Src kinase inhibitor saracatinib (AZD0530) was evaluated and showed similar results to those once triggered by odanacatib.\textsuperscript{73}

\textbf{Chloride Channel and Proton Pump Inhibitors}

Other strategies involve inhibition of Atp6v0d2, a subunit of v-ATPase that is required for acidification and the voltage-gated chloride channel CIC-7. The chloride channel inhibitor NS3736 prevents bone loss through a marked antiresorptive effect, without impeding on bone formation markers.\textsuperscript{74}

\textbf{Anabolic Drugs}

\textbf{Teriparatide (1-34 PTH)}

Two forms of parathyroid hormone, rhPTH 1-84 (intact hormone) and rhPTH 1-34 (N-terminal fragment, teriparatide), are approved for the treatment of osteoporosis. PTH is a potent hormone with catabolic and anabolic effects in bone. Teriparatide (Forteo, recombinant human PTH (1-34)) has been shown to be effective in osteoporosis management.\textsuperscript{75,76} It stimulates osteoblasts, thus increasing their activity. Currently, teriparatide is used mostly for patients with established osteoporosis who have particularly low
BMD, several risk factors for fracture, or no tolerance of oral bisphosphonates. It is given as a daily injection with a pentype injection device. The use of PTH or teriparatide has been demonstrated to have strong potential for oral and craniofacial bone regeneration.77

The response of the alveolar bone to PTH has been evaluated by several investigators.78-80 In an animal study by Miller and collaborators,79 PTH was found to significantly increase crestal bone levels in the mandibles of ovariectomized rats. A recent preclinical investigation demonstrated the ability of teriparatide to promote dental implant osseointegration.81 Recent evidence has suggested strong potential of teriparatide to promote clinical attachment level gain and alveolar bone regeneration when combined with periodontal surgical procedures.82 Furthermore, there is proof-of-concept data that teriparatide may have a place for the treatment of ONJ.83

Other Emerging Approaches

Sclerostin Antibody

The gene SOST encodes the osteocyte-specific protein known as sclerostin. Inactivating mutations of this gene result in two rare bone disorders characterized by high bone mass, van Buchem disease, and sclerosteosis.84,85 These findings highlight the role of sclerostin in the homeostasis of bone mass and provide the bases to target sclerostin with monoclonal antibodies to enhance bone formation. In a preclinical postmenopausal osteoporosis study, treatment with a sclerostin antibody increased bone mass at all skeletal sites and completely prevented bone loss associated with estrogen deficiency.86 In a phase 1 study, a single dose of a sclerostin antibody was well tolerated and increased bone formation markers.87 More recently, the delivery of monoclonal antibodies inhibiting SOST have shown the potential to inhibit alveolar bone loss in a preclinical model of periodontal disease. The administration of sclerostin antibodies (Scl-Ab) was able to both prevent and treat experimental periodontitis in a rodent model system. This approach suggests that bone anabolics such as SOST inhibitors have potential in increasing alveolar bone density in the context of periodontal diseases.88

EFFECTS OF OSTEOPOROSIS THERAPY ON THE ORAL CAVITY

Osteoporosis therapy in general is primarily aimed at improving BMD values as measured by DEXA, a characteristic that is associated with reduced risk of osteoporosis fracture. However, important bone quality properties dependent on bone turnover and its variations are often affected and result in undesirable conditions. The oral cavity, because of the constant high mechanical demands and complex microbial challenges, is at an increased risk of developing debilitating sequelae secondary to pharmacologic osteoporosis therapy. Therefore, it is necessary to support the need for comprehensive oral health screenings before initiating a pharmacologic regimen that could lead to altering bone quality properties. This is of great importance in the case of long-term-acting medications such as bisphosphonates, particularly with its intravenous high-dose regimens.

Bisphosphonates, potent inhibitors of bone resorption, should in theory protect from periodontal and systemic bone loss, since the two processes are fundamentally similar. A small number of placebo-controlled, randomized trials have been conducted to test this hypothesis. The results are collectively equivocal. However, a positive effect in subjects with low alveolar bone mass at baseline and re-
ceiving bisphosphonate therapy in addition to proper periodontal maintenance has been reported. A more recent trial based on the local delivery of a 1% alendronate gel in periodontal disease patients undergoing scaling and root planing significantly improved clinical parameters of periodontal health. The local administration of bisphosphonates promotes osseointegration and dental implant fixation. However, bisphosphonates for alveolar bone loss is considered cautionary because of its reported association with ONJ lesions.

The American Society of Bone and Mineral Research (ASBMR) defines ONJ-confirmed lesions as areas of exposed bone in the maxillofacial region that have not healed within 8 weeks after identification by a healthcare provider in a patient who received bisphosphonate treatment and was not exposed to radiation therapy in the craniofacial region. Based on the review of both published and unpublished data, the risk of ONJ associated with oral bisphosphonate therapy for osteoporosis seems to be low, estimated at between 1 in 10,000 patients and less than 1 in 100,000 patient-treatment years. However, the incidence of ONJ is rapidly evolving, and the true incidence may be higher. The risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates is clearly higher—in the range of 1 to 10 per 100 patients (depending on the duration of therapy). For this reason, oral bisphosphonate therapy is probably to be preferred, and prescribing advice now recommends any necessary dental work to be carried out before initiating treatment. It is important to highlight that, although this area is the focus of multiple efforts across disciplines, an objective assessment of risks and benefits of this class of drugs for alveolar bone health remains a difficult task owing to the lack of consistency for the diagnosis of these cases.

Another important, modifiable factor contributing to increased bone fragility and loss is inadequate intake of vitamin D. Results of recent studies corroborate its value to oral bone health, revealing that subjects taking oral calcium (1,000 mg or more daily) and vitamin D (400 IU or less daily) supplementation had better clinical parameters of periodontal health and less periodontal attachment loss compared with individuals who did not take supplements. Furthermore, vitamin D deficiency at the time of periodontal surgery has been reported to negatively affect treatment outcomes for up to 1 year—an important suggestion that implicates vitamin D status as a valuable indicator to enhance postsurgical periodontal healing.

Hormone replacement therapy (HRT) has also been associated with a positive effect on the oral cavity. In a cohort of 488 elderly women, Krall and collaborators found an association between postmenopausal HRT and tooth retention. They also found an association between duration of HRT and tooth retention. The odds of being edentulous were reduced by 6% for each year of HRT therapy. Their study suggests that postmenopausal HRT protects against tooth loss and reduces the risk of edentulism.

**SUMMARY**

Although the causality between systemic bone loss and oral bone loss has not been fully elucidated, the current evidence demonstrates a plausible association between the two disease entities. Studies suggest that individuals with either systemic or oral bone loss should be closely managed with a clinical protocol that minimizes further deterioration of systemic or oral bony structures. Additional ran-
domized, controlled clinical trials are needed to clarify the causality and/or association between systemic and oral bone loss.

Acknowledgment
This work has been supported by NIH/NIDCR DE 13397 and DE 19872. The authors thank Mr. Kenneth Rieger and Mr. Chris Jung for their assistance with the figures.

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CHAPTER 12
Periodontitis and Rheumatoid Arthritis
P. Mark Bartold, Angelo J. Mariotti

INTRODUCTION
Two of the most common chronic inflammatory diseases affecting humans are periodontitis and rheumatoid arthritis. Both conditions are characterized by an exuberant inflammatory reaction in the local tissues associated with significant soft and hard tissue destruction. Furthermore, these conditions have similar patterns of natural history, and their pathogenesis—orchestrated by immunogenetics, cellular infiltration, enzymes, and cytokines—is similar. It is not surprising that the treatment and management implications of both periodontitis and rheumatoid arthritis include treatment of the clinical symptoms, modulation of the inflammatory response, and surgical options.

Onset of inflammation in periodontitis is related to host responses to bacteria within the subgingival biofilm, but the offending stimulus in rheumatoid arthritis remains unknown. Nonetheless, given the very similar pathologic processes, when periodontitis and rheumatoid arthritis coexist in the same patient, the plausibility of a common underlying pathogenic mechanism (not etiology) is worthy of further consideration.

Since this chapter was first published in 2010, there has been increasing interest and activity in investigating the association between periodontal disease and rheumatoid arthritis. This revised chapter provides an updated commentary using new literature published from 2008 to March 2013. During this time, 54 scientific articles (not including reviews) were identified as providing either confirmatory or new knowledge to this field. This chapter’s aim is to provide an update on the association between these two chronic inflammatory diseases.

The learning objectives for this chapter are:
1. Understand the potential associations between rheumatoid arthritis and periodontitis.
2. Explore the various hypotheses underlying the association between oral health, periodontal disease, and rheumatoid arthritis.
3. Understand the clinical relevance of such an association.

PERIODONTAL DISEASES
Although periodontal diseases manifest as a wide variety of inherited and acquired conditions affecting the periodontium, gingival diseases and destructive periodontal diseases (e.g., chronic periodontitis) comprise the majority of periodontal conditions. Plaque-induced gingivitis, as its name suggests, is confined to the gingival tissues, whereas the various forms of periodontitis affect all components of the periodontium (gingival, alveolar bone periodontal ligament, and cementum). In general, both conditions demonstrate all the classic signs and symptoms of chronic inflammation, including redness and swelling of the tissues, loss of architectural form, and reduced function (Figure 1). If the inflammatory response is not contained by the host, or is left untreated, then inflammatory destruction can be so severe as to put the teeth at risk, with tooth loss as the possible outcome of periodontal disease. The diagnosis of gingivitis or periodontitis is largely based on the results of a dental and medical history and of a clinical examination investigating parameters such as pocket depth, gingival inflammation, clinical attachment loss, furcation involvement, tooth mobility, radiographic evidence of bone loss, and tooth loss. Although a plethora of laboratory
Figure 1. Clinical and Radiographic Appearance of Periodontitis and Rheumatoid Arthritis

A. Clinical appearance of chronic periodontitis.
B. Radiographic appearance of chronic periodontitis.

C. Clinical appearance of rheumatoid arthritis.
D. Radiographic appearance of rheumatoid arthritis.

diagnostic tests have been proposed, to date, none has proved to be particularly useful.

Currently, periodontitis is considered to be a family of related diseases that may differ in their natural history, cause, rate and pattern of progression, and response to treatment. Etiologic, genetic, and environmental factors are thought to account for this variability. The critical factor in establishing the presence of periodontitis is the development of a subgingival bacterial biofilm. However, note that although the bacterial infection is necessary, it is not sufficient for the disease to develop, and many other factors must be present for overt periodontitis to become clinically evident.

**RHEUMATOID ARTHRITIS**

Rheumatoid arthritis is a chronic inflammatory disease and, like periodontal disease, demonstrates the classic signs of inflammation—swelling, pain, heat, and loss of function. Clinically, this condition is characterized by joint swelling, joint tenderness to palpation, morning stiffness, severe motion impairment and progressive degeneration of synovial-lined joints, and radiographic evidence of joint changes (see Figure 1).

Onset of rheumatoid arthritis can be acute or subacute and may include a polymorphic onset, monoarticular presentation (both slow and acute forms), extra-articular synovitis (tenosynovitis, bursitis), polymyalgia-like onset, and general symptoms (malaise, fatigue, weight loss, fever). Several laboratory tests assist in the diagnosis of rheumatoid arthritis, which include measurement of erythrocyte sedimentation rate, acute-phase proteins, plasma viscosity, and measurement of citrullinated proteins. Of these, erythrocyte sedimentation rate and serum C-reactive protein levels provide the best information about the acute-phase response. C-reactive protein levels correlate well
with clinical assessment and radiographic changes. Recently, a test that is positive for citrullinated peptides has been established, with its high sensitivity and specificity, and is very close to a diagnostic test for rheumatoid arthritis. Historically, the extent of anatomic changes occurring in joints of patients with rheumatoid arthritis has been assessed by radiography. More recently, ultrasonography and magnetic resonance imaging have gained acceptance for studying joint, tendon, and bursal involvement in those with rheumatoid arthritis. The clinical course of rheumatoid arthritis fluctuates, and its prognosis is unpredictable. In most situations, rheumatoid arthritis is considered a multifactorial disease, resulting from a combination of host, environmental, and genetic influences.

**TYPES OF RHEUMATOID ARTHRITIS AND PERIODONTITIS**

In general, rheumatoid arthritis can be classified into three types, depending on its manifestation and the patient’s response to treatment: self-limited, easily controlled, and progressive. It appears that for most people diagnosed with rheumatoid arthritis, disease progression is inevitable. Even after treatment with second-line medications, only a very small percentage of patients undergo remission of longer than 3 years. Moreover, most patients experience disease progression while taking these medications. In general, patients with rheumatoid arthritis have a number of poor prognostic indicators (Table 1). This implies that they have significant systemic impairment of the inflammatory and immune responses, which would normally be protective against such a disease.

As with rheumatoid arthritis, periodontitis manifests in three general forms: rapid progression, moderate progression, and no progression of periodontal disease. More recently, these forms have been termed aggressive or chronic and may exist in either stable or active disease.

**INFLAMMATION**

In both rheumatoid arthritis and periodontitis, inflammation is likely initiated by antigen stimulation (in the form of peptide or virulence factors), and the subsequent cascade of acute and chronic inflammation leads to a vicious cycle of continuous release of proinflammatory mediators perpetuated by the host’s own cells. Both the resident cells (synovial cells in rheumatoid arthritis; keratinocytes, fibroblasts, and osteoblasts in periodontitis) and the migrating inflammatory cells all are active players responsible for the

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**Table 1. Disease Activity in Periodontitis and Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Periodontitis</th>
<th>Rheumatoid Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well-Maintained Periodontitis</strong></td>
<td><strong>Self-limiting Rheumatoid Arthritis</strong></td>
</tr>
<tr>
<td>Periodontitis commences but, by following simple treatment, can be contained, and with appropriate maintenance, very little progression occurs.</td>
<td>After commencement of the disease it does not progress to more severe forms.</td>
</tr>
<tr>
<td><strong>Downhill Periodontitis</strong></td>
<td><strong>Easily Controlled Rheumatoid Arthritis</strong></td>
</tr>
<tr>
<td>Established periodontitis can be largely controlled with a combination of simple and complex treatments. Some further progression may occur but is usually small.</td>
<td>When the disease becomes established, its progression can be largely controlled through simple treatments such as first-line medications.</td>
</tr>
<tr>
<td><strong>Extreme Downhill Periodontitis</strong></td>
<td><strong>Progressive Rheumatoid Arthritis</strong></td>
</tr>
<tr>
<td>Once established and despite various treatment protocols, the disease progresses over time (not necessarily in a linear manner) and may even result in tooth loss.</td>
<td>After becoming established, the disease continues to progress and cause significant joint damage. Advanced treatments such as second-line medications and disease-modifying antirheumatic drugs are of little help in stopping disease progression.</td>
</tr>
</tbody>
</table>

Adapted from Mercado et al., 2003.
destruction observed in these two chronic inflammatory diseases (Figure 2).

During the pathogenesis of both periodontitis and rheumatoid arthritis, an abundant release of cytokines and other proinflammatory mediators occurs (Table 2). Although these mediators are present during normal tissue homeostasis, it is during inflammatory processes, as seen in periodontitis and rheumatoid arthritis, that they become uncontrolled and tissue destruction ensues. However, the precise molecular and cellular mechanisms controlling the release and action of these molecules are still poorly understood.

Cytokines released by lymphocytes, macrophages, and fibroblasts are different and are responsible for specific aspects of the inflammatory reaction. Though involved in the initiation of immune responses, these cytokines have a wide range of effects on many cells, leading to cell proliferation and increased tissue destruction.

Tissue damage in periodontitis and rheumatoid arthritis is mainly orchestrated by cytokines and enzymes released by resident and migrating cells that act via direct and indirect means. The enzymes degrade most extracellular matrix proteins and are largely responsible for matrix destruction seen in periodontitis and rheumatoid arthritis. The major enzymes responsible for tissue destruction are the matrix metalloproteinases (MMPs). These constitute a very broad family of enzymes with a variety of substrates and functions (Table 3). The cells that release MMPs in periodontitis and rheumatoid arthritis are polymorphonuclear leukocytes (PMNs), monocytic phagocytes, and fibroblasts. Both interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α) may induce the production of collagenase and other neutral proteases by most of these cells.

For both rheumatoid arthritis and periodontitis, disease progression occurs as a result of very high tissue levels of IL-1β and TNF-α and low levels of cytokines such as

**Figure 2.** Histologic Appearance of Inflamed Gingival and Synovial Tissues

![Histologic appearance of inflamed gingival (A) and synovial (B) tissues. Note heavy inflammatory cell infiltrates in both specimens. Histologic appearance of bone resorption occurring in periodontal (C) and rheumatoid (D) tissues. Note areas of active bone resorption associated with osteoclasts (arrows).](image-url)
Table 2. Cytokines Involved in Periodontitis and Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Properties</th>
</tr>
</thead>
</table>
| Chemokines | Produced by: macrophages, endothelium, fibroblasts, platelets, T cells  
Functions:  
Leukocyte chemotaxis, activation |
| IFN-α and IFN-β | Produced by: macrophages (α), fibroblasts (β)  
Enhanced by: bacterial endotoxin, TNF-α, IL-1  
Functions:  
All cells: antiviral state, increased class I MHC expression  
NK cells: activation |
| IFN-γ | Produced by: NK cell, T cells  
Enhanced by: IL-2  
Functions:  
Macrophages: activation of microbicidal function  
Stimulation of some antibody responses |
| IL-1 | Produced by: macrophage, endothelium, epithelium  
Induced by: bacterial endotoxin, leukotrienes, C5a, TNF, IL-6  
Functions:  
Endothelial cell activation: inflammation, coagulation  
PMN: activation  
Hypothalamus: fever |
| IL-10 | Produced by: macrophages, T cells  
Functions:  
Macrophages inhibition of IL-12 production  
Reduced expression of co-stimulators and class II MHC molecules |
| IL-12 | Produced by macrophages, dendritic cells  
Functions:  
NK and T cells: IFN-γ synthesis, increased cytolytic activity  
T cells: Th1 differentiation |
| IL-15 | Produced by: macrophages  
Functions:  
NK cells: proliferation  
T cells: proliferation |
| IL-18 | Produced by: macrophages  
Functions:  
NK and T cells: synthesis of IFN-γ |
| IL-6 | Produced by: macrophages, endothelium, T cells  
Induced by: bacterial endotoxin, leukotrienes, C5a, TNF, IL-6  
Functions:  
Liver: acute-phase proteins  
B cells: proliferation of antibody-producing cells |
| TNF | Produced by: macrophages, T cells  
Induced by: bacterial endotoxin, viruses and protozoa, C5a, immune complexes, substance P, IL-1, IL-2, TNF-α  
Functions:  
Endothelial cell activation: inflammation, coagulation  
PMN: activation  
Hypothalamus: fever  
Liver: acute-phase proteins  
Muscle, fat: catabolism |
IL-10 and transforming growth factor β, which suppress the immunoinflammatory response. In addition, an imbalance between tissue inhibitors of metalloproteinases (TIMPs) and MMPs secreted by macrophages, fibroblasts, and other resident and inflammatory cells is characteristic of the active phases of both rheumatoid arthritis and periodontitis.

Bone destruction is a common finding in periodontitis and rheumatoid arthritis. This occurs as a result of disruption to the normally balanced processes of bone resorption and bone formation. The major mediators of bone resorption are prostaglandin E₂ (PGE₂), IL-1, TNF-α, and IL-6.

In both periodontitis and rheumatoid arthritis, the immune response is regulated by genes that control T-cell responses to foreign antigens. In this way the nature of the protective antibody response as well as the magnitude of tissue-destructive inflammatory responses are determined.

**ROLE OF GENETICS**

The role of genetics in periodontitis and rheumatoid arthritis is of considerable importance. For both chronic periodontitis and rheumatoid arthritis, there is considerable variation in clinical manifestation of the disease. Much of this can be accounted for by genetic factors. Many differences in disease manifestations can be related to the overexpression or underexpression of numerous cytokines and other inflammatory mediators. Of these, IL-1, TNF, and PGE₂ have been found to be under strong genetic control. Numerous studies have been published concerning the so-called “hyper-responsive monocyte genetic traits,” which have common genetic regions that influence the susceptibility to inflammatory diseases. Typical of this trait is the overproduction of proinflammatory mediators such as IL-1β, TNF-α, and PGE₂ and is typically seen in patients with aggressive periodontitis. The concept of a monocytic hypersecretory state has also been described for patients with rheumatoid arthritis.

Many of the genes that regulate the cytokine profiles and responses of monocytes have been mapped to the HLA-DR region of chromosome 5 in the area of the TNF-β genes. Because both rheumatoid arthritis and periodontitis have been associated with this HLA complex, a common genetic basis exists for the observed monocyte trait, linking rheumatoid arthritis and periodontitis.

**ENVIRONMENTAL FACTORS**

For some time, the clinical manifestation of chronic diseases such as periodontitis and rheumatoid arthritis have been recognized as being significantly influenced by environmental or “modifying” factors. These factors are anything that might modify or alter the host inflammatory response, such as demographic, socioeconomic, lifestyle, diet, hormonal, and psychological variables. Since genetic factors may account for up to 50% of the risk for both periodontitis and rheumatoid arthritis, other factors, including environmental influences and gene–environment interactions, must explain the rest.

Of the environmental risk factors identified to date, smoking is probably the single most important environmental factor making an impact on many chronic diseases. Through its adverse effects on the cardiovascular system, immune cell function, and general tissue physiology, it is not surprising that smoking is considered a major risk factor for the development of both rheumatoid arthritis and periodontitis.

Another environmental factor of interest is socioeconomic status. This may be a significant factor in the outcome of many chronic diseases, including both rheumatoid arthritis and periodontitis. The reasons are not entirely clear; although suggestions have been made that persons from lower socioeconomic status may be less compliant
<table>
<thead>
<tr>
<th>Protein</th>
<th>Collagenous Substrates</th>
<th>Noncollagenous ECM Substrates</th>
<th>Nonstructural ECM Component Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-1</td>
<td>Collagen types I, II, III, VII, VIII, X, and gelatin</td>
<td>Aggrecan, casein, nidogen, serpins, versican, perlecan, proteoglycan link protein, and tenasin C</td>
<td>α1-antichymotrypsin, α2-antiprotease inhibitor, IGFBP-3, IGFBP-5, IL-1, L-selectin, ovostatin, recombinant TNF-α peptide, and SDF-1</td>
</tr>
<tr>
<td>MMP-2</td>
<td>Collagen types I, IV, V, VII, X, XI, XIV, and gelatin</td>
<td>Aggrecan, elastin, fibronectin, laminin, nidogen, proteoglycan link protein, and versican</td>
<td>Active MMP-9, active MMP-13, FGF R1, FGF-BP3, FGF-BP5, IL-1β, recombinant TNF-α peptide, and TGF-β</td>
</tr>
<tr>
<td>MMP-3</td>
<td>Collagen types II, IV, IX, X, and gelatin</td>
<td>Aggrecan, casein, decorin, elastin, fibronectin, laminin, nidogen, perlecan, proteoglycan, proteoglycan link protein, and versican</td>
<td>α1-antichymotrypsin, α2-protease inhibitor fibrinogen, IGFBP-3, L-selectin, ovostatin, pro-HB-EGF, pro-IL-1β, pro-MMP-1, pro-MMP-8, pro-MMP-9, pro-TNF α, and SDF-1</td>
</tr>
<tr>
<td>MMP-7</td>
<td>Collagen types I, II, III, IV, and X</td>
<td>Aggrecan, casein, elastin, enaectin, laminin, and proteoglycan link protein</td>
<td>β1 integrin, decorin, defensin, E-cadherin, Fas-L, plasminogen, pro-MMP-2, pro-MMP-7, pro-TNF α, transferrin, and syndecan</td>
</tr>
<tr>
<td>MMP-8</td>
<td>Collagen types I, II, III, V, VII, VIII, X, and gelatin</td>
<td>Aggrecan, laminin, and nidogen</td>
<td>α1-antiplasmin and pro-MMP-8</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Collagen types IV, V, VII, X, and XIV</td>
<td>Fibronectin, laminin, nidogen, proteoglycan link protein, and versican</td>
<td>CXCL5, IL-1β, IL2-R, plasminogen, pro-TNF α, SDF-1, and TGF-β</td>
</tr>
<tr>
<td>MMP-10</td>
<td>Collagen types III, IV, V, and gelatin</td>
<td>Fibronectin, laminin, and nidogen</td>
<td>Pro-MMP-1, pro-MMP-8, and pro-MMP-10</td>
</tr>
<tr>
<td>MMP-11</td>
<td>Elastin</td>
<td>Laminin</td>
<td>α1-antiprotease inhibitor, and IGFBP-1</td>
</tr>
<tr>
<td>MMP-12</td>
<td>Elastin</td>
<td>Plasminogen</td>
<td></td>
</tr>
<tr>
<td>MMP-13</td>
<td>Collagen types I, II, III, IV, V, IX, X, XI, and gelatin</td>
<td>Aggrecan, fibronectin, laminin, perlecan, and tenasin</td>
<td>Plasminogen activator 2, pro-MMP-9, pro-MMP-13, and SDF-1</td>
</tr>
<tr>
<td>MMP-14</td>
<td>Collagen types I, II, III, and gelatin</td>
<td>Aggrecan, dermatan sulphate proteoglycan, fibrin, fibronectin, laminin, nidogen, perlecan, tenasin, and vitronectin</td>
<td>αβ, integrin, CD44, gC1qR, pro-MMP-2, pro-MMP-13, pro-TNF α, SDF-1, and tissue transglutaminase</td>
</tr>
<tr>
<td>MMP-15</td>
<td>Collagen types I, II, III, and gelatin</td>
<td>Aggrecan, fibronectin, laminin, nidogen, perlecan, tenasin, and vitronectin</td>
<td>Pro-MMP-2, pro-MMP-13, and tissue transglutaminase</td>
</tr>
<tr>
<td>MMP-16</td>
<td>Collagen types I, III, and gelatin</td>
<td>Aggrecan, casein, fibronectin, laminin, perlecan, and vitronectin</td>
<td>Pro-MMP-2 and pro-MMP-13</td>
</tr>
<tr>
<td>MMP-17</td>
<td>Gelatin</td>
<td>Fibrin and fibronectin</td>
<td></td>
</tr>
<tr>
<td>MMP-19</td>
<td>Collagen types I, IV, and gelatin</td>
<td>Aggrecan, casein, fibronectin, laminin, nidogen, and tenasin</td>
<td></td>
</tr>
<tr>
<td>MMP-20</td>
<td>Aggrecan, amelogenin, and cartilage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-21</td>
<td></td>
<td></td>
<td>α1-antitrypsin</td>
</tr>
<tr>
<td>MMP-23</td>
<td>Gelatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP-24</td>
<td>Gelatin</td>
<td>Chondroitin sulfate, dermatan sulfate, and fibronectin</td>
<td>Pro-MMP2 and pro-MMP-13</td>
</tr>
<tr>
<td>MMP-25</td>
<td>Collagen type IV and gelatin</td>
<td>Fibrin and fibronectin Pro-MMP-2</td>
<td></td>
</tr>
<tr>
<td>MMP-26</td>
<td>Collagen type IV and gelatin</td>
<td>Casein, fibrinogen, and fibronectin</td>
<td>β2-protease inhibitor</td>
</tr>
<tr>
<td>MMP-28</td>
<td>Casein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Many of these substrates are found in both the periodontium and the synovium. Adapted from Somerville RPT, Olsander SA, Apte SS. Matrix metalloproteinases: old dogs with new tricks. Genome Biol 2003;4:216-26.
with regard to their general healthcare and have less access to the full range of health-
care. However, these explanations do not fully explain this relationship. In this regard,
allostatic load has also been proposed to de-
scribe dysregulation of physiologic adaptive
processes, including immune function, which
in health maintain stability to stressors. It
has been proposed that allostatic load may
follow a socioeconomic gradient that is in part
responsible for inequalities in chronic dis-
ases such as periodontitis and rheumatoid
arthritis. In this model, low socioeconomic
status results in increased exposure to psy-
chosocial stress, which activates primary allo-
static mediators, including a wide range of
inflammatory mediators. Under these condi-
tions, dysregulation of a range of immu-
nomodulatory functions occurs, which
can lead to alterations in the extent and
severity of chronic diseases.

PERIODONTITIS AND RHEUMATOID
ARTHRITIS—COMPLEX OR
ECOGENETIC DISEASES

In recent times, periodontitis and rheumatoid
arthritis have been considered “complex” or
“ecogenetic” diseases. A complex disease is
a condition with a genetic component that
does not follow the simple single-gene domi-
nant or single-gene recessive mendelian law
(Table 4). Since both inherited genetic varia-
tion and environmental factors such as
smoking, hygiene, and pathogenic bacteria in-
teract to determine a person’s risk for peri-
donitis and rheumatoid arthritis, these two
diseases fit the definition of complex diseases.
Hence, in response to an initiating event in
these diseases, environmental agents interact
with genetic factors to influence disease sus-
cceptibility (Figure 3). Such interactions initiate
and regulate immunoinflammatory reactions
that ultimately manifest as the clinical signs of
rheumatoid arthritis or periodontitis. Al-
though our understanding of the role of
dental plaque as being pivotal in the initiating
events for periodontal disease is well under-
stood, the initiating events for rheumatoid
arthritis are less clear.

Interactions between environmental risk
factors and genetics are now providing us
with valuable clues as to the nature of
complex diseases such as periodontitis and
rheumatoid arthritis. One of the best-recog-
nized environmental risk factors for both dis-
eases is smoking. A relation between
smoking and HLA-DR–shared epitope
genes, the main genetic risk factors for
rheumatoid arthritis and periodontitis, has
been shown to impart increased risk for
both rheumatoid arthritis and periodontitis.
From these types of studies, it is possible to
define the various environmental risk factors
that, in certain genetic contexts, will initiate
adverse immune reactions, ultimately leading
to the clinical symptoms in various subsets
of susceptible patients.

In recent years there has been consider-
able interest in identifying single nucleotide
polymorphisms (SNPs) and statistical genetic
strategies, such as haplotype mapping, to
identify genes that may be important in
complex diseases such as rheumatoid arthri-
tis and periodontitis. Even though simple
one-to-one mapping between disease gene
and disease phenotype does not occur in

Table 4. Features of Complex or
Ecogenetic Diseases

- Interact with ecology, molecular genetics, toxicol-
  ogy, public health medicine, and environmental
  epidemiology.
- Are common chronic diseases with adult onset
  that show familial aggregation but do not follow
  mendelian family patterns.
- Appear to be caused by an unknown number of
  multiple genes, which interact with environmental
  factors.
- Only a small percentage (less than 1%-7%) of
  those affected show a single mutant gene transm-
 itted by mendelian inheritance with characteristic
  transmission.
- Often have an earlier age of onset and more
  severe clinical manifestations.
Figure 3. Disease Interactions Between Periodontitis and Rheumatoid Arthritis

The periodontal diseases and rheumatoid arthritis are classified as ecogenetic or complex diseases involving intricate interactions among host responses, environmental factors, etiologic factors, and genetics.

complex disease, this should not reduce the importance of trying to identify genes that determine individual differences in disease susceptibility for rheumatoid arthritis and periodontitis. An understanding and identification of gene mutations in complex diseases, using genome-wide association studies, may account for genetic sources of variation in disease risk and should enable us to better understand environmental effects.

SIGNIFICANT INTERRELATIONSHIPS BETWEEN PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS AND OTHER SYSTEMIC CONDITIONS
The focus of this volume is the association of periodontal diseases with a large number of systemic conditions, including diabetes, preterm low-birth-weight infants, cardiovascular disease, pulmonary disease, obesity, and osteoporosis. In the context of this chapter, considering the potential interaction between periodontitis and rheumatoid arthritis, it is of interest that all these diseases have also been associated with persons suffering from rheumatoid arthritis (Table 5). Even after

Table 5. Systemic Conditions Reported to Be Associated with Both Periodontitis and Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Obstetric problems</td>
</tr>
<tr>
<td>Pulmonary conditions</td>
</tr>
<tr>
<td>Renal conditions</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
</tbody>
</table>
accounting for variable confounders, including various medications, many studies have been able to demonstrate significant associations between rheumatoid arthritis and systemic conditions. The underlying feature seems to be dysregulated chronic inflammation in both periodontitis and rheumatoid arthritis.

**WHAT IS THE EVIDENCE FOR A RELATIONSHIP BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS?**

For over 80 years, reports have existed in the literature concerning a possible relation between rheumatoid arthritis and periodontitis. A number of reviews and commentaries on this topic have been published.20-25

**Clinical Reports**

Several studies have reported little or no association between rheumatoid arthritis and periodontal disease; however, most of the literature on this topic supports such an association. Although the least convincing in terms of scientific design, simple pilot studies analyzing data obtained from self-reported illnesses have indicated a higher incidence of self-reported rheumatoid arthritis in patients with periodontitis.22

Many case-control studies have also been carried out. Since our last review in 2008, 16 additional case reports have been published, 14 of which supported a positive relation between rheumatoid arthritis and periodontal disease and two did not support an association. For these studies, periodontal conditions were variously measured as number of teeth missing, gingival bleeding, attachment loss, probing pocket depth, and radiographic bone loss.

Studies also have investigated several clinical and laboratory parameters to further ascertain whether a relation exists between periodontitis and rheumatoid arthritis. These parameters include cytokine profiles, inflammatory mediators, HLA-DR antigens, and hormones. All these studies have supported the notion that periodontitis and rheumatoid arthritis are interrelated, which has led various authors to conclude that inflammation (and its dysregulation) may be the central link between periodontitis and rheumatoid arthritis. Recent studies have demonstrated that increased inflammatory mediator levels in rheumatoid arthritis patients, despite long-term use of anti-inflammatory drugs, suggests a propensity in these patients to overproduce a number of inflammatory mediators. However, one recent study has refuted such a conclusion.

**Does Periodontal Treatment Influence Rheumatoid Arthritis?**

As early as 1985, a case study was published reporting remission of rheumatoid arthritis after periodontal treatment. This study remained largely forgotten until the publication of two additional studies that indicated that periodontal treatment could reduce the severity of rheumatoid arthritis. More recently, three studies indicate that periodontal therapy has the potential to reduce the severity of active rheumatoid arthritis. This effect may be independent of any medications used to control the arthritic condition. Although these studies are interesting, they have involved relatively few subjects and highlight the need for larger well-controlled randomized clinical trials to address this important question.

**Does Rheumatoid Arthritis Treatment Influence Periodontal Disease?**

If the relation between rheumatoid arthritis and periodontal disease is truly bidirectional, then not only should periodontal treatment influence the outcomes of the clinical signs and symptoms of rheumatoid arthritis, but the converse should also hold true. Several studies have been published reporting the influence of various rheumatoid therapies on
periodontal conditions in patients with both rheumatoid arthritis and periodontal disease. Many of these studies have considered the effect of medications used in the management of rheumatoid arthritis such as blockers of TNF-α and IL-6. To date, data are limited to suggest that such agents can reduce local periodontal inflammation in rheumatoid arthritis patients with periodontitis.70

**Animal Models**

Further support for a significant relation between periodontitis and rheumatoid arthritis has been highlighted in a number of animal studies. Of these studies, two have demonstrated the very intriguing finding that induction of experimental arthritis can lead to alterations in the periodontal tissues. Conversely, one of these studies demonstrated that induction of experimental periodontitis can lead to synovial joint changes consistent with the development of arthritis.71,72

**Significance of These Studies**

Careful assessment of the data reported from many of the previously mentioned studies allows us to make some important observations. First, few of these studies support the commonly held tenet that patients with rheumatoid arthritis have impaired oral hygiene (judged by plaque and bleeding scores) because of their “disability.” It is variously reported that oral hygiene is no different between rheumatoid arthritis patients with periodontitis and non-rheumatoid arthritis patients with periodontitis.73,74

Another important observation from recently published studies is that those with severe rheumatoid arthritis are more likely to suffer from advanced periodontitis and vice versa. However, the association seems to be in favor of rheumatoid arthritis making an impact on periodontitis (RR: 4.1) rather than periodontitis making an impact on rheumatoid arthritis (RR: 1.5).73 Also, it is important for longitudinal studies of this association to be carried out to establish the temporal sequence. Finally, from the studies published to date, the influence of medications, which rheumatoid arthritis patients may be taking, on periodontitis is interesting. Many, if not all, of these medications are anti-inflammatory agents and, as such, have the potential to suppress periodontal inflammation and affect periodontal disease progression. Nonetheless, reports indicate that significant periodontal destruction can still be seen in patients who may be taking anti-inflammatory medications for rheumatoid arthritis.73,74 It has been proposed that before symptoms of rheumatoid arthritis develop, periodontitis was most likely also developing and not detected.23 Thus, in an analysis of the association between rheumatoid arthritis and periodontitis, consideration of disease duration (for both periodontal and rheumatoid) is a critical factor. Future studies concerning the relation between periodontitis and rheumatoid arthritis should address and document the disease with regard to the severity and duration of both diseases.

**PROPOSED MECHANISMS FOR THE RELATION BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS**

Several mechanisms for a relation between periodontitis and rheumatoid arthritis have been proposed. The principal mechanisms may involve either changes to blood vessels or infection of host tissues.

**Vascular Alterations**

Recent investigations into the association between osteoclast activation and vascular damage suggest a common pathway in the development of periodontitis and rheumatoid arthritis. It has been hypothesized that both rheumatoid arthritis and periodontitis share common molecular pathways within the RANK/OPG/TRAIL (receptor activator of NF-kappa B) axis whereby a decrease in os-
te protegerin (OPG) leads to reduced vascular protection. In addition, increases in RANKL and TRAIL levels within inflamed tissues may result not only in the possible development of vascular damage but also in activation of osteoclasts and subsequent bone resorption.

Another vascular model proposes that microvascular involvement is one of the first stages of a number of chronic diseases, such as periodontitis and rheumatoid arthritis. In this model, reduced caliber of capillaries and greater number and elongated capillaries are noted in both periodontal tissues and rheumatoid synovium.

**Bacterial Infection**

Data from several animal models demonstrate that arthritis can develop secondarily to different stimuli and through different effector pathways, including exogenous infections. If the observations in animal models are also applicable to human rheumatoid arthritis, we might anticipate that different types of infections as well as other environmental exposures with capacity to induce excessive proinflammatory cytokines in genetically susceptible persons may contribute to disease either together with some autoimmune reaction or by themselves.

Many periodontal pathogens exhibit characteristics similar to those of microorganisms suspected to induce rheumatoid arthritis in a genetically susceptible host. Periodontal pathogens incite a chronic continuous inflammation within the periodontal tissues and also serve as an abundant supply of lipopolysaccharides. Thus, the possibility that an ongoing periodontitis can trigger or exacerbate rheumatoid arthritis in genetically susceptible individuals is biologically plausible. A number of studies have reported elevated serum antibodies to a number of periodontopathic bacteria including *Porphyromonas gingivalis*, *Prevotella intermedia*, *Prevotella melaninogenica*, *Bacteroides forsythus*, and *Aggregatibacter actinomycetemcomitans*.

Elevated antibodies and DNA for *B. forsythus*, *P. intermedia*, *P. gingivalis*, and *Fusobacterium nucleatum* have also been found in synovial fluid. Taken together, these findings suggest the possibility that periodontal pathogens (either whole or DNA) may translocate from the periodontal tissues to the synovium, where they could then exacerbate the inflammatory processes occurring within rheumatoid joints.

**Citrullination—the Missing Link?**

A novel hypothesis for the development of rheumatoid arthritis via the humoral response to oral bacteria found in periodontitis has been proposed. In this model, an autoimmune disease to proteins partially altered by bacterial enzymes in genetically susceptible individuals may develop (Figure 4). Central to this hypothesis is the appearance of rheumatoid factors and anticyclic, citrullinated peptide autoantibodies during

**Figure 4. The Humoral Immune Response to Citrullination**

<table>
<thead>
<tr>
<th>Periodontal infection</th>
<th>Citrullination of proteins by <em>P. gingivalis</em> or inflammation</th>
<th>Production of autoantibodies to citrullinated proteins</th>
<th>Cross-reactivity with cartilage components</th>
<th>Autoimmunity to self-antigens</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
</table>

Citrullination occurring within the periodontal tissues may provide a stimulus for development of rheumatoid arthritis or exacerbation of the inflammatory process in rheumatoid joints.
the development of rheumatoid arthritis. The production of deimination enzymes by periodontal pathogenic bacteria, such as *P. gingivalis*, can induce autoantibodies, allowing a link between periodontal infection and the development of rheumatoid arthritis.

Recently, two studies have identified citrullinated proteins in inflamed periodontal tissues. These findings complement another recent report detailing the autoantibody repertoire in periodontitis in which the induction of autoimmunity to citrullinated proteins may be related to citrullination occurring within the periodontal tissues. These findings raised the intriguing question as to whether citrullination occurs in the periodontium during the inflammatory process. If this is the case, then the possibility exists that priming anti-CCP (anti-cyclic citrullinated peptide) antibodies may be produced during the development of periodontitis. If a later event such as joint inflammation results in citrullination, then, in a primed individual, the subsequent antibody response could be very robust. This fits well with the so-called two-hit model proposed for the development of chronic inflammatory disorders such as rheumatoid arthritis. Such a response is in keeping with recent observations that experimental animals with a preexisting chronic infection or periodontitis develop experimental arthritis at a faster and more pronounced rate than nonprimed animals.

CLINICAL RELEVANCE OF AN ASSOCIATION BETWEEN PERIODONTITIS AND RHEUMATOID ARTHRITIS

The association between advanced rheumatoid arthritis and advanced periodontal destruction has significant clinical implications regarding the management of rheumatoid arthritis in patients who are at risk of also having periodontitis. Even though most clinical protocols for rheumatoid arthritis patients include an assessment for oral pathology, to date, these protocols do not routinely include a full periodontal assessment. Because many of the signs and symptoms of periodontitis are painless and subtle and may advance rapidly without the patient being aware of the problem, this aspect of clinical assessment has been overlooked. In light of current data, persons suffering from rheumatoid arthritis seem to have a higher risk of developing periodontal problems. Furthermore, early evidence has suggested that treatment for periodontitis can reduce the clinical symptoms of rheumatoid arthritis. Therefore, early intervention to prevent periodontal destruction occurring in those with rheumatoid arthritis should be considered to reduce the impact of rheumatoid arthritis.

CONCLUSIONS

For several decades it has been suspected that because periodontitis and rheumatoid arthritis share many common pathologic features, they may be clinically related or associated diseases. It is now becoming apparent, mainly from case-control and laboratory studies, that both disease severity and extent may be related among those suffering from both rheumatoid arthritis and periodontitis. Although causality between the two diseases is very unlikely, the fact that both diseases can make an impact on each other is becoming apparent. Indeed, emerging evidence suggests that both diseases can have an impact on the other in a bidirectional manner.

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**Supplemental Readings**


CHAPTER 12 Periodontitis and Rheumatoid Arthritis


REFERENCES


27. Yusof Z, Porter SR, Greenman J, Scully C. Levels of


51. Havemose-Poulsen A, Sorensen LK, Stoltze K, Bendtzen K, Holmstrup P. Cytokine profiles in peripheral blood and whole blood cell cultures asso-


circ 2007;37:229-35.


INTRODUCTION
Periodontitis is a chronic immunoinflammatory reaction to bacteria that reside within the subgingival plaque biofilm. In addition to pathogenic microorganisms in the biofilm, genetic and environmental factors contribute to the pathogenesis of this disease, which results in the destruction of the periodontal tissues and alveolar bone supporting the teeth. During these responses, complications or other influences may impact systemic health via bacteremia or dissemination of locally produced inflammatory mediators. Also, bacteremia has the potential to result in a general systemic inflammatory response. Moreover, locally produced inflammatory mediators disseminated into the circulation can result in increased levels of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukins 1 beta and 6 (IL-1β and IL-6), and prostaglandin E2 (PGE2), as well as acute-phase proteins such as C-reactive protein. This can result in a chronic inflammatory burden on distant organ systems.

Recent studies have demonstrated associations between periodontal disease and several systemic diseases, including cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, respiratory diseases, osteoporosis, and rheumatoid arthritis.

With increasing attention focused on oral/systemic interactions, studies have suggested that periodontal disease may be associated with increased cancer risk.¹ Interest for such an association stemmed from early studies that investigated the association of poor oral health and missing teeth on both oral cancer and cancer of other systemic organs. Although tooth loss may be a poor indicator of periodontal disease, it has been used as a major surrogate marker for this disease in older persons.² Indeed, tooth loss can be a result of either dental caries or periodontal diseases; however, age can also be a major contributing factor in these two conditions. Thus, in early studies, tooth loss in older persons was assumed to be a more likely result of periodontal disease than of caries. In more recent times, such assertions would almost certainly be challenged. Current understanding indicates that tooth loss in older persons may be a result of periodontal disease, but this association may not always be particularly strong. Therefore, it is surprising that very few studies investigating the role of oral health and cancer have undertaken specific periodontal assessments.

The potential interaction between cancer and periodontal disease is important, and many studies imply that a specific association between periodontitis and cancer (both oral and general) is feasible. However, larger, more defined studies are needed to determine whether the association can be confirmed and how this might impact our understanding of the etiology of various cancers, their prevention, and control.

In this review, studies address the association of general oral condition (e.g., oral hygiene, restorations, prostheses, tooth brushing), tooth loss, and periodontal disease with both oral cancer and cancers of other organs.

The educational objectives for this chapter are:
1. Understand the potential associations among oral health, periodontal disease, and various cancers.
2. Recognize the limitations of these studies with regard to confounding factors in risk assessment.
3. Explore the various hypotheses underlying the association among oral health, periodontal disease, and cancer.
ORAL HEALTH, PERIODONTITIS, AND ORAL CANCER
Since one of the earliest case-control reports on oral cancer was published more than 50 years ago, numerous studies have investigated the role of oral health and oral cancer (Table 1). Alcohol and smoking are considered two of the most important risk factors for oral cancer, but poor oral hygiene and poor dental status have also been reported to carry a significant risk for development of oral cancer.

Studies of the Relation Between General Oral Health and Oral Cancer
An early study investigating the role of dentition, diet, tobacco, and alcohol on risk for oral cancer was a case study by Graham et al.

Table 1. Summary of Findings from Studies Published to Date Showing Relation Between Oral Conditions and Oral Cancer

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Design</th>
<th>Tooth Loss</th>
<th>Poor Oral Hygiene</th>
<th>Gingival Bleeding</th>
<th>Poor Oral Condition</th>
<th>Irregular Check-ups Dental</th>
<th>Periodontal Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham et al., 1977</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
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</tr>
<tr>
<td>Zheng et al., 1990</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
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</tr>
<tr>
<td>Winn et al., 1991</td>
<td>Case-control</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Marshall et al., 1992</td>
<td>Case-control</td>
<td>Yes</td>
<td>Not significant</td>
<td>—</td>
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</tr>
<tr>
<td>Bundgaard et al., 1995</td>
<td>Case-control</td>
<td>Yes</td>
<td>—</td>
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<td>Yes</td>
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<tr>
<td>Schildt et al., 1998</td>
<td>Case-control</td>
<td>—</td>
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<tr>
<td>Velly et al, 1998</td>
<td>Case-control</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Talamini et al., 2000</td>
<td>Case-control</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Moreno-López et al., 2000</td>
<td>Case-control</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>No</td>
<td>—</td>
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<tr>
<td>Garrote et al., 2001</td>
<td>Case-control</td>
<td>Yes</td>
<td>—</td>
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<td>Yes</td>
<td>—</td>
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<tr>
<td>Campisi &amp; Margiotta, 2001</td>
<td>Male</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
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<tr>
<td>Balaram et al., 2002</td>
<td>Case-control</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
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<tr>
<td>Lissowska et al., 2003</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Tezal et al., 2005</td>
<td>NHANES</td>
<td>—</td>
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<td>Rosenquist et al., 2005</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Tezal et al., 2007</td>
<td>Case-control</td>
<td>—</td>
<td>—</td>
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<td>Yes</td>
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<tr>
<td>de Rezende et al., 2008</td>
<td>Case-control</td>
<td>No</td>
<td>—</td>
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<td>Yes</td>
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<tr>
<td>Divaris et al., 2010</td>
<td>Case-control</td>
<td>Yes</td>
<td>—</td>
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</table>
al. The case patients consisted of 584 men with cancer of the oral cavity at the Roswell Park Memorial Institute, Buffalo, New York. Controls at the same institute consisted of 1,222 males with no neoplastic diseases. Interviews were carried out to obtain information regarding dentition, diet, tobacco, and alcohol consumption.

From this study, a higher risk of developing cancer was reported in heavy smokers and heavy drinkers. Poor oral hygiene was also associated with increased risk for oral cancer. When controlled for other factors, each of these three factors demonstrated a higher risk. When combined, heavy smokers and heavy drinkers with a poor dentition had a risk for oral cancer 7.7 times higher than that of men with none of these features.

In another case-control study carried out in Beijing, Zheng and colleagues investigated the dentition and oral hygiene status for risk of oral cancer. The subjects consisted of 404 patients with histologically confirmed oral cancer and a similar number of control patients whose hospitalizations were for minor conditions. Subjects were interviewed to obtain information regarding alcohol use, tobacco use, dentition, and oral hygiene. Oral examination included recording the total number of teeth, jagged teeth, filled teeth, decayed teeth, and the presence of gingivitis or periodontal disease. After adjustment for tobacco smoking, alcohol intake, years of education, gender, and age, males who had lost teeth had an increased risk for oral cancer with an odds ratio (OR) of 2.4 (95% confidence interval [CI]: 1.3–4.5) for those with replacement teeth and an OR of 3.7 (CI: 2.2–6.4) for those with no tooth replacement. The data for females showed an even stronger effect of tooth loss on increased risk for oral cancer; with an OR of 5.6 (CI: 12.2–14.5) for those with replacement teeth and an OR of 8.3 (CI: 3.5–19.6) for those with no tooth replacement. When oral hygiene was assessed according to whether the teeth were brushed, men had an adjusted OR of 6.9 (CI: 2.5–19.4) and women an adjusted OR of 2.5 (CI: 0.9–7.5) for increased risk of oral cancer if they did not brush their teeth. Interpretation of the findings indicated that missing teeth and poor oral hygiene were risk factors for oral cancer independent of the known risks associated with smoking and alcohol consumption.

In a study aimed primarily at investigating the effect of mouthwash use on oral cancer, Winn et al. studied 1,114 oral cancer patients from four population-based registries in the United States. Control subjects (n = 1,268) were noncancerous individuals selected by random dialing to select individuals of suitable age and gender-matched status. Interviews were carried out to obtain information regarding tobacco use, alcohol use, diet, occupation, and oral health status. The oral health parameters included number of teeth, use of dentures, tooth brushing frequency, and the presence of bleeding gingiva. The presence of other oral diseases as well as the frequency, intensity, duration, and reason for use of mouthwashes were recorded. A highly significant relation between mouthwashes of high alcohol content and oral cancer was noted for both males (OR: 1.5; CI: 1.1–2.1) and females (OR: 2.0; CI: 1.3–3.1). In contrast to most other studies, this study found no relation between oral/dental conditions and oral cancer.

In another US investigation, Marshall and colleagues carried out a case-control study in three western New York counties to investigate the contribution of alcohol, dentition, and diet to oral cancer. The cohort consisted of 290 pathologically confirmed cases of oral cancer selected from hospital records, whereas matched controls were obtained through neighborhood matching. Case patients and controls were interviewed to gather information concerning smoking and tobacco use, alcohol consumption, dental history (i.e.,
tooth loss, tooth replacement, oral hygiene, and dental check-up practices), and diet. Compared with individuals who had lost no teeth, an increased risk for oral cancer was noted for those who had lost more than 11 teeth (OR: 3.9; CI: 1.3–11.3). When further analyzed, people who smoked cigarettes, drank alcohol, and had lost teeth without having them replaced had an increased risk for developing oral cancer (OR: 12.8; CI: 4.9–33.8). The effect of oral hygiene in this study was determined to be insignificant.

A population-based case-control study in a Danish population has examined whether the risk of oral squamous cell carcinoma could be related to occupation, marital status, dental status, and consumption of coffee, tea, alcohol, and tobacco. In this study, the cases consisted of 161 consecutively admitted patients with histologically verified intraoral squamous cell carcinoma. Four-hundred age- and gender-matched controls were selected from the neighborhood. Information was gathered by interview, and no clinical dental examination was carried out. After correcting for alcohol and tobacco consumption, dental status was found to be a significant factor associated with oral squamous cell carcinoma manifestation. Those with fewer than five teeth had an OR of 2.4 (CI: 1.3–4.1) compared with that of those with 15 or more teeth. Furthermore, individuals who had irregular dental check-ups had an OR of 2.1 (CI: 1.3–3.3) compared with that of those who had regular dental check-ups. Though significant, these findings were determined to be less important than tobacco or alcohol use with regard to risk for oral squamous cell carcinoma.

In a case-control study of a Swedish population, Schildt et al. investigated the association of oral infections and other dental factors with risk of oral cancer. For this study, 410 cases of oral cancer and 410 matched controls were sampled. All subjects received a mailed questionnaire concerning different exposure factors of interest for oral cancer including oral infections, dental prostheses, radiographic exposure, restorations, tooth loss, and presence of calculus. Recurrent oral infection was found to be associated with increased risk of oral cancer (OR: 3.8; CI: 2.1–6.9). Other dental factors such as restorations, dentures, and dental radiographs were of no significance.

In a study investigating the association between dental factors and risk of upper digestive tract cancer, Velly and colleagues studied 717 patients from three centers in Sao Paulo who had newly diagnosed carcinomas of the tongue, gingiva, floor of mouth, and other parts of the oral cavity. Controls (non-cancerous patients) were selected from the same institutions, and data were collected from two controls matched to each case on the basis of gender, 5-year age group, trimester of hospital admission, and study site. Information collected by interview included information on socioeconomic variables, health conditions, environmental and occupational exposures, tobacco and alcohol consumption, and diet and oral hygiene. The dental health information was obtained only by interview and included information concerning broken teeth, use of dentures and sores caused by dentures, and frequency of tooth brushing. The association between cancer and dental factors was assessed using a number of adjustments for a priori and empirical confounders, including tobacco and alcohol consumption, diet, and socioeconomic variables. The risk for all oral cancer in general was significantly associated with dentures (OR: 0.7; CI: 0.52–0.96), history of oral sores caused by dentures (OR: 0.91; CI: 0.6–1.3), broken teeth (OR: 1.42; CI: 1.1–1.9), and infrequent tooth brushing (OR: 2.2; CI: 1.6–3.1). After adjustment of several confounders and for all dental factors, only the association with tooth brushing frequency was significant (OR: 1.8; CI: 1.2–2.8 and OR: 1.7; CI: 1.1–2.8, respectively). When assessed on a subsite basis, only less-than-daily
tooth brushing was a risk for tongue cancer (OR: 1.3; CI: 0.6–3.0) and other parts of the mouth, including the gingiva (OR: 2.4; CI: 1.3–4.4). For laryngeal cancer, only broken teeth (OR: 1.8; CI: 1.3–2.7) and infrequent tooth brushing (OR: 1.9; CI: 1.2–2.9) were significant risk markers. For pharyngeal cancer, only infrequent tooth brushing (OR: 1.5; CI: 1.0–2.2) was determined to be a significant risk factor. The authors concluded that poor oral hygiene, due to infrequent tooth brushing and denture-related oral sores, were significant risk factors for cancer of the mouth and upper digestive tract, and that these associations were not due to insufficient controlling for confounding factors.

Talamini and colleagues\textsuperscript{11} carried out a case-control study on an Italian population investigating the effect of oral hygiene and dentition status on oral cancer risk. The cohort consisted of 132 first-incident persons with oral cancer identified in three northern Italy hospitals. One hundred and forty-eight hospital-based control subjects, who had been admitted for acute conditions unrelated to smoking or drinking habits, were also recruited for this study. Case patients and controls were interviewed to obtain information relating to sociodemographic characteristics, smoking and drinking habits, as well as dental information related to oral hygiene, gingival bleeding, mouthwash usage, wearing of dentures, and dental check-up history. A visual examination determined number of missing teeth, presence of calculus, decayed teeth, and mucosal condition. Gingival bleeding was found to be significant (OR: 3.9; CI: 1.2–12.6) when compared with those whose gingiva did not bleed at all. When the general oral condition was assessed as being poor on the basis of calculus, decayed teeth, and mucosal irritation, the risk for oral cancer had an OR of 4.5 (CI: 1.8–10.9) compared with those who had good oral condition. In contrast to previous studies, the number of missing teeth was not found to be a significant factor.

The role of tobacco, alcohol, and oral hygiene in the appearance of oral cancer was investigated in a case-control study by Moreno-López et al.\textsuperscript{12} For this study, the cases consisted of 75 histologically confirmed oral squamous cell carcinomas. The control group consisted of age- and gender-matched individuals in the same healthcare center who did not suffer from cancer and did not have any medical or oral disease or oral manifestation of any systemic disease. An interview was used to obtain information related to demographic variables, tobacco use, alcohol consumption, frequency of dental check-ups, and level of tooth brushing. No intraoral examination was carried out. Although no statistical significance could be found for dental visits, a significant relation to tooth brushing frequency indicated this to be a protective factor (OR: 0.31; CI: 0.18–0.56).

In a case-control study on a Cuban population, the effect of smoking, alcohol, food, oral hygiene, and sexually transmitted diseases on risk for oral cancer was evaluated. Garrote et al.\textsuperscript{13} compared 200 patients with cancer of the oral cavity and pharynx with 200 frequency-matched age and gender controls from the hospital. Interviews were held to obtain information regarding sociodemographic characteristics, smoking and alcohol use, prior occurrence of sexually transmitted infections, family history of cancer, and dietary information. Indicators of oral hygiene were self-reported via nine specific questions, whereas the number of missing teeth that had not been replaced and the general oral condition with regard to presence of calculus, decayed teeth, and mucosal irritation were evaluated visually by the interviewing dentist. After allowance for confounding factors such as education, smoking, and drinking habits, those with more than 16 missing teeth had a higher risk of having oral cancer (OR: 2.7; CI: 1.2–6.1). In addition, poor general oral condition was more common among cancer patients than controls (OR: 2.6; CI: 1.2–5.2).
In a population derived from three regions of India (Bangalore, Madras, and Trivandrum), Balaram et al. investigated the role of smoking, paan chewing, and oral hygiene on risk for oral cancer. In this study, 591 incident cases of oral cancer and 582 hospital controls that were frequency-matched by age and gender were studied. Information regarding smoking habits, paan chewing, and oral hygiene habits was obtained by interview. Visual oral inspection allowed assessment of missing teeth and general oral condition based on the presence of calculus, decayed teeth, and mucosal irritation. Regular dental check-ups were found to be protective for women but not for men (OR: 0.4; CI: 0.19–0.87). Significantly elevated risk for oral cancer for both genders was noted among those with gingival bleeding (men = OR: 2.8; CI: 1.7–4.7 and women = OR: 3.4; CI:1.8–6.1), those with six or more missing teeth (men = OR: 3.9; CI: 2.5–6.1 and women = OR: 7.6; CI: 3.9–14.9), and those with interviewer-reported poor general oral condition (men = OR: 4.9; CI: 3.1–7.8 and women = OR: 6.0; CI: 3.00–12.00).

In a European case-control investigation, Lissowska et al. studied a Polish population to investigate the effect of smoking, alcohol, diet, dentition, and sexual practices on risk for oral cancer. The study population consisted of 122 patients with histologically confirmed cancer of the oral cavity and pharynx. The controls consisted of 124 age- and gender-matched patients admitted to the hospital for non-neoplastic conditions unrelated to tobacco and alcohol. The subjects were interviewed to obtain information regarding demographics, smoking, alcohol consumption, family history of cancer, and oral hygiene. After adjusting for smoking and alcohol, and poor dentition as assessed by number of missing teeth (OR: 9.8; CI: 2.3–42.8), the frequency of dental check-ups (OR: 11.9; CI: 3.3–42.5) and of tooth brushing (OR: 3.2; CI: 1.2–8.5) were found to be the most significant risk factors for oral cancer. It was concluded that poor oral hygiene may be an independent risk factor for oral and oropharyngeal cancer.

In a population-based case-control study from the Carolina Head and Neck Cancer Study, the incidence of squamous cell carcinoma of the head and neck in 1,289 cases was examined in subjects who were age, race, and gender matched and compared with 1,361 controls. Oral health was assessed using tooth loss, tooth mobility, mouthwash use, and frequency of dental visits from an interview of the subjects. After controlling for covariates, tooth loss did not yield an association with squamous cell carcinoma of the head and neck (16–28 versus 0–5 lost teeth: OR: 1.21; CI: 0.94–1.56), but routine dental visits were associated with a 30% reduction in the incidence of squamous cell carcinoma of the head and neck (OR: 0.68; CI: 0.53–0.87).

Studies of the Relation Between Periodontitis and Oral Cancer
In the first study in which the periodontium was assessed, Tezal and colleagues used a cross-sectional analysis of data extracted from the Third National Health and Nutrition Examination Survey (NHANES III; National Center for Health Statistics 1994). For this study, subjects who were 20 years and older with at least six natural teeth were included. Subjects requiring antibiotics before a dental examination were excluded. Periodontal measurements included assessment of clinical attachment loss, whereas other oral assessments were number of missing teeth, caries, restorations, and the presence of partial or full prostheses. After adjustment for age, gender, race, ethnicity, education, tobacco use, alcohol consumption, and occupational hazard, clinical attachment loss was significantly associated with the presence of oral tumors (OR: 4.6; CI: 2.3–9.3). Additional analyses considering the interactions between clinical attachment levels (CAL) and smoking indicated that CAL was a signifi-
cant risk for tumor (OR: 21.76; CI: 3.6–131.63) in current smokers, suggesting that it is a risk modifier. This concept is strengthened by the observation that CAL had no effect on tumor risk for former smokers or for people who never smoked; hence, CAL is probably not an independent risk factor.

Shortly after the Tezal et al. study, Rosenquist et al. published results from a study that also used a comprehensive periodontal assessment. In this case-control study of a Swedish population, alcohol consumption, tobacco use, oral hygiene, dental status, and dental radiographic status were evaluated for increasing risk for oral cancer. The case subjects consisted of 132 oral and oropharyngeal cancer patients, who were selected from a population residing in the southern healthcare region of Sweden. Age- and gender-matched controls were selected from the same region with no previous cancer diagnosis (except for skin cancer). The oral condition was assessed via interview for frequency of dental check-ups, visual assessment of plaque score, modified gingival bleeding index, number of missing teeth, defective teeth, tooth mobility, furcation involvement, and presence of dentures. A radiographic examination of the dentition evaluated marginal bone levels, loss of bone along root surfaces, angular bony defects, and furcation defects. A mucoosal assessment was also provided. In an unadjusted analysis, those with average oral hygiene (OR: 3.0; CI: 1.7–5.1) or poor oral hygiene (OR: 10.0; CI: 5.1–20.1), as assessed by plaque scores, were significantly at risk for oral cancer. After adjusting for smoking and alcohol use, individuals with an average plaque score had an OR of 2.0 (CI: 1.1–3.6), whereas those with a poor plaque score had an OR of 5.3 (CI: 2.5–11.3). The number of missing teeth was also found to be a significant risk factor, with more than 20 missing teeth being statistically significant in unadjusted (OR: 6.1; CI: 2.7–14.0) and adjusted analyses (OR: 3.4; CI: 1.4–8.5). Those with more than five missing teeth also had significant risk in both unadjusted (OR: 4.8; CI: 2.0–11.4) and adjusted (OR: 3.1; CI: 1.2–8.2) analyses. On radiographic assessment, a high level of marginal bone was noted to be associated with an increased risk for oral cancer in unadjusted analyses (OR: 3.00; CI: 1.0–8.7); however, this failed to reach significance in adjusted analyses. Regular dental check-ups were noted to be associated with a decreased risk of oral cancer in adjusted analyses (OR: 0.4; CI: 0.2–0.6).

In a subsequent study, Tezal et al. carried out a case-control study of preexisting data for patients seen at the Roswell Park Cancer Center (1999–2005) to assess the role of periodontitis in risk for tongue cancer. The subjects consisted of 54 non-Hispanic white males with primary squamous cell carcinoma of the tongue. Age- and gender-matched non-Hispanic white men seen in the same hospital department but not diagnosed with any cancer or oral dysplasia served as controls (n = 54). The periodontal assessment consisted of evaluation of alveolar bone loss from panoramic radiographs. Other dental information including caries, restorations, and endodontic treatment was determined from the radiographs. Analyses after adjustments for the confounders of age, smoking habit, and number of missing teeth indicated that for every millimeter of alveolar bone loss, a 5.2-fold increase was found in the risk of tongue cancer (OR: 5.2; CI: 2.6–10.4). Other variables, including caries, restorations, and root canal treatment, failed to show any significant association with tongue cancer.

The most recently published study assessing the association among oral hygiene, periodontal disease, and oropharyngeal and oral cancer was a cross-sectional prospective case-control study. Fifty subjects with untreated oral and oropharyngeal squamous cell carcinoma were compared with 5,009 cancer-free subjects matched for age and gender. An oral health questionnaire was used to assess tooth brushing as well as use of mouth rinses, dental
floss, and other oral hygiene aids. An oral examination was carried out to determine Community Periodontal Index of Treatment Needs (CPI TN) scores, missing teeth, caries, restorations, and prostheses, but no consideration was given to smoking status or alcohol consumption. After very simplistic statistical analyses, the authors reported that advanced periodontal disease was greater in the subjects with oral and oropharyngeal cancer. Up to 76% of the cancer subjects had periodontal probing pockets greater than 6 mm compared with 20% of the patients without cancer. No statistically significant differences could be found for caries, missing teeth, restorations, or prostheses.

In addition to clinical studies evaluating the relation between periodontal diseases and oral cancers, other investigations have examined the effect of putative periodontal pathogens on oral squamous carcinoma cells. In two in vitro studies, *Porphyromonas gingivalis* was found to be intimately associated with squamous carcinoma cells. More specifically, *P. gingivalis* was found to be abundantly present in malignant oral epithelium, and this species of bacteria was able to induce the expression of B7-H1 and B7-DC receptors in squamous carcinoma cells, thereby making them more evasive to the immune system.

**Summary of the Relation Between Oral Health and Oral Cancer**

Many oral conditions, including tooth loss, poor oral hygiene, poor oral condition, and general periodontal condition clearly are significant risk factors for oral cancer (Table 1). Because of the great variability in statistical analyses, it is difficult to determine the real significance of many of these studies. Nonetheless, investigators in several studies have tried to remove confounding influences and have been able to demonstrate that many of these oral conditions remain significant risk factors. Perhaps the main confounding factors are smoking and alcohol consumption. When considered together (smoking, alcohol, and oral conditions), risk for oral cancer seemed to increase significantly. When two of these confounders (smoking and alcohol) were removed, oral conditions remained highly significant risk factors. The interplay between oral condition and oral cancer, already induced by recognized risk factors such as alcohol and tobacco, needs to be further investigated. It has only been in recent years that an evaluation of periodontal condition has been assessed as a potential risk factor. Although early data indicate a putative role for periodontal disease, there is considerable scope for further studies to investigate in more detail specific periodontal parameters, as well as types of periodontitis in the periodontal diseases-oral cancer axis.

**ORAL CONDITIONS AND VARIOUS TYPES OF CANCER**

**Oral Conditions and Upper Gastrointestinal Cancer**

One of the first reports to suggest an association between oral condition and gastrointestinal (GI) cancer was a case-control study carried out in Germany. The subjects included stomach cancer patients (n = 257) and healthy, noncancerous control subjects (n = 766). Information was obtained from patient interviews and 20 variables were found to be significantly associated with gastric cancer. Of these, early tooth loss was identified as a prominent variable.

During the 1990s, several case-control studies were conducted to investigate the association of oral health and upper GI cancer. Demirer and associates studied a Turkish population, principally to investigate the relation between diet and stomach cancer, but used some oral measurements as well. The patients with cancer (n = 100) had histologically proven adenocarcinoma of the stomach, and age-, gender-, and residential area-matched subjects with no GI disease were used as controls (n = 100). Information was
obtained by interview with regard to food and beverage intake, frequency of tooth brushing, and number of missing teeth. In this study, patients with gastric cancer brushed their teeth less frequently ($P < 0.0001$) and had more missing teeth ($P < 0.0001$). The relative risk and confidence intervals for these data were not reported.

A case-control study on Chinese populations from three areas in Shanxi province (North-Central China) was carried out to determine the influence of diet, smoking, drinking habits, sociopsychological factors, and family history on the etiology of esophageal cancer. As part of this study, information concerning dental hygiene habits was obtained. The case patients ($n = 326$) had been diagnosed previously with histologically confirmed esophageal cancer, and controls ($n = 396$) were matched by age, gender, and residence location. Demographic, social, and medical information was gathered by interview and included dental hygiene habits. Of the parameters evaluated, frequency of tooth brushing was found to be associated with reduced risk for esophageal cancer (OR: 0.2; CI: 0.1–0.5). In another case-control study, Watabe and associates studied a Japanese population to investigate the etiologic relation between gastric cancer and lifestyle. The patients with gastric cancer ($n = 242$) and the control group ($n = 484$) were matched for age, gender, and place of residence. Oral condition was determined according to number of teeth present. The results from this study indicated that tooth number was inversely associated with a high OR for development of gastric cancer. After correcting for some confounders, the number of missing teeth was still found to be significantly associated with gastric cancer.

Several recent case-control, cohort, and cross-sectional studies have been carried out to ascertain the relation between oral health and gastric cancer. In a large case-control study of a Chinese population, Abnet et al. investigated the relation between tooth loss and risk of developing esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma, or gastric noncardiac adenocarcinoma. The cases had been diagnosed previously through histologic confirmation of upper GI cancers ($n = 2,204$). The controls ($n = 27,715$) were cancer-free, came from the Linxian area of China, and were part of the Linxian General Population Trial cohort in 1985. Tooth loss was assessed from subject interview and also visual inspection. Tooth loss was high in this population, with 74% of participants having lost at least one permanent tooth. The median number of teeth lost was six, and median age for first tooth loss was 39. Further analyses indicated that tooth loss was significantly ($P < 0.01$) associated with each of the three cancer sites studied. When assessed for each cancer site, tooth loss was associated with a relative risk (RR) of 1.3 (CI: 1.1–1.6) in the esophagus, an RR of 1.3 (CI: 1.0–1.6) for the gastric cardiac, and an RR of 1.8 (CI: 1.1–3.0) for the gastric noncardiac. Additional analyses indicated that the increased risk was strongest for the first teeth lost in younger persons.

In a similar study, Abnet et al. carried out a prospective cohort study to determine whether tooth loss was associated with increased risk of gastric noncardiac adenocarcinoma in a cohort of Finnish smokers. The study population comprised 29,124 subjects, which included 49 esophageal squamous cell carcinomas, 66 esophageal/gastric cardiac adenocarcinomas, and 179 gastric noncardiac adenocarcinomas. Interviews enabled information to be collected on general background characteristics, smoking, and dietary history. The dentition was assessed by interview and related to the number of missing teeth. Tooth loss was found to be significantly associated with an increased hazard ratio (HR) for gastric noncardiac cancer, whereby the HR for edentulous people versus those with less than 10 teeth lost was 1.65 (CI: 1.1–2.5). For
esophageal squamous cell carcinoma and esophageal/gastric cardiac adenocarcinoma, no statistically significant associations were found with tooth loss.

In another cross-sectional study of a rural Chinese population, Wei and colleagues\(^9\) investigated the risk factors for oropharyngeal squamous dysplasia. The study population (Linzhou, formerly Linxian, China) was chosen because of a very high incidence of esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma. A screening study of 724 adults who were apparently healthy was carried out. An interview was conducted to obtain general information on personal characteristics, smoking and alcohol use, and living conditions. Dental examinations followed the NHANES III protocol and included a tooth count. Of the 720 subjects, 230 people had a prevalent squamous dysplasia. Subjects who had lost between 12 and 31 teeth had higher odds for developing dysplasia (OR: 1.91; CI: 1.2–3.2). These findings were similar to those of the earlier report by Abnet and colleagues.\(^{28}\)

A cross-sectional study by Dye et al.\(^{30}\) investigated the oral health of a nonrepresentative sample of adult participants in an esophageal cancer study. Subjects (n = 718) were recruited from three regions within Linzhou, China. They were examined by esophageal cytology and interviewed to obtain information regarding health history and risk behavior. A dental examination was also executed according to the NHANES III protocol, which included assessment of the number of teeth present. The periodontal examination consisted of assessing gingival inflammation, CAL, and bleeding on probing. As noted previously,\(^{27}\) tooth loss was prevalent, with 17% of the study population being edentulous. In an unadjusted model, those who had 12 to 31 teeth had an increased risk for esophageal cancer (OR: 1.7; CI: 1.03–2.83). Poor oral health was derived from both periodontal status and caries experience and was found to be associated with increased risk of esophageal cancer (OR: 1.58; CI: 1.0–2.7), and when adjusted for nonsignificant covariates, OR was 1.59 (CI: 1.06–2.39). No associations were noted when all covariates were considered. The authors interpreted this to indicate that the extent and severity of poor oral health could be important contributing factors in the prevalence of esophageal cancer.

Of the previous eight studies mentioned in this section, four have been published by the same group using essentially similar study designs and similar population groups. Nonetheless, from all of the studies published to date concerning oral conditions and upper GI cancer, evidence has accrued suggesting that tooth loss may be an important risk factor for GI cancer. How well tooth loss correlates with periodontal conditions is still open to question. It has, however, been used as a surrogate marker for periodontal disease and poor oral health. With only one study seriously considering periodontal parameters, it is too early to determine whether periodontal health is also a risk factor for this condition.

**Oral Conditions and Lung Cancer**

Very few reports exist in the literature concerning the relation between oral disease and lung cancer. The most widely quoted study is population-based and derived from data obtained from the NHANES I Epidemiologic Follow-up Study.\(^{31}\) Data were gathered from 11,328 adults between the ages of 25 and 74 who underwent a medical examination, a standardized medical history, and standardized dental examination in 1971 to 1975. The subjects were followed up, with a 96.2% success rate until 1992. Death certificates of the deceased were obtained, and the analysis considered those who had died from malignant neoplasms, including lung and bronchus; and pancreas; colon; gingiva; oral cavity; and any other cancer. The dental examinations included measuring the extent of gingival inflammation and the size of peri-
odontal pockets. A periodontal score was obtained using the Russell Index. Associations between cancer types and periodontal status were examined controlling for age and gender. These associations were described using odds ratios and their 95% confidence intervals. More detailed analyses included using Cox proportional hazards models to determine whether individuals with gingivitis, periodontitis, or edentulism at the commencement of the study were at higher risk for developing fatal neoplasms during the study period to 1992. Following these analyses, it was determined that although periodontitis patients had an elevated risk of death from cancer, it was significant only for lung cancer (OR: 1.94; CI: 1.16–3.26). After a Cox proportional hazards analysis adjusting for demographic factors, the HR was determined to be 2.14 (CI: 1.30–3.53). With further adjustment for socioeconomic status, smoking status, alcohol consumption, and intake of vitamins A and C, the HR was reduced to 1.73 (CI: 1.01–2.97). No association between periodontitis and lung cancer was detected if the analyses were limited to people who had never smoked. However, if the analysis was restricted to smokers, then periodontitis became significantly associated with lung cancer (HR: 1.94; CI: 1.14–3.30). The authors interpreted these findings to imply that an association between periodontitis and lung cancer, after adjustment for known risk factors, could be demonstrated. However, they cautioned that this periodontitis-cancer association could be spurious.

In an analysis of the Health Professionals Follow-Up Study, US male health professionals responded to a questionnaire posted by the Harvard University School of Public Health. The principal analysis of 48,375 men showed a significant association for those with a history of periodontal disease and lung cancers (HR: 1.36; CI: 1.15–1.60); however, no association between periodontal disease and lung cancer was noted in never-smokers.

Similar to that found in other published reports, the relation of periodontitis to lung cancer does not support a link. In this study, associations between tooth loss and mortality patterns in a cohort from Glasgow were studied in 223 subjects (median age at baseline was 19 years) who were followed up for up to 57 years. The cause of death was recorded and related to dental data including missing teeth, decayed teeth, and restored teeth. Missing teeth were used as the index of oral health. After extensive statistical analyses, the authors concluded that no association existed between external causes of death and tooth loss as a continuous (HR: 0.97; CI: 0.92–1.03) or categorical variable for missing five to eight teeth (HR: 0.74; CI: 0.45–1.21) or missing nine or more teeth (HR: 0.89; CI: 0.42–1.88). In addition, no evidence of an association between lung cancer and tooth loss was found, with or without adjustment for smoking.

Although the literature is scant on this topic, to date it does not seem to support any association between periodontal condition and lung cancer.

**Oral Conditions and Pancreatic Cancer**

In light of earlier observations that oral hygiene and tooth loss could be associated with increased risk for upper GI cancers, Stolzenberg-Solomon et al. hypothesized that tooth loss may be associated with pancreatic cancer. This was a cohort study of Finnish men, ages 50 to 69, who smoked more than five cigarettes per day and had no history of any malignancy apart from non-melanoma of the skin or carcinoma in situ. Baseline information obtained by interview included medical, dental (number of teeth), smoking, and dietary history. Of the 29,104 participants, 174 developed pancreatic cancer. Cox proportional hazards models were used to account for age, smoking, education, urban living, and height. In this study, tooth loss, as accounted for by total edentulism,
was associated with pancreatic cancer when compared with that for individuals missing 10 or fewer teeth (HR: 1.63; CI: 1.09–2.46). However, for people missing 11 to 31 teeth, this association was not significant (HR: 1.23; CI: 0.82–1.85). The authors concluded that further studies were needed to fully evaluate the association between tooth loss and pancreatic cancer.

Hujoel et al.,31 in their study using the NHANES I data to investigate the association between periodontitis and various cancers, found no association with pancreatic cancer.

A subsequent study by Michaud et al.2 investigated the association of periodontitis in 216 males diagnosed with pancreatic cancer from a larger cohort of 48,375 men participating in the Health Professionals Follow-up Study in the United States. The study period was 16 years. At baseline, participants reported the number of natural teeth; this was updated every two years. It was reported that a periodontal disease analysis was carried out at baseline and every two years thereafter. However, no details were provided as to the nature of these analyses. Subjects who were assessed to have periodontal disease at baseline had an increased risk of pancreatic cancer (RR: 1.83; CI: 1.36–2.45). When adjusted for age, smoking, profession, race, geographic location, physical activity, diabetes, body mass index, height, cholecystectomy, nonsteroidal anti-inflammatory drug use, multivitamin use, dietary factors, and total calories, the RR was 1.64 (CI: 1.19–2.26). Most of this attenuation could be accounted for by smoking. The number of teeth present at baseline was not significantly associated with pancreatic cancer. However, in a joint analysis, tooth loss in conjunction with periodontal disease resulted in a 2.7-fold increase (RR: 2.71; CI: 1.70–4.32) in pancreatic cancer when compared with either no periodontal disease or no recent tooth loss. Additional analyses indicated that the influence of periodontal disease was stronger in people who had never smoked (RR: 2.09; CI: 1.18–3.71). Furthermore, the influence of periodontal disease was also stronger in those with a body mass index of less than 25 kg/m² (RR: 2.2; CI: 1.34–3.61). The authors concluded that this indicated that smoking and obesity were unlikely to explain the association between periodontal disease and pancreatic cancer. Nonetheless, they concluded that if the association is to be proved, additional studies are required.

In an interesting follow-up to the Michaud et al.2 publication, Taguchi,35 in a “Letter to the Editor” commented that Michaud and colleagues did not adjust for the effects of passive exposure to cigarette smoke, which could havenegated their findings. In addition, Taguchi suggested that to better understand the relation between periodontal disease and pancreatic cancer, it would be helpful to demonstrate an association between duration and grade of periodontal disease and pancreatic cancer risk. In response to these comments Michaud et al.3 argued that notwithstanding the lack of data concerning environmental tobacco smoke, controlling for passive smoking in their study may have attenuated their findings but not eliminated the association between periodontal disease and pancreatic cancer. It was noted that the twofold increase in risk for pancreatic cancer in people with periodontal disease who had never smoked is greater than the reported association between passive smoking and pancreatic cancer. Furthermore, it was pointed out this twofold increase in risk for pancreatic cancer among patients with periodontal disease who had never smoked is of a similar magnitude to the association between current smoking and pancreatic cancer. With regard to the need for assessment of duration and severity of periodontal disease, Michaud was in agreement. Indeed, this should be a requirement for all future studies investigating the association between periodontal disease and any cancer.
Using the European Prospective Investigation into Cancer and Nutrition, Michaud and colleagues\textsuperscript{36} measured antibodies to various oral bacteria in 405 pancreatic cancer patients and 416 matched controls. From the data, individuals with antibodies to \emph{P. gingivalis} were associated with a twofold higher risk of pancreatic cancer than those with low levels (≤ 200 ng/mL) of these antibodies (OR: 2.14; CI: 1.05–4.36). Since \emph{P. gingivalis} is a putative periodontal pathogen associated with chronic periodontitis, it was surmised, though not proved, that this species of bacteria may have a direct effect on the pathogenesis of pancreatic cancer.

**ORAL CONDITIONS AND REPRODUCTIVE ENDOCRINE CANCERS**

The relation between the periodontium and the reproductive systems of men and women has been comprehensively documented,\textsuperscript{37,38} whereas the possible effects of periodontal diseases on the initiation and/or progression of malignant diseases that affect the reproductive systems of men and women have not been noted because of the relative paucity of data. Only recently a few reported studies have suggested an association between gender-related cancers and periodontal diseases. Up to this time, most studies have relied on collecting self-reported data from subjects to determine whether putative links exist between diseases of the reproductive systems of men and women. This has been a limitation in these studies. For example, in a prospective co-twin study of 15,333 Swedish twins using data between 1963 and 2004, Arora et al.\textsuperscript{39} using a questionnaire, noted an association between tooth mobility (i.e., a surrogate measure of periodontal disease) and the incidence of prostate cancers. The analysis of their data suggested that periodontal disease was associated with prostate cancer (HR: 1.47; CI: 1.04–2.07). In contrast to the previous study, questionnaires regarding the relation of periodontal disease and prostate cancer in 48,375 US male health professionals failed to demonstrate an association between prostate cancer and periodontal disease.\textsuperscript{32}

A longitudinal prospective study was also used to examine periodontal disease in relation to cancers that are predominant in women. Using a group of Finnish men and women, the association between breast cancer and periodontal disease was examined in 1,676 subjects.\textsuperscript{40} Although the number of remaining teeth, gingival inflammation, oral hygiene status, calculus index, and probing depths were recorded for a cohort of patients in this study, the definition of periodontal disease was not noted by the authors. The study reported that 1.75% of subjects with periodontal disease and/or missing molars developed breast cancer compared with a breast cancer incidence of 1% in the periodontally healthy patients. Furthermore, the absence of any molar from the mandible was statistically associated with breast cancer in women (OR: 2.36; CI: 1.07–5.21).

Like most carcinomas, the etiology of neoplasms associated with the male reproductive tract or the breast are not well understood. The addition of periodontal diseases to a growing list of putative causes does not clarify what, if any, relation destructive periodontal diseases have to disorders of the reproductive tract or other hormone-sensitive tissues. Therefore, at this time, the relation between periodontal diseases and sex hormone-sensitive malignancies cannot be established.

**PERIODONTAL DISEASE, CANCER, AND MORTALITY**

To date, very few studies have investigated the association between periodontal disease and cancer by assessment of the clinical parameters of periodontal status. By far, most studies have reported the association between tooth loss and cancer risk. Such approaches may be flawed, since tooth loss may also result from
trauma or, more commonly, from caries. However, these studies claim that because teeth lost at an older age are more likely due to periodontal disease compared with those lost at younger ages (which may be due more to dental caries), tooth loss in older persons can be a good surrogate marker of periodontal disease. Therefore, assessment of tooth loss may provide an insight into the overall role of oral health and its effect on cancer risk. The cumulative influence of age on tooth loss and its relation to periodontal disease can be seen in the study by Michaud et al. In this study, which ran for more than 16 years, the number of teeth lost at baseline was not related to risk of pancreatic cancer. However, by the end of the study, tooth loss within the previous four years was noted to be a predictor of pancreatic cancer risk. When those with both periodontal disease and recent tooth loss were assessed jointly, the risk of pancreatic cancer increased significantly compared with that of individuals who did not have periodontal disease and had not experienced any recent tooth loss. These results suggest that in this population, recent tooth loss may be a marker for severity of periodontal disease, whereas baseline tooth loss may reflect loss due to factors other than periodontitis.

Another complicating factor in interpreting many of the published studies is the influence of known risk factors, which include smoking, alcohol consumption, and socioeconomic status. Smoking is a well-recognized risk factor for oral and lung cancer, but it is also a recognized risk factor for periodontal disease and tooth loss. Thus, some authors have questioned any reported association between tooth loss and cancer as being due to confounding factors rather than a real risk factor. This may be true for lung cancer; however, other cancers appear to be less influenced by smoking and indeed, tooth loss persists as a significant risk factor for both gastric and pancreatic cancer after adjusting for smoking status. Similarly, alcohol consumption can be a significant risk factor for cancer and is also a possible risk factor for periodontitis. Thus, alcohol consumption must be accounted for when investigating the effect of tooth loss on cancer risk. In cancers of the oral cavity, this is particularly relevant, since alcohol is a significant risk factor for oral cancer. Many studies have adjusted for alcohol intake and found that tooth loss persists as a significant risk factor for this cancer. Socioeconomic status is also considered an important risk factor for periodontitis; hence, there is further potential for socioeconomic status to be a confounding issue in studies considering the effect of tooth loss on cancer. Most studies have included socioeconomic status in their questionnaires, but adjustment for this component has not always been a prominent feature of the statistical modeling.

Although smoking, alcohol consumption, and socioeconomic status may be the three commonly recognized confounders for many studies concerning cancer risk and periodontal disease, it is highly likely that many other previously unidentified confounding factors could be at play and need to be identified before these associations can be confidently accepted.

With these caveats in mind, several scientific reports attempt to evaluate the relation among periodontal disease, cancer, and mortality. One of the first to report that periodontitis was positively associated with cancer was Hujoel et al. in 2003. This study has been described in more detail in the previous section dealing with lung cancer. Briefly, Hujoel and colleagues followed up 11,328 individuals over a 10-year period and compared periodontal status with fatal cancer. Associations between cancer types and periodontal status were examined, controlling for age and gender. Of the six fatal cancers studied as the main outcome measures, only lung cancer was found to have a significant association with periodontitis. The association between periodontitis and lung cancer mortality could be found even after adjusting for known risk
factors for lung cancer such as smoking (OR: 1.94; CI: 1.16–3.26).

Further prospects for a relation between oral health and increased risk of total death and death from cancer have been made from a cohort study on rural Chinese. This was a follow-up to the Abnet et al. study on a Chinese population in Linxian, China, in which 29,584 rural Chinese participated over a 10-year period. Tooth loss was used as the measure of oral health, and mortality outcomes were studied as well as total death, upper GI cancer death, other cancer death, heart disease death, and fatal stroke. It was found that those with more than the age-specific median number of teeth lost had a statistically increased risk of total death (RR: 1.13; CI: 1.09–1.18) and death from upper GI cancer (RR: 1.35; CI: 1.14–1.59). After accounting for the confounding effect of smoking, these associations were generally still significant. Risk of death at other cancer sites showed no significant associations with tooth loss. Tooth loss was concluded to be significantly associated with increased risk of total death from cancer and from upper GI cancer.

In contrast to the above findings, Cabrera et al. investigated the relation between tooth loss and chronic disease and found no associations between tooth loss and total cancer mortality after adjusting for known confounders (RR: 1.16; CI: 0.90–1.49). This was a prospective study of females residing in Gothenburg, Sweden, over 24 years. The dental examination consisted of determining tooth number; mortality outcomes were death from cardiovascular disease and all-site cancer. Despite no association between tooth number and all-site cancer mortality, no assessment of site-specific cancers was made. Similar findings were noted by Tu et al. in the previously described Glasgow cohort study. Moreover, after adjusting for a variety of confounders, no association was found between all-cause mortality for each additional missing tooth (HR: 1.01; CI: 1.00–1.02) or cancer mortality (HR: 1.00; CI: 0.98–1.02). From this study, it appeared that any relation between tooth loss and cancer mortality could be explained by other causal or confounding mechanisms.

Tramini et al. investigated tooth loss and associated factors in elderly patients in France who had been institutionalized long term. In this cross-sectional study of 321 elderly patients, socioeconomic, behavioral, medical, and oral information was recorded. Multivariate logistic regression analyses were carried out to test the associations between these covariates and tooth loss. The results indicated that “cancerous disease” was the most significant condition associated with partial tooth loss. The type of cancerous disease was not qualified. From these data, the authors concluded that the number of remaining teeth has a strong effect on oral health-related quality of life.

Söder et al. published the results of a 16-year longitudinal study investigating periodontitis and premature death. The causes of death for 3,273 individuals were recorded and subsequently related to dental findings. The dental assessment at baseline included recording missing teeth, gingival inflammation, oral hygiene status, calculus scores, and periodontal probing pocket depth. An individual was considered to have periodontitis if he or she had at least one tooth with a probing pocket depth of 5 mm or more. After logistic relation analysis of being dead (dependent variable) and several independent variables including age, gender, education, income, smoking, dental visits, dental plaque, gingival inflammation, missing teeth, and missing molars, the total number of people who died from neoplasms was significantly higher in the periodontitis group who had missing molar teeth (OR: 3.62; CI: 1.28–10.16). It was concluded that young periodontitis patients with missing molars were at higher risk for premature death by neoplasm than their more healthy counterparts.
In another case-control study, Hiraki et al.\textsuperscript{45} examined the relation between tooth loss and the risk of 14 types of cancers in a Japanese population. The cohort consisted of 5,240 cancer subjects and 10,480 noncancer controls who were age- and gender-matched. Information on lifestyle, smoking, alcohol consumption, diet, exercise, and number of teeth present was collected. Of the 14 cancers studied, tooth loss was found to be associated with esophageal cancer (OR: 2.36; CI: 1.17–4.75) and lung cancer (OR: 1.54; CI: 1.05–2.27). After adjusting for age, these associations remained significant but were decreased. These findings are in agreement with the more focused studies on upper GI cancer and lung cancer.

In a detailed study, Michaud et al.\textsuperscript{35} analyzed periodontal disease, tooth loss, and cancer risk in a male health professional cohort. This prospective study was carried out on the same Health Professionals Follow-up Study as described in the previous section on pancreatic cancer. Commenced in 1986, 51,529 (97% male) participants answered a questionnaire on lifestyle, smoking history, alcohol consumption, physical activity, diet, and medical history. Follow-up questionnaires were completed every two years until 2002. Dental assessments were also carried out, which consisted of self-reported experience of periodontal disease and tooth loss. Cancer experience was recorded by the participants who were required to report any new cancer diagnosis on the biennial questionnaires.

The data were analyzed and multivariate hazards ratios and 95% confidence intervals were calculated by Cox proportional hazards models for periodontal disease experience and number of missing teeth at the baseline measurement. From this study, the five main cancers experienced by this cohort were colorectal, melanoma of the skin, lung, bladder, and prostate. After adjustment for known cancer risk factors such as smoking history and diet, persons with no reported history of periodontal disease were compared with those with a self-reported history of periodontal disease. The latter demonstrated an increased risk for total cancer (HR: 1.14; CI: 1.07–1.22). For specific cancers, a history of periodontal disease was associated with increased risk for lung (HR: 1.36; CI: 1.15–1.60), kidney (HR: 1.49; CI: 1.12–1.97), pancreas (HR: 1.54; CI: 1.16–2.04) and hematologic cancers (HR: 1.30; CI: 1.11–1.53). These findings for lung and pancreas were in agreement with previously published studies. The findings for kidney and hematologic cancers were new and have not been reported previously. In contrast to that found in previous studies, the association for esophageal cancer, though increased, was not significant after adjusting for smoking status. Missing teeth, which was also noted to be associated with smoking status, was found to be associated with increased risk for lung cancer only (HR: 1.7; CI: 1.37–2.11). The associations were strongest for periodontal disease and missing teeth when smoking was not considered a covariate; this indicates that smoking was a strong confounder for these associations. For pancreatic and kidney cancers, the associations remained strong even after controlling for smoking. For lung cancer, smoking was found to be a very strong confounder and was probably largely responsible for risk of this cancer. Removal of confounding factors for kidney and pancreatic cancers such as diabetes and obesity did not significantly change the associations, indicating that these two known risk factors were not likely to be responsible for the noted association of periodontal disease with pancreatic and kidney cancers. Overall, the authors concluded that periodontal disease appeared to be associated with a small but nonetheless significant risk for cancer in general. Some influence of smoking was noted in smokers but the associations persisted in people who had never smoked. Whether some of these associations were due to direct effects of periodontal disease on cancer or were the result of being more like a
surrogate marker requires further investigation.

**PERIODONTITIS, VIRUSES, AND ORAL CANCER**

In recent years, several reports have suggested that viruses may be associated with various forms of periodontitis. In particular, Epstein-Barr Virus (EBV) has been implicated in the pathogenesis of advanced and aggressive forms of periodontitis.6 It has been hypothesized that EBV proteins may lead to an up-regulation of growth factors and cytokines involved in cell transformation of EBV-associated oral malignancies.47 This is an interesting theory; nevertheless, considerably more research is needed to determine the exact role, if any, that viruses play in periodontitis and oral malignancies.

**ORAL CONDITIONS, HELICOBACTER PYLORI, AND CANCER**

*Helicobacter pylori* is associated with chronic gastritis, duodenal ulcers, and an increased risk of gastric adenocarcinoma.48,49 Since *H. pylori* can be isolated in the oral cavity, especially in those with periodontitis who have the bacterium in their GI tract,50 it has been proposed that the oral cavity may act as a reservoir for *H. pylori*-associated gastric cancer. It has been suggested that *H. pylori* cannot survive in the oral cavity, but there are studies that support the notion that *H. pylori* can be found in dental plaque and periodontal pockets.51,52 Nonetheless, it is generally accepted that the presence of *H. pylori* in the oral cavity may be independent of infection status of the stomach and no good evidence exists for the presence of periodontal disease, oral *H. pylori*, and gastric cancer.53

**POSSIBLE MECHANISMS FOR THE ASSOCIATIONS BETWEEN ORAL CONDITIONS AND CANCER**

A number of hypotheses have been proposed to explain the observed associations between periodontal disease and cancer, including poor diet, mechanical irritation, chronic infection, systemic inflammation, and immune suppression, as well as increased exposure to carcinogens.1,41

**Diet and Mechanical Irritation**

The role of poor oral condition and tooth loss with trauma has been well discussed for both oral and upper GI cancer. For decades, an association between poor restorative dentistry and ill-fitting prostheses and oral cancer has been recognized.54 However, more recently it has been proposed that tooth loss may alter dietary patterns, which may be a contributing factor in the development of upper GI cancer.41 In addition, it has been suggested that tooth loss may result in inadequate mastication and that the resulting poorly chewed food bolus could have an irritating effect on the esophagus, leading to increased risk of cancer through mechanical irritation.55 To date, these hypotheses have not been proved. In light of findings that tooth loss and chewing efficiency are not related and that tooth loss is associated with increased risk for GI cancer, the fact that the GI system is a site that is unlikely to be affected by food bolus size mitigates against mechanical-trauma hypotheses.41

**Inflammation**

Inflammation appears to play an important role in carcinogenesis, and the presence of inflammation may enhance cellular proliferation and mutagenesis, reduce adaptation to oxidative stress, promote angiogenesis, inhibit apoptosis, and increase secretion of inflammatory mediators.56 This is demonstrated with chronic pancreatitis being associated with an increased risk of pancreatic cancer.57 Indeed, inflammation has been shown, at least in animal studies, to be associated with the progression of liver and colon cancer.58 Since periodontal disease is an inflammatory disease with elevated levels of circulating inflammatory cytokines, a suggestion has been made that this could be a plausible link leading to
the breakdown of normal cell growth control and potential carcinogenesis. Thus, the host response in periodontal disease may lead to a systemic exposure to proinflammatory cytokines, which in turn may lead to increased risk of neoplastic transformation at distant sites. However, the situation may not be as simple as this, because most studies investigating the link between cancer and inflammation consider the effect of local inflammation at the site of the cancer rather than systemic elevation of inflammatory mediators. It is possible that elevated systemic levels of inflammatory cytokines may encourage subthreshold neoplastic states to become neoplastic, but local inflammation and local release of inflammatory mediators at a site of potential neoplastic transformation seems more likely. Alternatively, it has been suggested that persons who suffer from both periodontal disease and cancer may share similar gene polymorphisms in genes encoding inflammatory cytokines. Thus, periodontitis may be merely a marker of an underlying genetic predisposing factor rather than a true risk factor for cancer.

**Infection**

Chronic infections have been associated with increased cancer risk. For example, bacterial infections such as *H. pylori* have been implicated in gastric cancer as well as hepatitis B and C viral infections implicated in hepatocellular carcinoma. Since periodontitis is a chronic infection, it has been postulated that periodontal bacteria within the subgingival plaque biofilm may be associated with carcinogenesis through the release of a multitude of toxic products (endotoxins, enzymes, hydrogen sulfide, ammonia), leading to cell mutations in tumor suppressor genes and proto-oncogenes or alter signaling pathways that affect cell proliferation or cell survival. In addition, chronic inflammation induced by periodontal pathogens results in chronic release of proinflammatory cytokines, chemokines, prostaglandins, growth factors, and enzymes that may have indirect effects on carcinogenesis by deregulating physiological cell turnover and cell growth. Another hypothesis proposes that periodontal pathogens may increase the level of certain carcinogens such as nitrosamines. The formation of endogenous nitrosamines in the oral cavity by nitrate-reducing bacteria is promoted by poor oral hygiene as well as by tobacco use and certain dietary factors. Increased production of carcinogenic nitrosamines by oral bacteria has been suggested as a possible mechanism for an increased risk of pancreatic cancer in individuals with reported periodontal disease.

**Immunity**

Periodontitis in susceptible patients may reflect a failure in the interaction between the innate and adaptive immune response to clear the bacterial challenge within the periodontal pocket. Deregulation of the immune response may also place a person at risk of inadequate cellular surveillance for tumor growth. In particular, the stable periodontal lesion consists of a predominantly helper T cell 1 (Th1) response and is associated with high levels of interferon-gamma (IFN-γ), an important cytokine in cell-mediated immunity and tumor surveillance. The progressive periodontitis lesion consists predominantly of a Th2 response with lower levels of IFN-γ and a poor innate immune response. Hence, periodontitis could merely be a marker of immune dysfunction rather than a true risk factor for cancer.

**CONCLUSION**

To date, only a limited number of studies have investigated the association between periodontal disease and cancer risk, although many reports have been published concerning the association among cancer risk and oral condition, oral hygiene, and tooth loss. Positive associations have been demonstrated even after controlling for
known risk factors such as smoking or when analyses are restricted to nonsmokers. However, these findings need to be interpreted with caution because additional confounding factors may exist that researchers are unaware of and that have not been included in the analyses for adjustment. More studies are needed of appropriate statistical power using appropriate markers for periodontal disease, appropriate consideration of the different types of periodontal disease, as well as the appropriate consideration of confounding factors.

**Supplemental Readings**


**REFERENCES**


CHAPTER 14
Dental and Medical Comanagement of Patients with Diabetes

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INTRODUCTION
This chapter discusses the comanagement of patients with diabetes mellitus by oral and medical healthcare providers. The need for comanagement of patients becomes evident when one considers the prevalence and chronic nature of diabetes and periodontitis (its major oral complication) and the link between the two diseases. Both topics are briefly reviewed in the following text. The role of dental and medical professionals in this setting is then reviewed separately and in detail. This chapter concludes by summarizing the principles related to a patient-centered, team approach to diabetes care.

Educational Objectives
After reading this chapter, the reader should be able to do the following:

• Appreciate the importance of dental and medical comanagement of the patient with diabetes
• Understand the responsibilities of oral healthcare professionals toward a patient with known diabetes and a patient who may have diabetes (or prediabetes) but is unaware of it
• Describe specific procedures required to manage such patients in dental practice
• Identify ways to prevent and treat emergencies related to diabetes in the dental office
• Understand the ways in which medical and dental professionals can work together to provide better care for their mutual patients with diabetes

DIABETES AND PERIODONTITIS: PREVALENT AND INTERRELATED CHRONIC DISEASES
Diabetes and periodontitis share many similar epidemiologic and clinical features. Both are very prevalent, easily screened, and interconnected by important pathophysiologic links. The successful treatment for either condition depends heavily on intensive intervention, active maintenance, and lifestyle modifications. Managing issues such as acute hypoglycemia, oral infection, and smoking cessation in diabetic patients is clinically relevant for dental as well as medical professionals. As the incidence of diabetes continues to rise and the understanding of the relation between diabetes and periodontitis deepens, the comanagement of patients with diabetes is expected to become the standard of care.

Diabetes
Diabetes is one of the most common chronic illnesses, affecting approximately 26 million people in the United States and more than 371 million throughout the world.1,2 In the decade from 1996 to 2006, the prevalence of diagnosed diabetes nearly doubled in the United States,3 presenting significant challenges for a wide range of healthcare professionals. The incidence of the disease is rapidly growing across all age and socioeconomic strata, but the highest expansion is seen among the elderly and ethnic minority populations.4 Despite being the leading cause of blindness, kidney failure, and lower limb amputations not related to accident or injury in the United States, about 25% of those with diabetes are unaware that they have the disease.5 Because the symptoms are neither specific to the disease nor accurately reflective of blood glucose concentration, the diagnosis of diabetes is frequently not made until severe symptoms or complications appear. Once diabetes is diagnosed, its clinical sequelae can be
prevented or delayed with strict metabolic control. Thus, the patient can play a critical role in how the disease progresses by committing to self-care; healthcare providers (beyond the treating physician) can contribute to the better management of affected persons by reinforcing the need for good metabolic control.

Prediabetes
According to the 2013 Standards of Medical Care in Diabetes by the American Diabetes Association, the term prediabetes applies to those with glycemic levels too high to be considered normal, but not meeting criteria for diabetes. These individuals are identified based on a hemoglobin A1c (HbA1c) result between 5.7% and 6.4%, or a blood glucose level following an overnight fast between 100 and 125 mg/dL (impaired fasting glucose [IFG]), or a blood glucose level after a 2-hour oral glucose tolerance test between 140 and 199 mg/dL (impaired glucose tolerance [IGT]). Prediabetes is a condition that has received little medical attention in the past, but has important public health implications. Prediabetes affects an estimated 79 million Americans 20 years or older, more than three times the number of diabetic cases, and totaling 35% of the adult population. People with prediabetes have a strong risk for developing type 2 diabetes and already have an increased risk of developing heart disease, stroke, and microvascular complications typical of those with fully developed diabetes. Evidence is strong that people with prediabetes who lose weight and increase their physical activity can prevent or delay diabetes and return their blood glucose levels to normal. As with diabetes, the paramount challenge is early detection and intervention.

Periodontal Diseases
In a similar sense, periodontal diseases are common chronic disorders, and are broadly grouped into gingivitis and periodontitis. Gingivitis includes inflammatory disorders of the nonmineralized tissues surrounding the teeth with no evidence of loss of support around the teeth (clinical attachment loss or CAL) or loss of alveolar bone surrounding the teeth. Periodontitis is associated with loss of attachment or loss of supporting alveolar bone and loss of teeth. The persistent inflammation and infection associated with periodontitis has been linked to an increased risk of many disorders, including cardiovascular and cerebrovascular diseases, diabetes complications, adverse pregnancy outcomes, respiratory disease, and kidney disease. Periodontitis generally takes many years to develop; more advanced disease is more common with advancing age. Once periodontitis is diagnosed, attendant morbidity (abscess formation, alveolar bone and tooth loss) can be reduced by strict adherence to a rigorous self-administered and professional oral hygiene regimen.

Defining the prevalence of periodontitis has been challenging because there has not been a generally accepted definition of periodontitis. When the definition includes evidence of periodontal destruction (e.g., 2 mm CAL, generally considered the lower limit of detection, in at least one tooth surface), most adults are identified as affected. It is clear, however, that this very mild form of periodontitis does not affect function or place a tooth at risk of being lost. In contrast, advanced forms of periodontitis affect 5% to 15% of different populations.

An interesting trend observed over the last 30 years in developed countries is increased tooth retention. Data from Sweden indicate a reduction in the percentage of the population affected by gingivitis and mild-to-moderate periodontitis and a corresponding increase in the percentage of the population with a healthy periodontium. As examples, the percentages of periodontally healthy persons in 1983, 1993, and 2003 were 23%, 22%, and 44%, respectively. However, the
percentage of those with severe disease remained essentially unchanged during this time (13%, 13%, and 11%).

In 2012, the prevalence of periodontitis in the United States was evaluated using data from the 2009 and 2010 National Health and Nutrition Examination Survey (NHANES).\textsuperscript{10} Earlier surveys used a partial-mouth examination format, whereas the 2009 and 2010 NHANES assessed six sites per tooth for both attachment level and probing depth. Using the Centers for Disease Control and Prevention/American Academy of Periodontology case definition\textsuperscript{11} for US adults age 30 years and older, 8.7% of the population had mild disease, 30% had moderate disease, and 8.5% had severe disease. Thus, the periodontitis burden of United States adults was found to be greater than estimated in earlier NHANES-based studies. Prevalence was greatest for men, Mexican Americans, current smokers, those with less than a high school education, and the poor.

Therefore, both diabetes and periodontitis are common and present for years before clinical symptoms are evident. In addition, proper management of both disorders requires affected persons to be involved in their own care. For those with diabetes mellitus, this means careful control of carbohydrate consumption, weight control, and adherence to other aspects of a healthy lifestyle. For those with periodontitis, this means focus on performance of proper oral hygiene. Appropriate professional care is also critical, and patients play an active role by keeping to their schedule of regular visits to their physician or dentist.

**Underdiagnosis of Diabetes and Difficulties in Achieving Optimal Metabolic Control**

A significant percentage of patients with diabetes remain undiagnosed, indicating the desirability of screening at multiple healthcare locations. Fortunately, some progress in diagnosis has been made over the last few years. Increased public attention and enhanced public health measures have led to a decrease in the percentage of undiagnosed patients with diabetes from 30% in 2005 to 24% in 2007 and 27% in 2010.\textsuperscript{3} Further improvement in the detection of diabetes can be achieved by expanding the number of contact points that undiagnosed individuals have with a wide range of healthcare providers. In the United States, there are only 17,000 certified diabetes educators and 4,000 endocrinologists\textsuperscript{12} whose primary focus is providing clinical care. These numbers pale in comparison with the escalating disease burden. Therefore, the brunt of the responsibility for diabetes screening and management has fallen on primary care physicians. A decrease in the number of primary care physicians in the workforce has generated new interest in enlisting more healthcare providers, such as dentists, to expand the diabetes screening effort. National data suggest that approximately 70% of Americans have visited a dental office in the preceding year,\textsuperscript{13,14} pointing to the potential for dental professionals to be involved in the identification of persons unaware of their diabetic status.

Despite greater understanding of the disease and the ever-expanding options for medical therapy, diabetes remains an incurable and difficult-to-control disease. Landmark studies such as the Diabetes Control and Complications Trial (DCCT)\textsuperscript{15} and the United Kingdom Prospective Diabetes Study (UKPDS)\textsuperscript{16} have convincingly demonstrated that lowering HbA1c levels was associated with significant reductions in risk for complications. In spite of the evidence, national data from 2007 to 2010 suggest that only 52.5% of diabetic adults in the United States achieved the glycemic goal of an HbA1c level of less than 7%, and almost 78% of diabetic adults met the less stringent criteria of an HbA1c level of less
than 8%.

The percentage of diabetic patients achieving the HbA1c goal of 7% for the period 2007 to 2010 appears significantly increased compared with earlier national data, but remains an unsatisfactory outcome (Figure 1). The underlying reasons for the inability of so many patients to achieve glycemic goals are not entirely clear, but it is evident that the daily challenges of managing diabetes are inseparable from the complexities of life. Managing diabetes often becomes a daily struggle balancing glycemic control with quality of life. Although the adoption of advanced medical regimens and devices has opened up unprecedented possibilities for improved diabetes care, successful outcomes can come about only by proficient application of diabetes self-management skills and concrete lifestyle changes. Particular areas of lifestyle modification, such as maintaining oral hygiene and smoking cessation, are beneficial for the management of periodontitis and diabetes, and provide strong rationale for members of the various healthcare disciplines to work together to improve health outcomes for patients.

Moreover, optimal diabetes management requires a delicate balance. Theoretically, reaching glycemic target should not be difficult as long as sufficient oral medication or insulin dosages are given. However, the practical challenge is that intensive diabetes therapy potentiates the risk of frequent and serious hypoglycemic events that in turn limit the intensity of treatment. Any interruptions such as fasting or stress factors have a significant impact on glycemic levels. All healthcare providers who routinely take care of diabetic patients should have a basic understanding of diabetes medications and the skills to manage acute hypo- and hyperglycemic emergencies.

**Underdiagnosis of Periodontitis and Complexities in Achieving Optimal Oral Hygiene Among Diabetic Patients**

Unrecognized oral changes and difficulties of diabetic patients in achieving optimal oral hygiene and in receiving professional dental care highlight the need for support by all healthcare providers.

Important changes in the oral cavity associated with diabetes mellitus may often go unrecognized and therefore untreated. Diabetes is an established risk factor for periodontitis and the only disease shown to independently and significantly increase this risk. Other oral diseases and disorders that may be linked to diabetes include *Candida* infections, reduced salivary flow, dental caries, and certain oral mucosal disorders (e.g., lichen planus, burning mouth syndrome). Periodontitis does not always mani-

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*Figure 1. Percentage of Diabetic Adults with HbA1c Levels Less Than 7.0% and Less Than 8.0%, from NHANES 1988–2010*

![Graph showing percentage of diabetic adults with HbA1c levels less than 7.0% and less than 8.0%](chart.png)

- *P < .01 and †P < .05, compared with 2007–2010 prevalence. Adapted from: *Diabetes Care* 2013;26:2271–9.*
fest with symptoms that are obvious to the patient. Furthermore, patients with diabetes are often unaware of their risk for periodontal disease, medical professionals may not discuss the link between diabetes and periodontitis with their patients, and oral care is often overlooked when trying to control other problems associated with diabetes. Thus, periodontal changes in diabetic patients may often go undiagnosed for several years.

Periodontitis is a classic chronic disorder and as such, once a patient is diagnosed, management depends on patient compliance for the most successful treatment outcomes. Patients are required to perform effective oral hygiene, which requires a daily commitment. Furthermore, maintaining regular appointments with their dentist for oral prophylaxis and examinations to determine whether the periodontal condition is stable requires a continuous decision to schedule and keep appointments. As with those with diabetes, patients with periodontitis are challenged on a daily basis to adhere to these regimens. In both cases, most patients are unable to maintain this commitment and need the support of all health professionals involved in their care.

Effect of Periodontal Infections on the Diabetic State

The relation of diabetes mellitus and periodontal disease is bidirectional. In addition to the well-documented increased prevalence and severity of periodontal disease in patients with diabetes, evidence suggests that periodontitis may adversely affect metabolic control. A recent report includes a review of how periodontal disease can affect metabolic management of diabetes, as well as the development of clinical complications of the disease.

The effect of periodontal disease on both metabolic control and ultimately on complications of diabetes is believed to be due to the effect of proinflammatory cytokines and other inflammatory mediators produced in the highly vascular periodontal tissue when periodontitis is present. Tumor necrosis factor-alpha as well as interleukins 1 and -6 are three of the many inflammatory mediators produced by the periodontal tissues. If these mediators gain entry to the systemic circulation, important adverse effects may result when diabetes is present. Of primary importance, these mediators may act as insulin antagonists.

Older reports have indicated that periodontitis in patients with diabetes is associated with subsequent development of clinical complications in these patients. Numerous recent studies have defined these associations. Saremi and colleagues examined a cohort of 628 members of the Gila River Indian Community in Arizona, a group with a very high prevalence of type 2 diabetes. Following this cohort for a minimum of 11 years revealed that those with severe periodontitis at baseline (compared with those with a healthy periodontium or mild or moderate periodontitis) had a 3.2 times risk of dying from cardiac or renal disease. In addition, another report examining the same community found that compared with no disease or mild periodontitis, individuals with moderate or severe periodontitis or those who were edentulous had a 2.0 to 2.6 times increased risk of developing nephropathy. The chance of developing end-stage renal disease was even higher for those with moderate or severe periodontitis or those who were edentulous. In both studies, the models were fully adjusted for potentially confounding variables.

More recently, Demmer and colleagues asked an intriguing question: Could the presence of periodontal disease predict the subsequent development of diabetes mellitus? Nearly 9,300 persons were included in this study; specifically, those who were part of the first United States National Health and Nutrition Examination Survey (NHANES I, 1971–1976), had received a dental examina-
tion, and were seen at least one other time (1982–1992). Periodontal status was determined by the Periodontal Index, and patients were graded on a 0 to 5 scale, with zero being periodontal health and all others grouped into quintiles by severity of periodontal disease. Diabetes was determined by evaluation of the death certificate (ICD-9 code for diabetes), use of diabetes medication as reported by the patient, and/or a stay at a healthcare facility necessitated by diabetes as determined by the discharge code. Odds ratios were calculated to assess the relation of periodontal disease to subsequent development of diabetes. Relative to periodontal health (score of zero), the risk of developing diabetes mellitus was not increased for those with scores of 1 or 2. In contrast, the odds ratios of developing diabetes were elevated in groups with scores of 3 (2.26, confidence interval [CI] 1.56 to 3.27); 4 (1.71, CI: 1.0 to 2.69); and 5 (1.5, CI: 0.99 to 2.27). For individuals without teeth, the odds ratio was 1.3 (CI: 1.0 to 1.7). Since the investigators used logistic modeling to account for the effect of other variables, these data suggest that periodontitis is an independent risk factor for the development of diabetes.

Furthermore, because infection is a risk factor for diabetes, the presence of periodontitis has been assessed in relation to an increase in HbA1c over time in nondiabetic persons. Individuals were categorized into four groups based on the percentage of sites with at least 5 mm of attachment loss at baseline. Over a 5-year period, the increase in HbA1c levels was 0.023%, 0.023%, 0.065%, and 0.106% (P = .02) for the groups with the lowest to highest severity of periodontitis. Comparing individuals without periodontal disease at baseline who did not evidence progression of periodontal destruction over 5 years with those with the greatest severity of disease at baseline who experienced further progression of disease, the change in HbA1c was 0.005% versus 0.143% (P = .003). These findings were observed in consideration of confounding variables and provide further evidence of the potential importance of periodontitis as a risk factor for dysglycemia.

Other studies have examined the relation of periodontitis to the development of incident diabetes and dysglycemia. These studies did not perform a complete periodontal examination; rather, they used indices that categorized patients according to the severity of the deepest probing depth in a sextant (Community Periodontal Index, CPI), or a partial-mouth examination with stratification into three levels of disease severity. These approaches reduce the impact of the reported findings. Examining the effect of baseline periodontal disease on subsequent glucose tolerance, persons with normal glucose tolerance at baseline but with periodontitis displayed abnormal glucose tolerance 10 years later. Confirmatory results were reported by Morita and colleagues in 2012. Following individuals with HbA1c below 6.5% for 5 years, those with periodontitis at baseline had an increased risk of having an HbA1c of 6.5 or higher (relative risk 3.4; P = .037).

In contrast, Ide and colleagues followed patients with and without periodontitis for the development of diabetes. After 7 years, moderate to severe periodontitis at baseline was associated with an increased risk of incident diabetes in an unadjusted model. However, in a fully adjusted analysis, this association was not observed.

Another approach to examining the effect of periodontitis on the diabetic state is via studies of the effect of periodontal therapy on metabolic control. As reviewed by Taylor and Borganakke, 20 studies were identified that examined the effect of nonsurgical periodontal therapy on metabolic control. Seven of these studies were randomized controlled trials (RCTs) and 13 were not (non-RCTs). Of the RCTs, four of seven
studies included the use of adjunctive antibiotics, and three of those studies demonstrated a positive effect of treatment on metabolic control. Of the 13 non-RCTs, eight reports were associated with an improvement in metabolic control. Five of the 13 reports included adjunctive antibiotics, and three of these studies demonstrated a positive effect. There is, however, great heterogeneity in terms of the design of the RCTs and the non-RCTs. It was concluded that the use of antibiotics as part of periodontal therapy to improve metabolic management in patients with diabetes has not been proved.

Subsequent systematic reviews examined the effect of periodontal therapy on glycemic control of patients with periodontal disease and diabetes mellitus. The therapy provided was usually nonsurgical (root planing and scaling), possibly with adjunctive antibiotics, but a few studies also included extraction of hopeless teeth and periodontal surgery. Two such reviews published in 2010 included five studies and seven studies, respectively. Both concluded that the reduction in HbA1c with periodontal therapy was 0.4% for a period of at least 3 months. A 2013 systematic review included studies published after the earlier meta-analyses. The reduction in the level of HbA1c was determined to be 0.36%.

All the previously mentioned studies emphasize the importance and significant implications of the link between diabetes mellitus and periodontal diseases. An emphasis must be placed on increasing professional and patient awareness of this relationship and of the need for medical-dental comanagement of affected persons.

To this end, a joint European Federation of Periodontology (EFP) and American Academy of Periodontology (AAP) Workshop and subsequent consensus report provided guidelines for both healthcare professionals and patients with diabetes. These guidelines alert physicians of the need to recognize periodontitis (and/or the risk for periodontitis) in their patients with diabetes and advise them accordingly. They also review suggestions for managing the patient with known diabetes or at risk for diabetes in dental settings. Finally, they include specific recommendations for affected patients.

**ROLE OF DENTAL PROFESSIONALS**

There is a great need for dental professionals (e.g., general dentists, periodontists, and hygienists) to assume a role in the management of the patient with diabetes.

Diagnosis and treatment of diabetes are clearly within the realm of the physician. However, dental professionals can evaluate signs and symptoms indicative of poor metabolic control in patients with known diabetes and can seek to identify patients who may remain undiagnosed and refer these patients to physicians for proper evaluation and treatment. A number of characteristics of dental practice are consistent with dentists assuming such a role: they treat large numbers of patients each year and often provide primary and preventive care. Dentists frequently see patients on a regular basis, and most visits are nonemergent in nature.

Managing the needs of patients with diabetes is not new to dentistry. The association between diabetes and periodontal disease, the possible other oral manifestations of this metabolic disorder, treatment guidelines, and special considerations with regard to the management of these patients in a dental setting all have been discussed in the dental literature, promoted by professional associations such as the American Dental Association and the American Academy of Periodontology, and taught in dental and dental hygiene schools for many decades. Similar to what has been shown within the medical profession, however, efforts to translate research into primary care have been met with resistance, and such a
gap between knowledge and practice appears to exist in the dental profession.

### Are Dental Professionals Involved?

The first reports to document the extent of US dentists’ practice activities with respect to the management of patients with diabetes demonstrated that a clear majority of general dental practitioners did not feel they had mastery of the knowledge involved, viewed such activities as peripheral to their role as caregivers, and did not believe that colleagues or patients expected them to perform such activities. Although periodontists generally performed risk identification and management for patients with diabetes more frequently than general practitioners, both groups tended to engage in activities that inquire and discuss, and rates of proactive patient management activities were low for both groups of clinicians. A subsequent study of general dentists in New Zealand showed striking similarities in attitudes and orientations compared with those identified in the US study.

These data suggested a need to increase involvement of dentists in the active management of the diabetic patient. Such actions can be expected to result in improved periodontal and general health outcomes. The evidence suggests, however, that approaches to changing dentists’ behavior should aim not only at increasing knowledge, but also at overcoming attitudes and orientations associated with actively managing patients who have diabetes. Basic views of the dentist’s role as a primary and preventive care provider need to be changed to facilitate the desired behavioral changes. When looking at predictors of active management of patients with diabetes, these appear different for general dentists versus periodontists. For the latter, variables that reflected feelings of confidence, involvement with colleagues and medical experts, and viewing active management of the diabetic patient as belonging in their sphere of professional responsibility were influential. Variables pertaining to patient relations, such as discussion with patients, patient expectations, and the Medicaid status of their patients were influential predictors for general dentists. These findings provided a first step toward identifying the components of targeted interventions aimed at increasing the level of involvement of specialists and general dentists in the management of the diabetic patient, thereby contributing to the improvement of the dental patient’s oral and systemic health.

More recent surveys of dental professionals and dental patients indicate support for dental professionals to be more involved in the management of patients with diabetes. A national sample of dentists indicated that most respondents believe that it is very important or somewhat important to screen for certain conditions, with nearly 80% believing that assessment should include diabetes. Furthermore, patients seen at an inner city dental clinic and those at private dental offices were asked about their feelings regarding chairside testing for certain medical conditions. The responses by clinic patients were overwhelmingly in support of such screenings. The responses from patients seen in private practice were also very supportive, but not to the same degree as clinic patients. This difference likely related to greater access to medical services for private practice patients. A national/international survey specifically focused on a blood test for diabetes performed in the dental office and revealed that more than 80% of dental professionals feel that such screening is important; the primary concern was about the time required to perform the test (22% of respondents).

### How Can Dental Professionals Be More Involved?

For dental professionals to provide safe and effective oral care to patients with diabetes, to be able to contribute to the patients’ better overall management, and to help in
the identification of those with prediabetes or even those with frank diabetes who remain undiagnosed, it is essential to have a thorough knowledge of certain aspects of this complex disorder. Dental professionals need to be aware of and appreciate the many risk factors involved in the development of diabetes, the types of treatments diabetic patients may be receiving, the risk for emergency episodes, the difficulties and everyday challenges that diabetic patients are faced with, and the constant support and reinforcement these patients need to properly manage their chronic condition.

Every dental care setting should have clinical protocols in place to provide for the dental needs of a patient with diabetes. These should include:

- criteria assessed and risk factors considered when screening patients with potentially unrecognized (pre) diabetes
- evaluation of every new diabetic patient
- routine care of a diabetic patient based on their level of metabolic control
- appropriate equipment, supplies, and training to prevent and/or manage a diabetic emergency during or after a dental appointment

In addition, guidelines should be in place to determine:

- the need for a medical consultation, referral, or follow-up
- how to perform risk assessment for oral/periodontal diseases
- the need for dental and/or periodontal therapy and the frequency of follow-up care
- the need to refer to a dental specialist

Taking a complete medical history is something that all dental practitioners are required to do every time they see a new patient, and updates should be performed at each maintenance/recall visit. However, once a patient identifies as having diabetes, the dentist should gather and record additional detailed information, including:

- type of treatment/medications the patient is receiving
- level of the patient’s metabolic control, including recent HbA1c values
- presence of any diabetic complications or other diabetes-associated conditions (e.g., obesity, hypertension, hypercholesterolemia)
- frequency of prior hypoglycemic episodes and precipitating factors

One very important next step is for the dentist to establish communication with the treating physician. This allows the dentist to confirm answers to the latter questions, especially when the patient is a poor historian. The dentist can then inform the physician about his/her dental treatment plan, discuss any concerns, and get advice about potential changes in the management of the patient if the plan includes any invasive and/or stressful procedures. Communication should be ongoing, especially when the planned dental treatment is extensive and the patient is poorly controlled.

An essential part of the oral disease risk assessment for patients with known diabetes is a detailed clinical evaluation. This should include:

- a thorough intraoral exam for oral mucosal lesions (e.g., lichen planus, aphthous stomatitis)
- identification of signs and/or symptoms of opportunistic infections (e.g., oral candidiasis)
- evaluation of salivary flow
- assessment of taste disturbances and signs/symptoms of burning mouth syndrome
- dental caries assessment
- a complete periodontal evaluation with whole-mouth probing depth and attachment loss measurements, assessment of the level of plaque and gingival inflammation, and radiographic evaluation of bone levels, as needed

Managing the dental care of diabetic
patients should not be a significant challenge in most cases. Any active infection must be immediately treated because it may also have a significant adverse impact on the diabetic state, especially the level of glycemic control. The patient with diabetes who is under good medical care and maintains good glycemic control generally can receive any indicated dental treatment.

Recommendations for proper home care are very important for patients with diabetes and must be discussed in detail before any therapy and reviewed at follow-up visits. The oral hygiene regimen should include an over-the-counter toothpaste and/or mouth rinse with antibacterial properties to help manage supragingival plaque and gingival inflammation. Patients must be encouraged to brush and floss after each meal, conduct self-examinations regularly, and contact the dentist or hygienist if they see signs of infection, such as edematous, bleeding gingiva or other oral changes, such as ulcers, burning mouth, or reduced salivary flow.

In patients with known diabetes, dentists should not only aggressively screen for, but also carefully treat periodontal infections. Important points for consideration follow:

- If periodontal or other oral surgery is needed, the level of glycemic control may determine healing and response to treatment.
- Elective therapy may be postponed until the patient demonstrates improved metabolic control.
- The response to initial periodontal therapy (scaling and root planing) should be closely monitored because it may help the dentist to better assign prognosis and predict outcomes of further treatment, including response to and healing capacity after periodontal surgery, extractions, implant surgery, or regenerative procedures.
- After active dental and/or periodontal therapy, patients should be scheduled for frequent recall appointments to prevent and monitor bacterial recolonization, reinforce proper oral hygiene, and treat any disease reactivation.
- There is no need for antibiotic premedication, but antibiotics may be considered pre-/postoperatively or in conjunction with periodontal therapy, especially if an overt infection is apparent.
- Since diabetes affects the host response to infection, adjunct therapies such as locally delivered antimicrobials, systemic antibiotics, or a subantimicrobial dose of doxycycline may be considered.
- The patient’s physician should be consulted about dietary recommendations and any modification to the type and dose of medications both pre- and postoperatively.
- Typically, diabetic patients should receive morning appointments when endogenous corticosteroids are at high levels (better stress management).
- Vital signs, blood pressure, and blood glucose levels should be assessed preoperatively and as discussed in detail in the text that follows.
- Appointments should be kept as nontraumatic, short, and stress-free as possible, because endogenous epinephrine release in response to stress and pain can antagonize insulin action and promote hyperglycemia.
- Epinephrine should be used in the dental anesthetics to ensure long-lasting and profound anesthesia.
- Postoperative analgesics should be provided to ensure that the patient is pain-free after tooth extraction, periodontal surgery, or any other invasive procedure.

**Prevention and Proper Management of Diabetes-Related Emergencies**

Glycemic variability is one of the most frequently encountered medical emergencies in dental offices. All dental professionals should
be trained to prevent, recognize, and properly manage both hypo- and hyperglycemic episodes.

*Hypoglycemia* is defined as plasma glucose level below 70 mg/dL and confirmed when symptoms are relieved after eating. It is important to note that diabetic patients may complain of symptoms suggestive of hypoglycemia at blood glucose levels higher than 70 mg/dL if they have had chronically elevated blood glucose. Hypoglycemia is commonly caused by missing or delaying meals while taking medication, consuming alcohol, exercising, or doing a combination of these. Some of the important questions to ask patients at the beginning of the office visit may include: “Did you miss or delay your meal?” “Did you exercise without snacking?” “Did you adjust your medication and how?”

The classic symptoms of hypoglycemia are hunger, shakiness, nervousness, sweating, and weakness. However, as the duration of diabetes and the frequency of hypoglycemic events increase, individuals with diabetes gradually lose these obvious adrenergic symptoms. The deficient release of counter-regulatory hormones and the blunted autonomic responses eventually result in a state of hypoglycemia unawareness. At this stage, the focus for the patient and office staff education should be on identifying a distinct set of less obvious neuroglycopenic symptoms, such as slow cognitive response, light-headedness, sleepiness, confusion, difficulty speaking, and anxiety.

The steps for intervention when hypoglycemia is suspected are outlined in Figure 2. The immediate treatment for hypoglycemia is to give glucose or carbohydrates that easily break down to glucose, such as glucose tablets, fruit juice, nondiet soda, or honey. Complex carbohydrates and foods that contain fat may delay the recovery process and are not recommended as first-line treatment. A commonly recommended treatment algorithm for hypoglycemia, also known as the 15-15 rule, includes (1) consume 15 g of simple carbohydrates; (2) wait 15 minutes to recheck blood glucose; and (3) repeat 15 g of carbohydrates when glucose level is still below target (70 mg/dL). If the initial glucose is below 50 mg/dL, consumption of 30 g of simple carbohydrates is indicated. Shortly after the immediate treatment, the patient should follow with a meal.

**Figure 2. Steps for Intervention When Suspecting Hypoglycemia**

1. Check blood glucose to confirm hypoglycemia (blood glucose < 70 mg/dL).
2. If patient is conscious, give 15 g of simple carbohydrates orally as immediate treatment.
   Options include 4 oz of fruit juice, 5–6 oz regular soda, 1 tablespoon of table sugar or honey, 7–8 Lifesaver candies, 3 tablespoons of jelly, 2 tablespoons of raisins, or 4–5 glucose tablets. If initial blood glucose is less than 50 mg/dL, give 30 g of simple carbohydrates.
3. Recheck blood glucose after 10–15 minutes. If blood glucose is less than 70 mg/dL repeat the treatment (step 2) until blood glucose returns to at least 90 mg/dL.
4. Follow with a meal or snack such as 6 saltine crackers, 3 graham cracker squares, or 1/2 peanut butter sandwich. Further glucose monitoring may be necessary.
5. If patient is unconscious, activate 911. Inject glucagon intramuscularly.
6. When patient is alert enough to swallow, give fruit or soda immediately and follow steps 2 to 4.
or snack. In practice, food such as ½ peanut butter sandwich, six saltine crackers, or three graham cracker squares provides complex carbohydrates and protein to prevent further hypoglycemia. Occasionally, blood glucose can plunge into the hypoglycemic range again after the return to a normal level. Therefore, further glucose monitoring may be necessary before leaving the dental office, especially before operating a motor vehicle. There always exists the temptation to overtreat hypoglycemia with a large amount of carbohydrates because of the urgency and discomfort associated with the symptoms. Yielding to this practice can lead to excessive rebound hyperglycemia, thereby generating vicious cycles of glycemic instability. In the event of severe hypoglycemia in which the person is unconscious or too confused to ingest carbohydrates, trained personnel in addition to activating the emergency medical service may use an intramuscular injection of glucagon, which is packaged as a 1-mg ampule of glucagon with diluent and a syringe. The glucagon injection is expected to restore the patient to consciousness within 10 to 15 minutes, but the effect may be short-lived. Every dental office should have staff capable of using a glucose monitor and glucagon. In addition, care should be taken to ensure that dental offices are equipped with glucose monitors, unexpired glucose testing strips, glucagon kits, and appropriate food/drink for treatment of a hypoglycemic episode.

Prevention and early recognition of hypoglycemia is obviously best and an important component in the planning for a dental procedure. Most office-based dental procedures do not necessitate an adjustment of diabetes medications. When fasting or sedation is required, proper medication adjustment should be made in advance to prevent an in-office diabetic emergency. Close communication among the healthcare providers should be a priority. Appointing diabetic patients early in the day can prevent hypoglycemic episodes associated with prolonged fasting or delayed or skipped meals.

Not all diabetes medications cause severe hypoglycemia. For the purpose of classifying drugs according to their risk for hypoglycemia, diabetes medications can be divided into either antihyperglycemic or hypoglycemic (Table 1). Technically, the antihyperglycemic class of medications includes agents that can lower glucose from the hyperglycemic range to near normal range without the risk of driving the glucose concentration into the hypoglycemic range. Most of these agents work by mechanisms distinct from direct stimulation of insulin production. For others, the stimulation of insulin release occurs in a glucose-dependent manner. Therefore these drugs have little potential to cause hypoglycemia when used alone. In other words, the glucose-lowering effect of these drugs moderates as glucose levels normalize. These drugs include biguanide, thiazoladinediones, alpha-glucosidase inhibitors, incretins, bile acid binders, and SGLT2 or dopamine agonists. The hypoglycemic class of medications lowers glucose levels either by insulin replacement or direct insulin stimulation. Sulfonylureas, short-acting insulin secretagoues, and the various insulin formulations have the highest hypoglycemic potential. Insulin-requiring patients are subject to hypoglycemic events and hypoglycemia unawareness, which can severely disrupt quality of life and compromise the ability to tighten glucose control. A common misconception is that all patients on insulin have type 1 diabetes. Although it is correct that individuals with type 1 diabetes must rely on insulin for survival, many with type 2 diabetes also require insulin at later stages of the disease. It is important to recognize that the use of antihyperglycemic agents is associated with a profound risk of hypoglycemia when combined with drugs from the hypoglycemic class.
Generally, there is no need for adjustment of the medication or insulin regimen before or on the day of the dental appointment. If the patient is asked to fast overnight before the office visit and basal insulin is used, then either the same dose or no less than 75% of its dose should be given the night before. If neutral protamine Hagedorn (NPH) insulin or premix insulin is generally taken at night, then no dose adjustment is required the night before the procedure. On the day of the dental visit, the fasted patient should be instructed not to take any antidiabetic oral medications or fast-acting insulin in the morning. If basal insulin is usually taken in the morning, either the same dose or no less than 75% of its usual dose should be given. Those who are on NPH or premix insulin in the morning should take only one third to one half of the usual dose. Glucose levels should be monitored before the procedure upon arrival in the office. During a prolonged procedure, periodic glucose monitoring may be necessary. The regular medication regimen can be resumed upon returning to normal diet after the procedure is finished. In general, and especially for long and stressful procedures, the dentist should consult with

Table 1. Classification of Diabetes Agents According to Their Potential to Lower Glucose Below Physiologic Range

<table>
<thead>
<tr>
<th>Hypoglycemic Agents</th>
<th>Anti-Hyperglycemic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Biguanide</td>
</tr>
<tr>
<td>Glyburide (Diabeta®, Micronase®)</td>
<td>Metformin (Glucophage®)</td>
</tr>
<tr>
<td>Glipizide (Glucotrol®, Glucotrol XL®)</td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting secretagogues</strong></td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Repaglinide (Prandin®)</td>
<td>Pioglitazone (Actos®)</td>
</tr>
<tr>
<td>Nateglinide (Starlix®)</td>
<td>Rosiglitazone (Avandia®)</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Alpha-glucosidase Inhibitors</td>
</tr>
<tr>
<td><em>Basal/intermediate to long-acting insulin</em></td>
<td>Acarbose (Precose®)</td>
</tr>
<tr>
<td>Detemir (Levemir®)</td>
<td>Miglitol (Glyset®)</td>
</tr>
<tr>
<td>Glargine (Lantus®)</td>
<td></td>
</tr>
<tr>
<td>NPH (Novolin N®, Humulin N®)</td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting insulin</strong></td>
<td>Incretins</td>
</tr>
<tr>
<td>Regular human insulin (Novolin R®, Humulin R®)</td>
<td>Exenatide (Byetta®)</td>
</tr>
<tr>
<td><strong>Ultra-short-acting insulin</strong></td>
<td>Sitagliptin (Januvia®)</td>
</tr>
<tr>
<td>Aspart (NovoLog®)</td>
<td>Liraglutide (Victoza®)</td>
</tr>
<tr>
<td>Lispro (Humalog®)</td>
<td>Exenatide LAR (Bydureon®)</td>
</tr>
<tr>
<td>Glulisine (Apidra®)</td>
<td>Saxagliptin (Onglyza®)</td>
</tr>
<tr>
<td><strong>Mixed insulin</strong></td>
<td>Linagliptin (Tradjenta®)</td>
</tr>
<tr>
<td>Aspart 70/30 (NovoLog mix 70/30)</td>
<td></td>
</tr>
<tr>
<td>Lispro 75/25 (Humalog mix 75/25)</td>
<td></td>
</tr>
<tr>
<td>Lispro 50/50 (Humalog mix 50/50)</td>
<td></td>
</tr>
<tr>
<td>Regular human mix 70/30</td>
<td></td>
</tr>
<tr>
<td>(Humulin 70/30, Novolin 70/30)</td>
<td></td>
</tr>
<tr>
<td>Regular human mix 50/50 (Humulin 50/50)</td>
<td></td>
</tr>
<tr>
<td><strong>Amylin analog</strong></td>
<td>Bile acid binder</td>
</tr>
<tr>
<td>Amylin (Symlin®)</td>
<td>Colesевelam (Welchol®)</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitor</strong></td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>Canagliflozin (Invokana®)</td>
<td>Bromocriptine mesylate (Cycloset®)</td>
</tr>
</tbody>
</table>
the treating physician regarding medication adjustments.

It is well known that chronically elevated glucose levels impair wound healing and predispose patients to infections. In contrast, transient hyperglycemia at levels lower than 300 mg/dL during an office appointment generally does not pose an immediate danger to most patients with type 2 diabetes, nor does it necessitate cancellation of the dental procedure as long as hyperglycemia is corrected shortly. Acute hyperglycemia can occur in the setting of pain, stress, or underdosing of diabetes medications related to the dental procedure. Reviewing recent HbA1c test results can help determine the recent glycemic trends. However, for patients with type 1 diabetes, significant ketoacidosis (also known as diabetic ketoacidosis or DKA) can occur at glucose concentrations usually above 250 mg/dL, in which additional insulin administration and hydration are urgently indicated. The telltale signs and symptoms of DKA include excessive thirst, fatigue, rapid breathing, fruity breath, nausea, and vomiting. Most patients with type 1 diabetes have the skills to manage hyperglycemia and mild DKA by aggressive rehydration and insulin administration; however, a consultation with the patient's medical provider is necessary when the symptoms become severe. A patient who is severely nauseated or unable to keep down fluids and with blood glucose above 250 mg/dL should be transferred to a hospital emergency room for medical intervention.

**Screening for Undiagnosed Diabetes in the Dental Office**

Early identification of diabetes and, in diagnosed patients, achieving and maintaining glycemic levels as close to normal as possible, have been the focus of efforts from the American Diabetes Association and the medical and public health communities for many years. With respect to testing for undiagnosed diabetes and prediabetes in asymptomatic patients, the American Diabetes Association currently recommends that such testing should be considered in adults of any age who are overweight or obese and who have one or more additional risk factors for diabetes. In those without risk factors, testing should begin at 45 years of age (Figure 3).

The increased risk is associated with certain demographic characteristics (minority race/ethnicity status, family history of diabetes), clinical characteristics (physical inactivity, hypertension, dyslipidemia), and prior evidence of abnormal glucose values (gestational diabetes, IFG, IGT).

Historically, the primary method used to diagnose diabetes mellitus has been the fasting plasma glucose test. Though valuable for making a diagnosis, this test tends to have low sensitivity. The HbA1c assay is based on the knowledge that blood glucose can bind to hemoglobin molecules. This reaction is not enzymatically driven and therefore is a measure of the exposure to glucose in the blood. Based on the 2013 revisions of the Standards of Medical Care in Diabetes by the American Diabetes Association, the HbA1c assay is also now accepted as a test to diagnose diabetes (with a cut point of ≥ 6.5%). In addition, this assay remains very valuable for monitoring glycemic levels and response to treatment, and it can be an excellent screening tool that does not rely on patient compliance, does not require fasting, and gives an indication of glucose levels over an extended period of time.

The importance of early diagnosis of diabetes cannot be overstated and clearly cannot be the sole responsibility of the medical community or of any single group of healthcare providers. Survey data from the American Dental Association published in 2008 show that 68.5% of adults had visited a dentist in the previous year, and data from the Behavioral Risk Factor Surveillance System suggest an even higher percentage.
Insurance utilization patterns indicate that individuals tend to seek routine and preventive oral healthcare on a more frequent basis than routine and preventive medical care.\(^a\) These facts allow dentists and dental hygienists to be at the front line of screening interventions and risk-reduction strategies.\(^b\) Yet can this happen in real world practice?

Previous studies have examined the performance of predictive models for diabetes screening in medical settings using a mix of self-reported and objective characteristics.\(^c\) The first report to explore a predictive model for undiagnosed diabetes\(^d\) that included measures of periodontal disease used national data from the third NHANES study and was published in 2007. Findings revealed that, for example, a 45-year-old person, with self-reported family history of diabetes, self-reported hypertension, self-reported high cholesterol levels, and clinical evidence of periodontal disease bears a probability of having diabetes (and being unaware of it) of between 27% and 53%, with Mexican-American men exhibiting the highest and white women the lowest.\(^e\) These probabilities increase among persons 60 years of age to between approximately 48% and 74%. These findings, combined with supportive data by subsequent NHANES-based studies,\(^f\) demonstrate that simple pieces of information from a patient’s medical history and an oral examination can be used effectively to identify patients at risk for undiagnosed diabetes in a dental care setting. The results of this novel approach afforded the opportunity to further test such a model in the clinic.

In a study published in 2011, individuals who presented for care at a dental school clinic and had never been told they have prediabetes or diabetes were recruited.\(^g\) To target those at some level of risk for diabetes, the inclusion criteria included (a) being ≥ 40 years old if non-Hispanic white or ≥ 30 years old if Hispanic or non-white, and (b) self-report of
at least one diabetes risk factor (family history of diabetes, hypertension, high cholesterol, or overweight). This resulted in 535 subjects who then received a periodontal examination and a point-of-care fingerstick HbA1c test, which provided additional variables to be used in the prediction models. Subjects were asked to return fasted for an FPG test, the result of which was used as the study outcome to signify potential diabetes or prediabetes, per American Diabetes Association guidelines at the time. Of 506 subjects who returned for the FPG test, 21 (4.2%) were identified as potentially diabetic (FPG ≥ 126 mg/dL), and 161 (31.8%) as prediabetic (FPG = 100–125 mg/dL). Performance characteristics of simple models to identify dysglycemia (FPG ≥ 100 mg/dL) were evaluated, and optimal cut-offs for each variable in a given model were identified. The presence of ≥ 26% teeth with deep periodontal pockets or ≥ 4 missing teeth correctly identified 73% of true cases; the addition of an HbA1c ≥ 5.7% increased correct identification to 92%. Both predictive models presented in this study had sensitivity similar to what has been reported for diabetes risk assessment approaches tested in medical settings. A limitation is that the population under investigation was predominantly Hispanic, and thus further studies to assess external validity of these models in diverse patient populations is needed.

Recently, more studies exploring the notion of screening for undiagnosed diabetes in dental settings have been published, and work has provided evidence that implementation of diabetes screening in dental settings is feasible and that patients and dental providers alike feel that the dental visit is a good opportunity for early diabetes identification.54–57

**Participation in the Management of Patients with Unrecognized or Known Diabetes**

Based on the above studies, the dentist or dental hygienist should assess the presence of risk factors for diabetes in their patients (Figure 4). A risk calculator is available from the American Diabetes Association, and dental professionals can also use that to assess (and discuss) levels of risk for diabetes in their patients.58 If they identify a patient at risk, they can either use a screening blood test in the office or refer to a physician for diagnostic testing. Regardless of the strategy used and the result of any testing, the concerns and findings need to be discussed with the patient and, in the case of a medical referral, the dental professionals need to follow up on the outcome.

Similarly, dental professionals should be involved in the ongoing efforts of patients with known diabetes (or prediabetes) to achieve appropriate glycemic control and modify behavior and habits, such as smoking, lack of physical activity, and unhealthy diet—all risk factors that may exacerbate diabetes-associated complications. Dentists and dental hygienists can help their patients by:

- evaluating and managing risks for oral complications
- providing guidance in goal setting
- helping with strategies to achieve goals and overcome barriers
- providing continuous education, reinforcement, and support

Dental practices should establish a system of referrals for routine preventive care as well as for urgent needs. A list of providers, with phone numbers and other contact information, can be very useful for quick reference. The dental team should also consider giving handouts to patients with referral information, or calling clinics directly. Multidisciplinary team care is key to both successful diabetes recognition and management.

**Patient Education**

A report from the United Kingdom in 2008 assessed the knowledge of diabetic patients regarding their risk for periodontal disease and their attitudes toward oral health.59 Only a third of the 101 patients who participated in the study were aware of their increased
Figure 4. Dental-Medical Collaboration is Key to Both Successful Diabetes Recognition and Management

Dental and medical professionals need to work beyond professional boundaries and strive for the best possible care of their mutual patients. Dental professionals can contribute to the identification of individuals with diabetes or prediabetes that remain undiagnosed, and medical professionals can screen for periodontal diseases and promote oral health in patients with diabetes.
risk for periodontitis as opposed to their knowledge of the risk for other diabetic complications, which ranged from 84% to 99%. History of dental care was sporadic, with 43% reporting seeing a dentist within the last year. An earlier study from Sweden60 had reported that 83% of diabetic patients were unaware of the link between diabetes and oral health, and that 48% believed that their dentist/dental hygienist was unaware that they even had diabetes. Oral health does not appear to be a priority for patients with diabetes.13,61-63 Tomar and Lester13 reported that diabetic individuals were less likely to visit a dentist than a nondiabetic individual in the preceding 12 months, and the leading reason for not seeing a dentist was “lack of perceived need.” Competing financial and time commitments may explain the inadequacy of routine dental care in patients with diabetes.64

Dental professionals have an opportunity and the responsibility to educate their patients about the diabetes-oral health link and promote good oral and overall health behaviors. They should play a supporting role in modifying patient behavior and habits related to risk factors that may exacerbate diabetes-associated complications. Specifically, as part of oral health education, oral health care providers can reinforce the need for regular dental visits and proper oral hygiene, but also the need for proper nutrition, exercise, smoking cessation, adherence to medication regimens, regular monitoring of blood glucose levels, and regular medical follow-up, as indicated by the patient’s physician. Patients should be encouraged to achieve the best glycemic control possible, since good control can improve oral health and lead to better and more predictable periodontal treatment outcomes. To this end, patients need to know that they are at greater risk for increased prevalence, severity, and progression of periodontitis and that periodontitis has been recognized as a condition often found in patients with diabetes. Indeed, the American Diabetes Association Standards of Medical Care in Diabetes recognize that every patient with diabetes needs to see a dentist for appropriate evaluation and treatment of oral diseases.4 Patients need to be informed that proper control of periodontal infections may even have a beneficial effect on their level of metabolic control and systemic inflammation, as well as the risk for vascular and kidney complications.22

Patients must comprehend the overarching principle that medical and dental professionals have common goals: providing the best possible care to their patients and helping them avoid complications (Figure 5). Multifactorial, complex diseases such as diabetes and periodontitis interrelate and can amplify one another, creating an imperative for a comanagement model that has the potential to improve patient outcomes.

**ROLE OF MEDICAL PROFESSIONALS**

Members of the medical and dental academic communities, dentists, hygienists, physicians, nurses, representatives from dental and diabetes professional societies, as well as representatives from dental/medical insurance carriers, have convened a number of workshops over the past years to address oral-systemic links and discuss issues related to communication among different healthcare professionals and patients.

As an example, two such symposia and their subsequent reports highlighted these issues and offered recommendations. Following the Scottsdale Project meeting in April 2007, a panel of experts presented a consensus report that stated, “it is appropriate to develop guidelines to assist medical providers in identifying patients who are at risk for periodontal disease or screening patients who may have undiagnosed periodontal disease.”65 Similarly, the report following the July 2007 Oral-Systemic Diseases: From Bench to Chair—Putting Information into Practice symposium stated, “there is a need for coor-
Figure 5. Key Messages All Healthcare Providers Can Reinforce

- Emphasize the importance of good control (HbA1c, blood pressure, cholesterol) for complication prevention
- Promote a healthy lifestyle
- Reinforce self-exams
- Explain the benefits of comprehensive multidisciplinary care and emphasize the importance of regular appointments with medical and oral healthcare providers

How Can a Busy Healthcare Provider Find the Time to Give Key Messages?
- Do not give every message at one appointment
- Customize and prioritize messages according to the patient’s needs
- Provide patient with a computer-generated reminder of key messages discussed
- Document what is accomplished at each appointment and the patient’s response
- Create pamphlets for office or use materials available through national diabetes or dental organizations and professional societies
- Include key messages in office newsletters

Source: Adapted from the 2007 National Diabetes Education Program publication Working Together to Manage Diabetes: A Guide for Pharmacists, Podiatrists, Optometrists, and Dental Professionals. Atlanta, GA. US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 2007.69

dination and cooperation between dental and medical health professionals with regard to screening for and diagnosing diseases or conditions that affect patients who traditionally have been cared for by other healthcare providers. Therefore, medical practitioners need to be aware of oral diseases and make appropriate recommendations and referrals.76

The concepts emphasized above are especially important for medical professionals who treat patients with diabetes (e.g., internists, diabetologists, nurses, diabetes educators), since these patients are more likely to have periodontal disease and more likely to have less regular dental care. Medical care providers need to discuss with their diabetic patients the importance of oral health and its relation to the diabetic state, and the potential sequelae of long-standing and untreated oral infections and to provide educational brochures and other relevant material. By simply asking whether they have a dentist and when they last visited a dentist, physicians can send a powerful message and play a significant role in promoting oral health and preventing oral complications in patients with diabetes. The recent EFP-AAP Workshop and subsequent consensus report mentioned earlier36 corroborated these concepts and provided guidelines for healthcare professionals who care for patients with diabetes.

Screening for Periodontal Changes and Key Questions to Ask

The guidelines for diagnosis of periodontal diseases include a detailed periodontal evaluation, including probing depth measurements and intraoral radiographs, which are not feasible in most medical settings. Nevertheless, medical providers can screen for periodontal diseases (Figure 4) based on patient history, symptoms (sore, bleeding gums, sensitive teeth, history of abscesses), and a
visual assessment of the patient’s mouth for relevant signs, such as:
• food debris or plaque around teeth
• red, swollen, receding, or bleeding gums
• loose teeth, separation of teeth
• oral abscesses
• missing teeth
• halitosis

If diabetic patients tell a member of the medical team that they have not seen a dentist in the last year, they should be immediately referred to one. If a patient has seen a dentist in the last year, but presents with detectable signs or symptoms of oral/periodontal infections, he or she should also be referred to a dentist. Finally, physicians should advise all poorly controlled diabetic patients to see a dentist/periodontist for evaluation and treatment on a regular, ongoing basis. Medical care providers should also facilitate communication with treating dental practitioners by offering information on the patients’ medical background, level of glycemic control, presence of complications, and comorbidities. Furthermore, physicians should be available to offer advice on modification of medical management that may be necessary and should be open to a meaningful professional interaction to ensure that patients receive the best possible care.

PATIENT-CENTERED TEAM CARE
Finally, the concept of a “syndemic approach to diabetes management,” as introduced and discussed in the dental literature by Hein and Small,49 deserves some mention. Syndemic is a term originally used to describe a set of two or more linked health problems, which synergistically contribute to excess burden in a population.67 A syndemic orientation has the potential to provide a framework that can guide more efficient and effective initiatives because healthcare providers do not approach diseases such as diabetes and periodontitis as discrete problems and are prompted to collaborate across and beyond professional boundaries.

The model of “working together” has been extensively discussed in the diabetes literature. In 2001, the National Diabetes Education Program (NDEP), a joint program of the National Institutes of Health and the Centers for Disease Control and Prevention, published a report titled, Team Care: Comprehensive Lifetime Management for Diabetes.68 This report was created to help organizational leaders of healthcare systems and purchasers of healthcare to implement multidisciplinary team care for people with diabetes in all clinical settings and to set forth an analysis of the evidence that supports team care as an effective method of chronic disease management.

The executive summary of this report stated that although primary care physicians currently provide 80% to 95% of diabetes care in the United States, they cannot do all that is required and often are discouraged that the current medical system does not function well for people with diabetes.68 The challenge is to find a way to meet the needs of patients with diabetes by broadening the opportunities for delivery of care. Team care meets this challenge by integrating the skills of different healthcare professionals with those of the patient and family members to create a comprehensive lifetime diabetes management program. The report highlights that if diabetes care is to achieve the health benefits that modern science has made possible, it must be:
• continuous, not episodic
• proactive, not reactive
• planned, not sporadic
• patient-centered rather than provider-centered
• population-based, as well as individual-based

CONCLUSION
Although the model of multidisciplinary, patient-centered care presents many challenges, all healthcare providers should strive
to participate in it. There is no doubt that by changing their thinking and trying to adopt these concepts into everyday practice, healthcare providers can render better health care and more predictable therapeutic outcomes, maximize their success in combating the diabetes epidemic, and play a significant role in promoting the oral and overall health of patients. In the Working Together to Manage Diabetes 2007 publication by the NDEP, all healthcare providers are called on to play a role in diabetes primary prevention and in diabetes control. Among others, dentists and dental hygienists can make a difference in primary prevention and management because patients are seen on a regular basis by them, patients trust them, and a few words from them can have a major impact on patients’ healthcare behavior.

**Supplemental Readings**


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CHAPTER 15
Dental and Medical Comanagement of Cardiovascular Disease

Timothy C. Nichols, David W. Paquette

INTRODUCTION
Cardiovascular disease (CVD) accounts for 29% of deaths worldwide, ranks as the leading cause of death, and is greatest in low-income and middle-income countries.\textsuperscript{1-5} Atherosclerosis, a major component of CVD, affects one in four persons and contributes to about 40% of deaths annually in the United States.\textsuperscript{4} Between 2010 and 2030, the cost of medical care for heart disease (in 2008 dollar values) is predicted to rise from $273 billion to $818 billion (http://newsroom.heart.org/news/1241). The pervasiveness of CVD makes it a natural target for prevention by all healthcare professionals. If prevention programs could reduce the acute treatment costs and associated morbidity of CVD by 20% per year, the savings would be at least $80 billion per year in healthcare costs. By comparison, in 2010, the federal government spent $62 billion on Part D, representing 12% of total federal spending for Medicare that year (https://www.cbo.gov/sites/default/files/cbofiles/attachments/12-01-MedicarePartD.pdf).\textsuperscript{5} This chapter reviews the known risk factors for CVD that are current targets for disease prevention and discusses a current and future rationale for oral, dental, and medical healthcare practitioners to work together to implement optimal CVD risk factor reduction.

The learning objectives for this chapter are:

1. Understand and define the pathogenesis of coronary atherosclerosis and recognize its acute and chronic clinical presentations.
2. Understand the scientific basis that identified risk factors for CVD.
3. Understand the rationale that justifies intervention by risk factor reduction.
4. Understand commonly used medications for patients with CVD and their impact on the delivery of oral and dental care.

ATHEROSCLEROTIC
CARDIOVASCULAR DISEASE
Pathogenesis
Atherosclerosis has been defined as a progressive disease process that involves the large- to medium-sized muscular and large elastic arteries. Coronary atherosclerosis may obstruct blood flow and result in ischemia to the myocardium that is dependent on the blood supply of the diseased artery. The lesions may also rupture, and the resulting thrombus may be clinically silent or cause a fatal myocardial infarction (MI; i.e., heart attack). About 40% of deaths in the United States are attributed to complications of atherosclerosis; about half of these sequelae are represented by coronary atherosclerosis complicated by thrombosis and MI.\textsuperscript{6}

Atherosclerosis generally begins in childhood and manifests as a flat, fatty streak usually detected only as an incidental finding at an autopsy performed for other reasons.\textsuperscript{7,8} The advanced, raised lesion is the atheroma, which consists of elevated focal intimal plaques with a central core containing necrotic cells, cholesterol ester crystals, lipid-laden foam cells, and plasma proteins including fibrin and fibrinogen. This central core is also associated with a cellular infiltrate composed of hypertrophic smooth muscle cells, macrophages, and sparse T lymphocytes.

One theory of atherogenesis is that the atherosclerotic plaque develops as a response to injury to the vascular endothelium and
that the endothelial injury is the primary event in atherogenesis. When the endothelium is even minimally injured, platelets and monocytes accumulate and attach to the damaged wall. As platelets aggregate around the injury, they release thromboxane, promoting further platelet aggregation and coronary vasoconstriction. Monocytes invade the intima and scavenge for lipids and other extracellular materials. These cells release various growth factors that attract more smooth muscle cells from the media of the artery with resultant intima hyperplasia. As the lesion progresses, fibrosis, lipid deposition, necrosis, and calcification may ensue to yield the complicated plaque. Inflammation and oxidative and mechanical stress by high blood pressure can induce primary injury of the arterial endothelium as well, by which the pathogenesis of atherosclerosis can be initiated and propagated.9

**Risk Factors**

Traditional major risk factors for atherosclerotic CVD include cigarette smoking, hypertension (> 140/90 mm Hg), high levels of low-density lipoprotein (LDL) cholesterol (> 100 mg/dL), low levels of high-density lipoprotein (HDL) cholesterol (< 40 mg/dL), insulin resistance, diabetes mellitus, family history of premature coronary heart disease (< age 45 years), age (men > 45 years, women > 55 years), obesity (body mass index > 30 kg/m²), physical inactivity, and an atherogenic diet (Figure 1). It is also recognized that these factors can interact with each other to increase risk of CVD.10 For example, the Framingham Heart Study contained over 3,000 patients and showed that for total cholesterol levels between 185 mg/dL and 335 mg/dL, cardiovascular risk was elevated further with the addition of each of the following risk factors: glucose intolerance, elevated systolic blood pressure, cigarette smoking, and left ventricular hypertrophy on electrocardiography.11

Data from the Framingham Heart Study and from two other large prospective cohort studies—the Chicago Heart Association Detection Project in Industry (N = 35,642) and the Multiple Risk Factor Intervention Trial (N = 347,978)—indicate that most patients with fatal coronary artery atherosclerosis or nonfatal MI present with at least one of four risk factors: cigarette smoking, diabetes mellitus, hyperlipidemia, and hypertension.12 With fatal MI due to coronary artery atherosclerosis, exposure to at least one risk factor ranged from 87% to 100% for all three cohorts. For nonfatal MI in the Framingham Heart Study cohort, prior exposure to at least one risk factor was found in 92% of men and 87% of women ages 40 to 59 years at baseline. Furthermore, another recent analysis involving 14 international randomized clinical trials (N = 122,458) showed that one of these four conventional risk factors was present in 84.6% of men and 80.6% of women with coronary artery disease.13

Recent attention has focused on elevated serum C-reactive protein (CRP) as a strong and independent risk factor or predictor of events due to coronary artery atherosclerosis such as MI or sudden death.14 CRP is an acute-phase reactant produced primarily by the liver in response to infection or trauma. Other tissues may be involved in its synthesis, including smooth muscle cells from normal coronary arteries and diseased coronary artery bypass grafts.15,16 CRP appears to be directly involved in augmenting the innate inflammatory response via induction of prothrombotic factors (e.g., plasminogen activator inhibitor-1, proinflammatory adhesion molecules, and monocyte chemoattractant protein-1) and interference with endothelial nitric oxide synthase.17

In the Physicians’ Health Study, an epidemiologic study of over 22,000 healthy middle-aged men with no clinical evidence of disease, increasing levels of serum high-sensi-
Figure 1. Cardiac Risk Factors for Coronary Atherosclerosis

Multiple risk factors are shown, many of which are known to increase risk in an additive fashion when present concurrently. A cross-section of an artery is shown with a raised atherosclerotic plaque that obstructs a portion of the lumen. From Netter’s Cardiology. Reproduced with permission.
tivity CRP at study entry were associated with up to a threefold increase in the risk of incident MI and a twofold increase in risk of ischemic stroke.\textsuperscript{18} In the Women’s Health Study (N = 28,263)\textsuperscript{19,20} of apparently healthy participants, CRP proved to be the single strongest predictor of cardiovascular risk when compared with other potential serum biomarkers such as homocysteine, lipoprotein(a), interleukin 6 (IL-6), intercellular adhesion molecule 1 (ICAM–1), serum amyloid A, and standard lipid measures. Accordingly, the relative risk ratio for the highest versus lowest quartile of serum CRP concentrations was 4.4 (95% CI: 1.7–11.3). Moreover, the addition of serum CRP to traditional cholesterol screening enhanced cardiovascular risk prediction and proved to be independent of LDL cholesterol. The poorest event-free survival in women was among those with high LDL cholesterol and high CRP levels, and the best event-free survival was seen among those with low LDL cholesterol and low CRP levels. Notably, persons with low LDL cholesterol levels but high CRP levels were at higher risk than those with high LDL cholesterol levels but low CRP levels.

Recent data suggest that treatment with HMG-CoA reductase inhibitors (statins) for asymptomatic individuals with elevated CRP levels but normal cholesterol levels reduces risk for future cardiovascular events.\textsuperscript{14} These provocative findings have triggered considerable debate yet may fundamentally alter our approach to primary prevention of coronary atherosclerosis. These data also reinforce applying the same logic for reducing systemic inflammation by treating other diseases associated with systemic inflammation such as periodontitis.\textsuperscript{21,22}

**Prevention of Coronary Atherosclerosis by Risk Factor Modification**

Because atherosclerosis continues to increase in prevalence in developed countries, it is counterintuitive that death rates from CVD overall have decreased by more than one third in the last two decades. The explanations most often given for this apparent paradox include success of primary and secondary prevention strategies, improvements in patient care, and rehabilitation. These findings underscore the importance of recognizing risk factors (see Figure 1) and optimizing strategies for risk factor reduction (Figure 2). These strategies constitute an opportunity for the medical and dental professionals to work for a common goal of continued improvement in cardiovascular health; nevertheless, there are formidable challenges to overcome to achieve this goal.

The first is to recognize that we are providing encouragement for lifestyle changes that patients may find very difficult, such as smoking cessation, weight reduction, dietary changes, regular exercise, and compliance with prescribed medications for elevated cholesterol, blood pressure, and diabetes mellitus. Although both dental and medical healthcare providers can fairly encourage all of these, continued patient support over time is essential. Second is to remember that atherosclerosis may be present but not clinically evident for years,\textsuperscript{23} underscoring the need for sustained efforts at risk factor reduction even in otherwise healthy persons.

**Clinical Presentation of Cardiovascular Disease**

Recognition of the symptoms of coronary atherosclerosis is essential and not always straightforward. Three classic clinical presentations are possible. Angina pectoris or chest pain is usually retrosternal pressure, tightness, heaviness, or discomfort that radiates to the left arm, jaw, or back, and is often associated with dyspnea, diaphoresis, nausea, and a feeling of impending doom (Figure 3). Angina with exercise or exertion, large meals, or emotional stress is usually predictable and relieved by rest, a pattern often called “stable
Figure 2. Non-Drug Therapy for Prevention of Coronary Atherosclerosis

Risk factors that can be addressed by all healthcare practitioners are shown. A standardized approach that provides patient education about these risk factors and support for adhering to these lifestyle changes is the foundation of risk factor reduction. Other risk factors are highly likely to be identified over time and this risk will be continually updated. From Netter’s Cardiology. Reproduced with permission.
angina.” More ominous is chest pain at rest or a sudden increase in frequency or ease of onset of angina, a pattern often termed “unstable or accelerating angina.”

Obtaining a history of angina requires time and patience and the recognition that there are several causes of chest pain. In addition, women and patients with diabetes mellitus may have a completely different pattern to their angina or have anginal equivalents, such as dyspnea alone or abdominal discomfort. A high index of clinical suspicion in patients with risk factors for coronary atherosclerosis is of paramount importance for recognition of anginal equivalents.

The second classic presentation of coronary atherosclerosis is MI or heart attack. Patients experiencing an MI usually complain of prolonged (> 5 minutes) and sustained chest pain not relieved by rest or nitroglycerin. Associated symptoms may also be present, such as nausea and vomiting, and palpitations signaling irregular heart rhythms. Also alarming is the presence of heart failure symptoms such as weakness and dyspnea. The interval between treatment and long-term prognosis is directly proportional; prompt recognition and early treatment are associated with marked improvement in outcomes.

The third manifestation of coronary atherosclerosis is sudden cardiac death, in which the heart has an irregular rhythm that is unable to support blood pressure, usually ventricular fibrillation. Tragically, coronary atherosclerosis first presents as sudden cardiac death in approximately 25% of patients. The availability of personnel trained to recognize and treat ventricular fibrillation and administer cardiopulmonary resuscitation is the primary determinant of outcome. Both community-based efforts and the presence of automatic external defibrillators (AEDs) have been important factors in the improved survival rates for patients experiencing sudden cardiac death.

MEDICAL MANAGEMENT OF CORONARY ATHEROSCLEROSIS

At present, 80 million Americans are thought to exhibit some form of CVD.2,3 Thus, many patients presenting to oral and dental healthcare providers have coronary atherosclerosis and are receiving therapy. It is important, then, to understand the basic classes of drugs that are used in patients with heart disease, especially drugs that might have a direct impact on oral health or complicate oral and dental procedures.

Antiplatelet Therapy
All patients with atherosclerosis should be on some form of antiplatelet therapy. The minimal cost and relatively profound effectiveness of aspirin makes it the treatment of choice in all patients who can tolerate taking this medication. Other currently available antiplatelet drugs are the thienopyridines: ticlopidine, clopidogrel, prasugrel, and ticagrelor. Often, patients are on both aspirin and one of the thienopyridines; this is often referred to as “dual antiplatelet therapy” or DAP. The rationale for DAP is to prevent thrombosis on drug-eluting stents that have been implanted inside one or more coronary arteries to open atherosclerotic obstructions. Although the recommendations for antiplatelet therapy are rapidly changing, it is generally agreed that abrupt cessation of the thienopyridines during the first year after placement of a drug-eluting stent can be associated with acute thrombosis, resulting in an otherwise preventable heart attack. The primary concern, however, for patients on DAP is bleeding, especially with invasive or surgical procedures. If the procedure requires temporary cessation of either of these two drugs, this should be done in consultation with the patient’s regular physician.4

New Oral Anticoagulant Therapy
The first new oral anticoagulants (NOACs) to be FDA-approved since the approval of
Figure 3. Angina Pectoris

Classic angina pectoris is retrosternal, radiates to the left arm or jaw, and feels like a heavy or constricting vise-like discomfort. This illustration shows common precipitating factors. From Netter’s Cardiology. Reproduced with permission.
Coumadin (warfarin) over 35 years ago include direct thrombin inhibitors (e.g., dabigatran) and factor Xa inhibitors (xabans: e.g., rivaroxaban). These drugs are approved for and being increasingly used therapeutically in patients with deep venous thrombosis (dabigatran, rivaroxaban) and with atrial fibrillation to prevent stroke (rivaroxaban). The challenge to all who deliver health care will be to maintain a current understanding of the uses, potential for drug interactions, and side effects of these novel therapies. The practical issue is that bleeding is becoming an even greater concern for patients on these drugs. As with the antiplatelet therapies, consultation with the patient’s physician is paramount in anticipating potential drug interactions if new drugs are being started and in planning for temporary interruption of oral anticoagulant therapy to achieve the balance between essential hemostasis and undesired thrombosis.3425

Beta Blockade
As with aspirin, beta blockade is recommended for all patients with CVD except those with a contraindication, such as untreated conduction disease in the heart with bradycardia, severe asthma, difficult to control diabetes mellitus, and in some cases severe atherosclerosis in arteries supplying the legs. In general, patients already receiving beta blockers should not experience any complications during dental procedures. In addition, cardiologists may recommend beta blockers for select patients with heart disease undergoing general anesthesia for oral or dental procedures. The American Heart Association provides guidelines for such situations.36 These issues are controversial, and the guidelines are constantly being revised as new data become available. Updated guidelines are scheduled for publication in 2014. Consequently, considerable planning and discussion between the cardiologist and the dentist would be required to start or stop beta blocker therapy for a dental procedure.

Angiotensin-Converting Enzyme and Angiotensin II Receptor Blockers
Patients with coronary atherosclerosis and depressed heart function are generally encouraged to take angiotensin-converting enzyme (ACE) inhibitors. If they cannot tolerate ACE inhibitors because of cough or other issues, they take angiotensin II receptor blockers (ARBs). Mortality rates have been shown repeatedly to be lower in post-MI patients on ACE inhibitors. Both ACE inhibitors and ARBs are powerful antihypertensive agents. For dental patients on stable doses, these drugs are not recognized to interfere with oral procedures or dental care.

Nitrates
Both short-acting (less than 10 minutes) and long-acting (several hours) nitrates are frequently used to relieve and prevent, respectively, myocardial ischemia. Nitrates may also be used to treat heart failure, especially in African Americans, as well as hypertension. A nitrate-free interval is recommended on a daily basis to prevent tachyphylaxis. For dental patients on stable doses, these drugs are not recognized to interfere with oral procedures or dental care.

Lipid-Lowering Therapy
The current National Cholesterol Education Program (NCEP) Guidelines recommend an LDL-cholesterol level of less than 100 mg/dL for patients with known CVD and a total cholesterol of less than 200 mg/dL. Secondary causes of hyperlipidemia are diabetes mellitus, liver disease, and renal failure. Regardless of the cause, all patients who have values higher than these levels should receive dietary counseling, suggestions for weight reduction, and encouragement to increase physical activity. The most common drugs used for hyperlipidemia are HMG-CoA reductase inhibitors or statins, which inhibit cholesterol synthesis. Pharmacologic intervention with the statin class of drugs is used to further
reduce serum lipids and the likelihood of cardiovascular events even in those with average LDL concentrations. Numerous clinical trials have consistently demonstrated that statin drugs reduce cardiovascular events by at least 25%.27 In contrast, the effect of statins and other lipid-lowering therapies on reducing the size of atherosclerotic plaques is much smaller.28 This finding has been the basis for seeking alternative explanations for why statins improve outcomes so profoundly. For example, statins may have secondary anti-inflammatory effects. Indeed, CRP concentrations decrease 15%–50% with statin therapy.14 Thus, the pleotropic effects of these drugs appear to improve outcomes and markers of atherosclerotic CVD. Fibrates reduce lipoprotein lipase activity, and nicotinic acid reduces tissue lipase activity and very-low-density lipoprotein synthesis. Both fibrates and nicotinic acid reduce triglyceride levels effectively. A cholesterol absorption inhibitor (e.g., ezetimibe) and a bile acid reabsorption inhibitor (e.g., cholestyramine) are often used in combination with other drugs to achieve target goals. Lipid-lowering drugs should not have an impact on the delivery of oral or dental care.

**LDL Apheresis**

In rare cases, patients with familial hypercholesterolemia do not respond to drug therapy and require apheresis. In this case, the patient’s blood is perfused over a column that binds and thereby reduces LDL levels. These patients develop coronary atherosclerosis by the second decade of life and should be carefully evaluated for all procedures.

**Coronary Angioplasty and Bypass Surgery**

For patients with severe symptomatic coronary atherosclerosis, interventions involve physically expanding stenotic vessels via angioplasty (with or without stenting) versus revascularization via coronary bypass surgery. As previously discussed, these patients are likely to be taking medications that can increase the likelihood of bleeding during dental procedures.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Dental and medical healthcare providers need to work together closely to provide optimal care for their patients with established CVD. A basic understanding of the pathogenesis of CVD and commonly used medications can provide a basis for preventing complications during the delivery of dental and oral health care in patients with CVD.

The role of the oral and dental health practitioner in prevention of heart disease has great potential. At present, he/she is uniquely poised to discuss risk factor reduction with patients, which is paramount for both oral and cardiovascular health. Preventive interventions (primary or secondary) for coronary atherosclerosis focus on recognition and reduction of modifiable risk factors in patients (see Figures 1 and 2). These approaches include blood pressure screening; weight reduction; exercise; smoking cessation; diet modification; medication compliance, especially with treatments for blood pressure and diabetes; patient counseling; and education. Initiating and maintaining these lifestyle changes are not easy tasks but are more likely to be adopted by patients who receive consistent advice and encouragement from all of their healthcare providers.

Currently, the future role of oral health in atherosclerosis remains a consistent association and not a causal risk factor.29 Human trials that directly address the role of periodontitis and atherosclerosis have been limited to the Periodontitis and Vascular Events (PAVE) study.30 This pilot study was designed to determine how many patients with combined symptomatic atherosclerosis and periodontitis would be needed to document that successful treatment of periodonti-
tis reduces subsequent coronary and carotid events. The reader is also referred to Chapter 8 that has a discussion on what would be the minimal criteria for definitively establishing that periodontitis is a risk factor for heart attacks and strokes. If periodontitis is proved to be a casual risk factor for CVD, cardiologists and oral and dental health practitioners need to work even more closely to provide optimal care of their patients.

Supplemental Readings


References


286  Periodontal Disease and Overall Health: A Clinician’s Guide


CHAPTER 16
Dental and Medical Comanagement of Pregnancy

Néstor J. López, Ricardo A. Gómez

INTRODUCTION
Pregnancy involves complex physiologic, physical, and psychological changes mediated by female sex hormones that have a profound impact even on healthy women. Physiologic changes during pregnancy can exacerbate already existing oral pathologic conditions, such as gingivitis, periodontitis, and caries lesions. Moreover, oral infections during pregnancy may be associated with adverse pregnancy outcomes. Prenatal care is an essential part of a successful pregnancy, and oral health assessment must be part of prenatal care. Changes produced by pregnancy present a number of unique management problems in dental treatment. The best approach to avoid pregnancy complications and adverse pregnancy outcomes is to apply preventive strategies. The most important objective in planning dental care for the pregnant woman is establishing a healthy oral environment free of inflammation and infection.

This chapter reviews the physiologic changes that occur during normal gestation and discusses the management of dental treatment in women with normal pregnancy, as well as women at risk for adverse pregnancy outcomes.

Educational Objectives
By the end of this chapter, the reader should be able to

1. Recognize the most important physiologic, physical, and psychological changes mediated by female sex hormones that have an impact on healthy pregnant women.
2. Identify the effects that pregnancy’s physiologic changes may have on oral health.
3. Enumerate the most common risk factors for pregnancy complications.
4. Explain the considerations that have to be applied to provide dental treatment to women with normal pregnancy.
5. List strategies for the prevention of medical and dental complications in pregnant women.
6. Describe the initiatives that can be taken by dentists and obstetricians in comanaging patients with oral diseases and who are at risk for adverse pregnancy outcomes.

PHYSIOLOGIC CHANGES IN PREGNANCY AND THEIR RELATION TO ORAL HEALTH
Pregnancy is characterized by dramatic endocrine changes. Placental tissues produce a significant increase in progesterone and estrogen concentrations, which in turn influence physiologic changes in systemic and oral tissues. The most important physiologic changes associated with pregnancy that have dental relevance are addressed in the following text.

Gingival Hyperplasia and Edema
The gingival vasculature appears to be sensitive to sex steroid hormones. Vasodilation, increased vascular permeability, and cell proliferation by pregnancy hormones result in the swelling of gingival and descamation cells, and a significant increase of gingival crevicular fluid.1,2 Changes described in the microcirculation of pregnant women include swelling of endothelial cells, adherence of granulocytes to vessel walls, generation of microthrombi, disruption of perivascular mast cells, and vascular proliferation.1,2 All the changes in
gingival tissues during pregnancy are associated with an exacerbated clinical inflammatory response. However, the level of inflammation is not associated with an increase in progesterone or estradiol levels in saliva or with changes in PGE2 or IL-1beta levels in gingival crevicular fluid. Immune adaptations that occur during pregnancy may further facilitate infections of oral tissues. For example, gingival fibroblasts exposed to progesterone downregulate the production of interleukin 6 and a variety of matrix metalloproteinases, making the gingiva more susceptible to inflammatory challenges elicited by bacteria.

Upper Gastrointestinal Changes
Beginning in the first trimester, endocrine changes induce a reduction in smooth muscle tissue tone and frequency of contractions. This affects gastric emptying and the functionality of the gastroesophageal sphincter, facilitating reflux of stomach content toward the esophagus and mouth. Psychological changes appear early in pregnancy and contribute to the nausea and vomiting syndrome called morning sickness. A small percentage (1% to 3%) of these patients progress to hyperemesis gravidarum, which is associated with weight loss, electrolyte imbalance, dehydration, and eventually ketonemia. Persistence of these symptoms despite treatment obligates one to rule out other disorders, such as pancreatitis, cholecystitis, hepatitis, psychiatric illness, and hyperthyroidism.

Salivary changes during pregnancy include an increase in volume that depends on oral-esophageal content delay rather than salivary flow rate. Rarely, patients lose more than 1 liter of saliva per day, a disorder known as ptyalism. Additional changes are a decreased salivary pH and elevations of protein and estrogen concentrations. Estrogens act locally by increasing the proliferation and desquamation of the oral mucosa, setting the conditions for bacterial growth. Recommendations for managing nausea and vomiting in the dental setting are provided in Pregnancy Complications, found later in the chapter.

Cardiovascular Changes and Establishment of Uteroplacental Circulation
As the placenta and fetus develop, flow through the uterine and placental arteries increases notably. Changes in the microcirculation and within the intervillus space (mimicking an arteriovenous shunt) decrease arterial resistance. Elevations in blood volume (especially at the expense of maternal plasma) and heart rate compensate for the changes in vascular resistance. As a consequence, cardiac output increases by 30% to 40% throughout pregnancy. Maternal blood pressure tends to lower during the first and second trimester, reaching baseline levels early in the third trimester. The growing uterus may compress the inferior vena cava, impairing the venous return to the heart and therefore the stroke volume. Compensatory mechanisms are set in action, leading to symptoms such as palpitations (due to tachycardia), nausea, hypotension, and dizziness. This chain of events is frequently observed during the second half of pregnancy when pregnant women are in the supine position. Dentists may reduce the likelihood of this supine hypotensive syndrome by elevating the right hip of the patient with a pillow or folded sheet, or rolling the patient to the left to alleviate vena cava obstruction.

Respiratory Changes
The most important physiologic adaptations at the respiratory level are derived from the pressure that the pregnant uterus imposes on the abdominal side of the diaphragm, reducing the height and increasing the transverse diameter of the thorax. A progesterone-driven hyperventilation compensates for the decreased residual capacity of the lungs. Dyspnea is not an uncommon sign during the third trimester; especially in patients with
twin gestation, large fetuses, or polyhydramnios. As previously stated, avoiding the supine position is central to the management of these patients.

Hematologic Changes
Red blood cells, leukocytes, and most coagulation factors are increased during pregnancy. Plasma volume increases above that of red blood cells, leading to the condition known as physiologic anemia of pregnancy. Because of this hematologic adaptation, pregnant women are diagnosed with anemia only when the hematocrit falls below 33%. On the other hand, leukocytosis during pregnancy is established when the white blood cell count is above 15,000 cells/mm³. This is important to know when evaluating laboratory tests in the setting of oral infections. Clotting factor production by the liver is stimulated by gestational hormones, leading to a hypercoagulable state, which predisposes to thromboembolism. Several disorders (e.g., antiphospholipid syndrome) aggravate this condition and may require the use of aspirin or heparin. Such patients should receive close treatment surveillance to determine whether dental procedures may be performed without the risk of excessive bleeding.

Endocrine Changes
Most of the physiologic adaptations previously described here are the result of primary endocrine changes during pregnancy. Moreover, elevated levels of estrogens, progesterone, cortisol, and placental lactogen mobilize the patient’s metabolic resources to secure fetal nutrition. As a result, a diabetogenic state develops, especially during the second half of pregnancy in which insulin resistance increases, eventually leading to gestational diabetes in 4% to 10% of patients. The resulting hyperglycemia state in women with poorly controlled diabetes provides a suitable environment for the development of dental infections.

DENTAL MANAGEMENT OF WOMEN WITH NORMAL PREGNANCY
Dental care during pregnancy is less common than expected. Data from surveys indicate that 30% to 50% of women do not receive dental care during pregnancy.6 Indeed, only about 10% of dentists provide complete treatment for conditions considered necessary during the gestation period, delaying most of them for the postpartum period.8 Pregnant women are also less likely to request dental treatment even in the context of free health services, such as those provided through the National Health Service in the United Kingdom.9 Moreover, only about 25% of patients are referred for a dental examination by healthcare providers during pregnancy.9 Collectively, these data indicate that both health professionals and patients tend to postpone dental treatments until after delivery.

Attitudes of Dentists, Physicians, and Patients Toward Dental Treatment During Pregnancy
The reluctance of dental practitioners to provide dental care to pregnant women may explain, among other reasons, the low percentage of women who receive dental care during pregnancy. Lydon-Rochelle and colleagues11 found that 58% of pregnant women in Seattle, Washington, received no dental treatment during pregnancy. Only 22% to 34% of women in the United States consult a dentist during pregnancy. Even when an oral problem occurs, only 50% of pregnant women attend to it.6

A common concern of dental practitioners is the timing for necessary procedures. The evaluation and management of pregnant women may require special consideration, but pregnancy does not preclude them from necessary dental care. There is no evidence that dental or periodontal treatment is damaging to the pregnant woman or her developing fetus. However, the American Dental Association suggests that elective
dental care should be avoided, if possible, during the first trimester and the last half of the third trimester. The recommendation for not doing procedures during the first trimester is because the developing fetus is at greatest risk of teratogenicity during the embryologic development (between the 2nd and 8th weeks) after conception and because the highest rate of spontaneous abortion occurs during the first trimester. Thus, there is concern that the patient may perceive that the cause of an eventual birth defect or spontaneous abortion is the dental procedure performed during that period. The last weeks of the third trimester are associated with greater discomfort and risk of supine hypotension syndrome, because of the large uterus and its content.

Concern about the maternal and fetal effects of pharmacologic agents commonly used in dentistry is another reason that may explain attitudes of dentists and women toward dental treatment during pregnancy. However, most drugs used during dental treatment are safe and listed likewise by the Food and Drug Administration (FDA) (Table 1). The recommendation is based more on fear of litigation than on evidence of harm. It is therefore remarkable that no evidence has emerged linking dental treatments and adverse pregnancy outcomes. On the contrary, there is a growing body of evidence, though controversial, that treatment of periodontal infections may reduce the rate of certain pregnancy complications.

Another factor that prevents dentists from performing treatment in pregnant women is the belief that dental procedures may initiate an inflammatory cascade leading to uterine response, preterm labor, and fetal loss. Although transient bacteremia is recognized as part of the pathophysiology following dental invasive procedures, the specific association between these procedures and pregnancy complications has not been demonstrated.

Safety of Dental Diagnostic and Therapeutic Procedures During Pregnancy

Dental treatments are preferably performed during the second trimester. Emergency dental procedures can be performed at any gestational age. During the first and second trimester, no specific positional requirement needs to be satisfied. On the contrary, patients with a large uterus (such as those in the third trimester or those with twin gestation or polihydramnios) are at risk for supine hypotension due to vena cava compression. Therefore, propping patients on their left side and frequent repositioning are necessary during the dental procedure.

A general principle used for all drugs and diagnostic tests during pregnancy is that the period before 12 weeks’ gestation is considered vulnerable for the embryo organogenesis. Specific drugs and tests may be administered during the first trimester only when the potential benefit surpasses the risks.

Radiography

Dental radiographs can be undertaken safely because they are associated with minimal fetal exposure to ionizing effects. The examination should be performed with the patient using a lead apron and thyroid shield. The limited x-ray exposure needed for dental diagnosis poses no risk of congenital malformations of the fetus. A study of a cohort of 7,374 mothers did not find a significant association between the use of x-ray scans and low birth weight or preterm delivery.

Pharmacologic Agents

Drugs used in dental treatment are fairly safe during pregnancy (see Table 1). Local anesthetics such as lidocaine and prilocaine are considered safe by the FDA (category B). When possible, coadjuvant epinephrine should be avoided, because it may impair uterine blood flow through the placenta. Epinephrine is contraindicated in patients with preeclampsia and chronic hypertension.
Table 1. Drugs Frequently Used by the Dental Professional During Pregnancy

<table>
<thead>
<tr>
<th>Drugs</th>
<th>FDA Category</th>
<th>Comments/Suggestions</th>
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<tr>
<td>Analgesics and anesthetics</td>
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<td></td>
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<tr>
<td>Acetaminophen</td>
<td>B</td>
<td>Safe throughout pregnancy</td>
</tr>
<tr>
<td>Aspirin</td>
<td>C</td>
<td>Avoid after 34 weeks</td>
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<tr>
<td>Ibuprofen</td>
<td>B</td>
<td>Do not use after 28 weeks</td>
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<tr>
<td>Codeine</td>
<td>C</td>
<td>Use with caution if benefit outweighs risks</td>
</tr>
<tr>
<td>Oxycodeine</td>
<td>B</td>
<td>Avoid in proximity of labor</td>
</tr>
<tr>
<td>Morphine</td>
<td>B</td>
<td>Avoid in proximity of labor</td>
</tr>
<tr>
<td>Meperidine</td>
<td>B</td>
<td>Avoid in proximity of labor</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>B</td>
<td>Safe throughout pregnancy</td>
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<td>Mepivacaine</td>
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<td>Prilocaina</td>
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</tr>
<tr>
<td>Clotrimazole</td>
<td>B</td>
<td>Safe throughout pregnancy</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>B</td>
<td>Safe throughout pregnancy. Do not use estolate</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>C</td>
<td>Safe when used in single dose</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>B</td>
<td>Avoid before 12 weeks</td>
</tr>
<tr>
<td>Penicillin</td>
<td>B</td>
<td>Safe throughout pregnancy</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>D</td>
<td>Do not use unless benefit outweighs risks</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>B</td>
<td>Prednisone, betamethasone, and dexamethasone, safe through pregnancy</td>
</tr>
<tr>
<td>Doxylamine</td>
<td>B</td>
<td>Safe throughout pregnancy</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>—</td>
<td>Avoid before 12 weeks</td>
</tr>
</tbody>
</table>

Acetaminophen is appropriate to treat patients with dental pain at any gestational age (category B), as well as ibuprofen in the first and second trimesters (category B). The latter drug should be avoided during the third trimester owing to known effects on both fetal ductus arteriosus and renal function. For severe pain, narcotics such as oxycodone may be used for a limited time during the first and second trimesters. Avoiding these drugs during both the third trimester and women with impending delivery prevents breathing/withdrawal complications in the newborn. If a dental procedure requires sedation, a safe choice is premedication with an antihistaminic such as doxylamine (category B), which also has an antiemetic effect. Benzodiazepines should be avoided throughout pregnancy unless a specific indication arises (mostly of a psychiatric nature). Nitrous oxide is a sedative-analgesic gas, and short-term use is considered safe during the second and third trimesters of gestation. It is contraindicated in patients with chronic obstructive pulmonary disease and drug-related dependencies.

**Antibiotics**

Antibiotics used for oral infections are generally safe for mother and fetus. Penicillin family agents are frequently used as coadjuvants in the treatment of periodontal disease, dental abscesses, and cellulitis. Cephalosporins fit into the same category. Except for patients with hypersensitivity, both antimicrobial agents are classified as safe by the FDA (category B). Erythromycin (with the exception of the estolate form, which may produce cholestatic hepatitis), and clindamycin (category B) are alternatives for penicillin-allergic patients. Metron-
idazole, an alternative for clindamycin in severe infections, may be administered as well during the second and third trimester (category B). Tetracyclines are contraindicated during pregnancy.

Antibiotic prophylaxis for infective endocarditis should be administered only to women with cardiac conditions associated with a major risk for developing endocarditis. A recent committee opinion from the American College of Obstetrics and Gynecology provided up-to-date indications for pregnant women with cardiac conditions who require certain dental procedures.20

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Specific congenital heart diseases: Unrepaired cyanotic cardiac disease (including palliative shunts and conduits), completely repaired cardiac anomalies with prosthetic material or device (whether placed by surgery or catheter intervention) during the first 6 months after procedure, and repaired cardiac disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Dental procedures eligible for prophylaxis involve manipulation of the gingival tissue or periapical region of the teeth. No prophylaxis is required in cases of general dental cleaning, cavity filling, taking of radiographs, adjusting orthodontic appliances, or injection of anesthetic into noninfected tissue. Appropriate antibiotics for infective endocarditis prophylaxis should be administered 30 to 60 minutes before the dental procedure and include the following:

- Ampicillin 2 g intravenously
- Cefazolin or ceftriaxone 1 g intravenously
- Amoxicillin 2 g oral

In patients allergic to penicillin, clindamycin 600 mg intravenously may be used. It should be noted that drugs other than ampicillin or amoxicillin do not cover enterococcus. If enterococcus involvement is suspected, vancomycin 1 g intravenously over 1 hour is the choice. Table 2 summarizes the principles guiding dental treatment during pregnancy.21

Table 2. Principles Guiding Dental Treatment During Pregnancy

<table>
<thead>
<tr>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Women should be advised to seek oral health care prior to becoming pregnant and throughout gestation.</td>
</tr>
<tr>
<td>2. Oral health care is safe and effective during pregnancy.</td>
</tr>
<tr>
<td>3. First trimester diagnosis (including necessary dental x-rays with adequate shielding) is safe.</td>
</tr>
<tr>
<td>4. Acute infection, abscess, and conditions predisposing to bacteremia and sepsis require prompt intervention regardless of the stage of pregnancy.</td>
</tr>
<tr>
<td>5. Necessary treatment can be provided throughout pregnancy. However, the period between the 12th and 22nd weeks represents the best time to provide oral services, especially scaling and root planing.</td>
</tr>
<tr>
<td>6. Elective treatment for conditions considered not progressive may be deferred until after delivery.</td>
</tr>
<tr>
<td>7. Delay in necessary treatment could result in significant risk to the mother and the fetus.</td>
</tr>
</tbody>
</table>

Treatment of Specific Dental Conditions During Pregnancy

During pregnancy, dental or periodontal care may be modified according to the individual characteristics of each patient and the conditions of the pregnancy, but there is no need to withhold treatment for any oral infectious condition. Extensive dental treatments, such as crown placement and reconstructive procedures that need long appointments, should not be performed during pregnancy.

The most important objective in planning dental care for the pregnant woman is establishing previous to pregnancy, or early during pregnancy, a healthy oral environment, free of inflammation and infection.

There is evidence that oral health influences systemic health and well-being. Maternal oral health has important implications for birth outcomes and infant oral
health. The most prevalent oral diseases—
dental caries and periodontal disease—influence maternal health status and may increase
the risk of other diseases. Periodontal disease
may increase the risk of atherosclerosis, diabetes, rheumatoid arthritis, and adverse pregnancy outcomes.

Maternal dental caries can also increase
the risk of early development of caries in children. Dental caries and periodontal disease are both preventable conditions. However, these conditions are highly prevalent in women of childbearing age, especially among low socioeconomic level populations. Both caries and periodontal disease are chronic diseases with few or no symptoms, making it difficult for the patient to be aware of the disease. The characteristics of both diseases, in addition to their high prevalence and insufficient treatment rates, induced the US Surgeon General to characterize dental and oral diseases as a “silent epidemic.”

Dental Caries and Pregnancy

One-fourth of women of reproductive age in
the United States have dental caries, and the prevalence of dental caries may reach 76% in young women of low socioeconomic status in developing countries. No definite data exist to indicate whether the incidence of dental caries increases during pregnancy. Since dental caries usually takes more than the 40 weeks of pregnancy to develop, it is difficult to determine the pregnancy-related incidence of caries. The main bacteria that produce caries are Streptococcus mutans, which is usually acquired by young children from their mothers through direct salivary contact. Since maternal oral flora are the strongest predictor of infant oral flora, maternal health status is critical to children’s oral health. Maternal dental educational and behavioral interventions such as use of fluorides, control of cariogenic diet, chlorhexidine mouthwashes, and varnishes can decrease caries activity and the associated oral flora, thus improving women’s oral health and reducing bacterial transmission to their children.

Pregnancy-Associated Gingivitis
Plaque-induced gingivitis is an inflammation of the gingiva resulting from bacterial infection, and it is one of the most common oral diseases in pregnant women. Pregnant women have more gingivitis than nonpregnant women, with a prevalence ranging from 30% to 75%. During pregnancy, the severity of gingivitis has been reported to be elevated, yet unrelated to the amount of dental plaque present. Approximately one of two women with preexisting gingivitis has significant exacerbation during pregnancy. Gingivitis is usually more evident during the second month of pregnancy and reaches a maximal level during the eighth month. The severity of gingivitis is correlated with sex steroid hormone levels during pregnancy. The characteristics of pregnancy-associated gingivitis are similar to plaque-induced gingivitis, but with a tendency to more severe inflammation.

The factors associated with higher gingival inflammation in pregnancy are increased levels of estrogen and progesterone, and a decreased immune response. Aggravation of gingival inflammatory symptoms during pregnancy is also associated with low concentrations of plasminogen activator inhibitor type-2 (PAI-2) in gingival fluid. PAI-2, produced by macrophages, is an important inhibitor of tissue proteolysis and has multiple other functions. Women showing a low inflammatory response to plaque have high concentrations of PAI-2, which probably protects connective tissue from excessive breakdown.

Changes in subgingival flora may occur during pregnancy. Early evidence from cultivation-based approaches indicated that hormonal surges during pregnancy may play a role in increasing subgingival levels of black-pigmented Bacteroides. However, more recent investigations using molecular methods did not
corroborate these findings. It is possible that the increased gingival inflammation in pregnant women had a greater contribution in altering the composition of the subgingival microbiome than female sex steroids.

Pregnancy epulis or pregnancy tumor is a pyogenic granuloma that appears in no more than 5% of pregnant women. It is a pedunculated, soft, erythematous lesion that grows from an interdental papilla and is associated with inflammation resulting from dental plaque and calculus accumulation. The lesion usually arises during the second trimester, shows rapid growth, bleeds easily, and tends to diminish after pregnancy. The lesion can be removed under local anesthesia and sometimes carries a risk of excessive hemorrhage because of its high vascularity.

There is some basis to support the hypothesis that gingivitis may be a potential risk factor for the occurrence of preterm birth. One of the hypotheses that explains the association between periodontal disease and preterm birth is that periodontal infection is a source of bacteria and bacterial products that may spread from the infected periodontium to the systemic circulation and, eventually, to the amniotic cavity. This is similar to transient bacteremia occurring in patients with periodontitis. Bacteremia commonly occurs in patients with gingivitis and bacteria or their products may conceivably reach the placental tissues, providing an inflammatory setting for the onset of labor (Figure 1). There is evidence that some periodontal pathogens can cross the placental barrier and produce infection in the fetal membranes. The prevalence of P. intermedia has been found to be significantly higher in preterm than in full-term neonates. The fetal antibody seropositivity for P. intermedia, as indexed by cord blood immunoglobulin M, suggests in utero exposure of the fetus to this bacterium or its products. Fusobacterium nucleatum is one of the most commonly recovered microorganisms from sites with gingivitis, and is frequently isolated from amniotic fluid cultures obtained from pregnant women with premature labor and intact placental membranes.

A study in pregnant mice showed that F. nucleatum can cross the placenta and spread to the amniotic fluid, producing preterm delivery and stillbirths. The association between pregnancy-associated gingivitis with preterm birth was explored in a randomized controlled trial. Women with gingivitis who received periodontal therapy before 28 weeks of gestation had a significantly lower incidence of preterm low birth weight than women who did not receive periodontal therapy.

Periodontitis and Pregnancy

Periodontitis, the destructive form of periodontal disease, affects 15% of women of childbearing-age in developed countries and 45% of women in undeveloped countries. In the United States, up to 40% of pregnant women of low socioeconomic status have some form of periodontal infection. In some developing countries, such as Chile, 76% of pregnant women of low socioeconomic status have some form of periodontal disease (López NJ, unpublished data).

Several studies have shown that maternal periodontal infection is associated with adverse pregnancy outcomes, such as preterm birth, preeclampsia, gestational diabetes, delivery of a small-for-gestational-age infant, and fetal loss. A more complete critical review of the studies showing association between oral infections and adverse pregnancy outcomes is presented in Chapter 9 of this book.

Preconception Oral Health

The American Academy of Periodontology released the recommendation that “all women who are pregnant or planning a pregnancy should undergo periodontal examination, and appropriate preventive or therapeutic services, if indicated, should be provided.” No defini-
tive evidence exists that the association between periodontal infection and adverse pregnancy outcomes is causal or is a surrogate for another maternal factor. However, the strong evidence of an association between periodontal disease and systemic health means that oral health care should be the aim of every person. This is especially important for pregnant women, since no evidence supports the concept that maternal oral health influences pregnancy outcome. The obvious and best cost-benefit strategy to reduce the effect of periodontal infections on pregnancy outcome is preconception preventive oral health care to ensure a healthy oral environment throughout pregnancy.

Patient education about the effects of oral health on systemic health and pregnancy outcomes should be given before pregnancy or early in pregnancy. The dentist should inform the pregnant woman of the oral changes she may expect during pregnancy and should discuss how to prevent dental problems that may arise from these changes. Pregnancy is a good time to obtain modifications in lifestyle behaviors because
women are more motivated to make healthy changes during this time.

Although no oral diseases are directly attributable to pregnancy, the physiologic and behavioral changes that occur during pregnancy can aggravate preconceptional existing gingivitis or periodontitis. Oral hygiene instructions to control dental plaque must be emphasized in pregnant women, and treatment of gingivitis and periodontitis should be performed if needed.

**PREGNANCY COMPLICATIONS**

**Nausea and Vomiting**

Pregnant patients may experience varying degrees of nausea and vomiting, especially during the first 3 months of gestation (morning sickness). Changes in the gingival tissue elicited by the hormonal profile of gestation, as well as a decreased use of oral hygiene due to nausea, predispose patients to gingival inflammation. Therefore, dental treatment is warranted for a percentage of these patients. Morning appointments should be avoided. When needed, premedication with antihistaminic agents provides significant relief of symptoms along with a sedative effect that is desirable when performing dental procedures. Doxylamine 25 mg orally is an approved choice for patients with nausea and vomiting during gestation, including the first trimester.

Frequent vomiting may cause an acidic mouth environment, leading to growth of dental caries pathogens as well as acid demineralization of the tooth enamel. Pregnant women should be advised to mouth rinse using a teaspoon of sodium bicarbonate in a cup of water after vomiting to counteract the demineralizing effect of stomach acid on the teeth. A fluoride-containing mouth rinse carried out immediately before bedtime helps to remineralize teeth.

**Threatened Abortion**

Approximately 10% of pregnant women experience uterine bleeding during the first 5 months of gestation. This condition is known as threatened abortion and leads to spontaneous abortion in 10% to 20% of cases, with 80% to 90% of women continuing with their pregnancies uneventfully. A definitive prognostic factor is the presence of a normal embryo/fetal ultrasound examination. Dental treatments may be preferably performed after bleeding stops, which usually takes a few days after diagnosis.

**Preterm Labor and Preterm Premature Rupture of Membranes**

Preterm delivery occurs in 3% to 12% of patients worldwide. Preterm labor and preterm premature rupture of membranes are the predecessors of preterm delivery in two thirds of cases, accounting for most perinatal mortality due to neonatal complications associated with prematurity. Both conditions have been linked to a heterogeneous group of etiologies (the preterm delivery syndrome; see Figure 1), including periodontal disease. Intrauterine infection is associated with both conditions, especially preterm premature rupture of membranes.

Preterm labor is a disorder characterized by regular uterine contractions and cervical changes occurring between 22 and 37 weeks of gestation. Of all patients diagnosed with preterm labor, only 50% actually deliver before 37 weeks. The clinical identification of this group is difficult at the time of admission to the hospital. The most important therapeutic measure is the administration of intramuscular corticosteroids to reduce the risk of neonatal complications attributable to prematurity. Drugs aimed at reducing uterine contractions (tocolytics, such as nifedipine, betamimetics, atosiban) are also used to delay delivery for at least 48 hours. Antibiotics are not used routinely in patients with preterm labor.

Preterm premature rupture of membranes is defined by the bursting of the
chorioamniotic membrane containing the fetus and the amniotic fluid, occurring before labor begins, before 37 weeks of gestation. Clinical presentation includes fluid leaking from the vagina followed by uterine activity in the majority of patients. Management includes administration of both corticosteroids and antibiotics to reduce the risk of neonatal complications, delay delivery, and decrease the likelihood of maternal and neonatal infections. Antibiotics frequently used are ampicillin, erythromycin, clindamycin, and metronidazole.\(^7\)\(^1\)\(^2\) Delivery is indicated when the pregnancy has reached 32 to 34 weeks. Tocolytics are not routinely used in patients with preterm premature rupture of membranes.

For the two conditions described in the previous text, essential dental procedures may be performed after the patient is admitted to the hospital or clinic, when treatment is established, and when uterine quiescence is obtained. Elective treatment may be postponed until after delivery.

**Preeclampsia/Eclampsia**

The development of both hypertension and significant amounts of protein in urine occurring during the second half of pregnancy and puerperium is referred to as preeclampsia. The progression to seizures or coma characterizes eclampsia. The disorder is multisystemic and affects 3% to 7% of pregnancies. The etiology of preeclampsia is heterogeneous, but a common terminal pathway characterized by endothelial dysfunction is the key pathophysiologic landmark of the disease.\(^7\)\(^3\) Patients with preeclampsia have an increased risk for maternal and perinatal mortality. Maternal complications include persistent hypertensive crisis, cerebral hemorrhage, liver/hematologic dysfunction, and premature placental separation (abruptio placenta). Fetal/neonatal complications are placental insufficiency (chronic fetal hypoxia), fetal growth retardation, and newborn complications derived from medically indicated premature delivery.

Progression of the disease is interrupted only by delivering the fetus and placenta. However, a significant percentage of patients with preeclampsia are suitable to expectant management to advance in gestational age and decrease the risk of neonatal complications derived from early delivery.\(^7\)\(^3\) Drugs commonly used for women with preeclampsia are hypotensors such as labetalol, methyl-dopa, and hydralazine. Magnesium sulfate is used in the prophylaxis and treatment of seizures, especially around labor and delivery. Patients at risk for preeclampsia may receive aspirin starting in the second trimester of pregnancy in an attempt to reduce the likelihood of developing the disorder.

Emergency dental treatment should be performed only after the preeclampsia patient is stabilized and goals regarding blood pressure and neurologic status are reached. The dentist should be aware that patients with preeclampsia suffer from a fragile neurologic condition. Informing adequately about the procedure and premedication with a sedative agent are to be considered. Epinephrine is contraindicated; thus anesthetic drugs with vasoconstrictors must be avoided. If the patient is under aspirin prophylaxis, increased bleeding time is expected. Elective procedures should be deferred after delivery until complete resolution of the disorder.

**Fetal Growth Restriction**

Fetal growth restriction is a common diagnosis during the second half of pregnancy. Diagnosis is made by ultrasound fetal biometry when the estimated fetal weight falls below the 10th percentile for a specific gestational age. The disorder is associated with increased perinatal morbidity and mortality, although most fetuses diagnosed with the condition are constitutionally small but otherwise healthy.\(^7\)\(^4\) This distinction is usually
made by ultrasound velocimetry of placental vessels and a detailed examination of fetal anatomy. The mother is generally not affected, unless she has evidence of maternal disease predisposing to poor fetal growth (e.g., hypertension, diabetes, renal disease). A significant percentage of fetuses reach 37 weeks of pregnancy under periodic ultrasound surveillance. Recent investigations have proposed that fetal growth restriction is associated with adult disease (diabetes, hypertension, and coronary heart disease). There are no specific medications for the treatment of fetal growth restriction. Intra-muscular corticosteroids may be necessary when preterm delivery is indicated. In general, fetal growth restriction does not alter dental treatment during pregnancy.

**Fetal Death**

Fetal demise or stillbirth after 22 weeks occurs in 5 to 10 per 1,000 births. Diagnosis is reached by establishing the absence of cardiac activity by ultrasound. The most common causes of fetal death are maternal diseases (preeclampsia, pregestational diabetes, renal disorders), placental insufficiency (often associated with fetal growth restriction), acute fetal hypoxia (due to placental abortion, uterine rupture, or cord accidents), congenital anomalies, chromosomal abnormalities, fetal infection, fetal anemia, and conditions specific to multiple gestation. A significant proportion (30% to 60%) of fetal deaths have no evident cause.

Of significance for the dental professional is a rare hematologic condition that develops when the deceased fetus remains in utero for more than 3 weeks. In these cases, fibrinogen levels may drop, leading to a subclinical coagulopathy that could progress to disseminated intravascular coagulation, characterized by systemic spontaneous bleeding and multiple organ dysfunction. Any dental procedure should be deferred until the condition is completely resolved.

**DENTAL MANAGEMENT OF WOMEN AT RISK FOR ADVERSE PREGNANCY OUTCOMES**

**Risk Factors for Preterm Birth**

Preterm birth is the most relevant adverse outcome for pregnant patients requiring dental treatment. Preterm birth should be thought of as a syndrome caused by multiple mechanisms, including infection, inflammation, uteroplacental ischemia, chorioamnionitis, hemorrhage, uterine overdistention, and stress (see Figure 1). A growing number of risk factors associated with these conditions have been described. The most important risk factors for the development of spontaneous preterm delivery include:

1. Spontaneous preterm birth occurring in a previous gestation
2. Intrauterine infection
3. Short uterine cervical length as determined by ultrasound in the mid-trimester
4. Inflammatory biomarkers in cervicovaginal fluid or maternal urine (e.g., fibronectin)
5. Low prepregnancy body mass index
6. Systemic inflammation
7. Vaginal bleeding of uterine origin during the second half of pregnancy
8. Multiple gestation
9. Cigarette smoking
10. Social vulnerability (African-American race, adolescent pregnancy, low socioeconomic status)

**Dental Care in Women at Risk for Preterm Birth**

Several review studies have shown that it is safe to provide dental care for pregnant women, although clinical trials supporting such evidence are scarce. The American Academy of Periodontology recommends that pregnant women with periodontal disease should receive periodontal treatment during pregnancy. The notion that periodontal treatment and routine dental treat-
ment do not carry a special risk for the preg-
nant patient is based on indirect obser-
vations derived mainly from clinical trials
aimed at determining the effect of periodon-
tal treatment on pregnancy outcomes.

Twelve randomized controlled trials of
periodontal treatment in pregnant women
have been published.14-16,51,78-85 The effect of
periodontal treatment to reduce preterm birth
yield controversial results, but all the trials,
with the exception of one,85 confirmed the
safety of providing dental treatment during
pregnancy, including oral prophylaxis, restora-
tions, extractions, and nonsurgical periodontal
treatment. The study by Macones et al.85 sug-
gested that treatment of periodontal disease
was associated with a trend toward an increase in indicated preterm delivery. However, some methodologic flaws in the study design of that trial raise reasonable
doubts regarding the validity of its conclu-
sion. The investigators defined the periodon-
tal status of the study participants as “early
localized chronic periodontitis,” and the only
criterion that they used for the diagnosis of
periodontal disease was periodontal attach-
ment loss of 3 mm or more on three or more
teeth.85 Attachment loss is more a measure of
past disease than of current periodontal
disease86 and can also occur as a consequence
of noninflammatory gingival recession. Peri-
odontal variables that reflect current inflam-
matory burden, such as bleeding on probing
and pocket depths, are the more appropriate
measures of periodontal disease as exposure
in the context of risk for systemic diseases.87
Use of attachment loss alone as the only cri-
iterion for diagnosing periodontitis can result
in mistakenly including women who do not
have periodontal disease, as may have
occurred in the Macones et al. study.88 Unfor-
fortunately, it is not possible to determine the
level of severity of the periodontal disease in
the women included in the study because the
periodontal characteristics of the participants
were not reported.

A recent workshop on periodontitis and
systemic diseases concluded that periodontal
therapy has been shown to be safe and leads
to improved periodontal conditions in preg-
nant women.88

Treatment Before and After 28 Weeks
of Gestation
López and colleagues44 performed a ran-
domized trial with 200 pregnant women
with moderate to severe periodontitis. The
study population showed several well-known
risk factors for preterm birth. All the women
were of low socioeconomic level, 22% were
unmarried, 4.7% had a history of preterm
birth, 15% smoked, 12% were underweight,
and 20% had begun prenatal care after 20
weeks of gestation. In addition, 11% had
urinary infections and 18% had bacterial
vaginosis during pregnancy. All these infec-
tions were medically treated. Two-hundred
women received periodontal treatment con-
sisting of plaque control instructions, scaling,
and root planing under local anesthesia
without vasoconstrictor before 28 weeks of
gestation. A control group of 200 women
received a periodontal examination at the
time they were enrolled. Patients were moni-
tored every 4 to 6 weeks during the gesta-
tional period, and another complete peri-
odontal examination was performed after 28
weeks of gestation. The control group
received periodontal treatment after delivery.
Cavities lesions were treated, and all teeth
indicated for extraction were extracted from
both groups. The incidence of spontaneous
abortions and of medically indicated
preterm deliveries were similar in the treat-
ment group and in the group who had not
received treatment during pregnancy. No
other adverse events that could be ascribed
to dental treatment were observed among
the participants of the study.

Treatment with Metronidazole
Jeffcoat and colleagues16 did not report
safety outcomes for 366 women randomized into a group who received a prophylaxis or scaling and root planing, with or without systemic metronidazole therapy. Unexpectedly, within this study, the lowest rate of preterm birth occurred in women who received scaling and root planing and placebo, and not in the group who received metronidazole. Metronidazole has been shown to be effective in controlling periodontal infection when given as an adjunctive of root planing. However, a later study by Carey and Klebanoff\(^9\) showed that oral metronidazole therapy may produce changes in the vaginal flora leading to a heavy growth of *Escherichia coli* and *Klebsiella pneumoniae*, which were associated with an increased risk of preterm birth. Thus, oral metronidazole used as the only antimicrobial for periodontal infection in pregnancy should be used with caution.

**Treatment of Extensive Pregnancy-Associated Gingivitis**

In another randomized trial,\(^31\) 570 women with extensive pregnancy-associated gingivitis received periodontal treatment before 28 weeks of gestation. Periodontal treatment consisted of plaque-control instructions, subgingival scaling, crown polishing, and mouth rinsing with 0.12% chlorhexidine once a day. Timing in which women received periodontal treatment is shown in Table 3.

The results of the study showed that treatment of gingivitis reduced preterm birth and low birth-weight infant rates by 68%.

**Table 3. Timing in Which Pregnant Women with Gingivitis Received Periodontal Treatment**

<table>
<thead>
<tr>
<th>Week of Gestation</th>
<th>Received Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Between 7 and 12 weeks</td>
<td>131</td>
</tr>
<tr>
<td>Between 13 and 20 weeks</td>
<td>376</td>
</tr>
<tr>
<td>Between 21 and 28 weeks</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>570</td>
</tr>
</tbody>
</table>

No adverse events ascribed to dental treatment were identified in the treatment groups during pregnancy, and no significant differences were observed when women of the treatment group were compared with the group who did not receive periodontal treatment. The results of this study show that periodontal treatment administered between 7 and 28 weeks of gestation is not associated with an increased risk of serious adverse events in women despite the presence of other risk factors associated with adverse pregnancy outcomes, such as low socioeconomic status, history of preterm birth, smoking, and genitourinary infections during pregnancy.

**Treatment of Periodontitis**

Offenbacher and colleagues\(^8\) randomized 74 women with mild periodontitis, 40 of whom received periodontal treatment early in the second trimester of pregnancy. Periodontal treatment consisted of plaque control instructions, scaling and root planing, and crown polishing; 34 women received only supragingival debridement. This study population represented a high-risk group of preterm birth because 60% of the participants were African American and tended to be economically disadvantaged, and 75% had previously experienced preterm births. The findings of this study indicate that the intervention was successful in treating periodontal disease, and no serious adverse events occurred in terms of either obstetric or periodontal outcomes that were attributed to periodontal treatment. The authors reported two cases of fetal demise during the study; however, neither the timing nor the group to which the women with these events belonged was specified.

Tarannum and Faizuddin\(^7\) evaluated the effect of periodontal therapy on pregnancy outcome in a randomized trial consisting of 200 women with periodontitis. The treatment group received plaque control
instructions and scaling and root planing under local anesthesia, as well as mouth rinse twice daily with 0.2% chlorhexidine. The control group received tooth-brushing instructions only. A significantly higher incidence of preterm birth was observed in the control group compared with that in the treatment group (76.4% vs 53.5%, $P < .001$). No adverse effects due to periodontal treatment were reported.

**Treatment of Slight-to-Moderate Periodontitis**

Michalowicz and colleagues$^{15}$ conducted a multicenter, randomized trial to determine whether periodontal therapy reduces the risk of preterm delivery. They concluded that treatment of periodontitis in pregnant women improves periodontal disease and is safe, but does not significantly alter rates of preterm birth. The data from this study were also used to investigate safety outcomes related to the provision of dental care in pregnant women.$^{13}$ Participants in the study had generalized, slight-to-moderate periodontitis, and they belonged to minority and underserved groups who had an elevated risk of adverse pregnancy outcomes. The population study consisted of African-American women (45%), Hispanic women (42%), and women with a history of preterm birth deliveries (9.3%). The authors randomized 413 pregnant women with periodontitis to a group who received scaling and root planing between 13 and 21 weeks of gestation. Dentists provided periodontal treatment over one to four visits, and topical or locally injected anesthetics were administered as needed. A control group of 410 women were monitored during pregnancy and treated after delivery.

Women of both groups were evaluated for essential dental treatment. The necessity for “essential” dental treatment was defined as the presence of one or more of the following: odontogenic abscesses, decayed teeth judged likely to become symptomatic during pregnancy if left untreated, and fractured or decayed teeth that could adversely affect the health of adjacent teeth. Affected teeth were treated with temporary or permanent restorations, endodontic therapy, or extraction at a time between 13 and 21 weeks of gestation. Four-hundred-eighty-three women needed essential dental treatment, and 72.7% of these women completed all recommended treatment. Serious adverse effects were recorded, including spontaneous abortion, stillbirth, hospitalization for more than 24 hours because of labor pains or other reasons, fetal or congenital anomalies, or neonatal deaths. The adjusted odds ratios for all adverse outcomes related to essential dental treatment were close to 1, showing that the dental treatments administered were not associated with any significant increase in risk for these outcomes.

Nonsignificant differences of adverse events were found in women who received essential dental treatment and who received or who did not receive periodontal treatment. The distribution of adverse events was not significantly different in women who received periodontal treatment nor in those who did not receive treatment during pregnancy. Thus, in a population with a high risk of adverse pregnancy outcomes, periodontal and dental treatments administered between 13 and 21 weeks of gestation did not increase the risk of serious medical adverse events, preterm deliveries, spontaneous abortion or stillbirths, or fetal anomalies. This study confirms the predominant notion in the obstetric community that few risks are associated with routine dental care during pregnancy.$^{80}$ Some experts advise deferring elective dental treatment during the first 12 weeks of gestation because of the potential vulnerability of the fetus.$^{80,91}$ However, there is no evidence that routine dental treatment or periodontal treatment may have adverse effects on fetal development or induce malformations.
This notion is confirmed by a retrospective study\textsuperscript{92} that examined the records of 23,441 pregnant women who delivered live births from singleton pregnancies in the United States. This study found that women who received preventive dental care during pregnancy had better birth outcomes than those who received no treatment ($P < .001$). No evidence of increased risk of adverse birth outcomes from dental or periodontal treatment was found.

**Treatment During Pregnancy and Risk of Preterm Birth**

Ideally, women should begin their pregnancy without periodontal infections, and preventive oral care services should be provided as early in pregnancy as possible. However, if a periodontal or dental infection is diagnosed at any time during pregnancy, the treatment should be administered as soon as possible to reduce the risk of preterm birth. In women with periodontal disease diagnosed late in the second or in the third trimester of pregnancy, and who have a high risk of preterm birth or symptoms of preterm labor, the administration of systemic antibiotics to control periodontal infection is advisable. The combination of metronidazole (250 mg) plus amoxicillin (500 mg) three times a day for 7 days, in conjunction with root planing, has been shown to be effective to control periodontal infections in patients with chronic periodontitis.\textsuperscript{93} Timing of the administration of antibiotics in relation to the scaling and root planing treatment is controversial, and protocols to determine the best timing to administer antibiotics have not been tested.

Apparently, the results of the administration of metronidazole and amoxicillin contrast with those of the administration of metronidazole alone in relation to changes in the vaginal microflora. This combination of antibiotics has been widely used to treat periodontal infection with no secondary effects on the vaginal flora reported. López and colleagues\textsuperscript{94} gave metronidazole and amoxicillin to 29 pregnant women with severe aggressive periodontitis as an adjunct to scaling and root planing. The treatment was administered between 16 weeks and 28 weeks of gestation; the administration of antibiotics began the day that scaling and root planing were initiated. No adverse effects that could have been attributed to antibiotic treatment were observed, and all the women had normal-term parturition.

**Managing Periodontal Infection in the Pregnant Adolescent Patient**

Maternal age under 18 years is a risk factor for preterm birth,\textsuperscript{95} and pregnant adolescents are at an increased risk for medical complications.\textsuperscript{96} In the United States, more than 6\% of adolescent females become pregnant every year. Of these pregnancies, 51\% end in live births, 35\% in induced abortion, and 14\% in miscarriages or stillbirth.\textsuperscript{96} Poor and low-income adolescents make up 38\% of all women ages 15 to 19 in the United States; yet they account for 73\% of all pregnancies in that age group. It is known that prevalence and severity of periodontal disease are also higher in disadvantaged populations. Teenage mothers are much less likely than older mothers to receive prenatal care and are more likely to smoke during pregnancy. As a result of these and other factors, babies born to teenagers are more likely to be preterm (<37 weeks’ gestation) and of low birth weight (<2500 g) and have a greater risk of serious and long-term illness, of developmental delays, and of dying in the first year of life compared with infants of older mothers.\textsuperscript{97} No studies exist about the oral health status in pregnant adolescents, but by extrapolating the information on prevalence of gingivitis and periodontitis from studies in nonpregnant adolescents, it can be expected that these diseases have similar prevalence. Gingivitis is common in
children, reaching a peak at puberty followed by a limited decline in adolescence.

To determine the effect of periodontal treatment on pregnancy outcomes, a cohort of 164 pregnant adolescents at high risk of preterm birth was recruited by Mitchell-Lewis and colleagues. The study population consisted of pregnant adolescents, ages 14 to 19. All were of low socioeconomic status; 60% were African American and 39% Hispanic. These sociodemographic characteristics—young age, minority ethnicity, and low socioeconomic status—are well-known risk factors for preterm birth. Periodontal examinations were performed to assess dental plaque, calculus, bleeding on probing, and pocket depth. Periodontal treatment consisted of oral hygiene instructions, scaling, and crown polishing. This treatment was given to 74 women; 90 women with no treatment were used as controls. Four plaque samples per subject were obtained during pregnancy and postpartum to study the prevalence of 12 bacterial species. Preterm low birth weight occurred in 13.5% of women who received periodontal treatment and in 18.9% of women who did not receive treatment. The difference was not statistically significant. However, preterm birth mothers had significantly higher levels of *Tannerella forsythia* and *Campylobacter rectus* and consistently higher levels of the other species studies. The reduction of 28.6% in the incidence of preterm low birth weight, even though not statistically significant, shows that periodontal intervention may reduce adverse outcomes in pregnant adolescents with periodontal infection. No adverse effects due to periodontal treatment were reported.

Pregnant adolescents are at high risk for adverse pregnancy outcomes; for those who have gingivitis or periodontitis, the risk may increase. The principles for medical and dental management of these patients are not very different from those used for adult women, but the higher incidence of complications combined with more serious social and legal issues when they are under the age of 18, make their overall management more complex.

**CONCLUDING PRINCIPLES**

- Women’s healthcare providers should know the importance of protecting oral health during pregnancy and educate their patients accordingly.
- Pregnant women should be advised that prevention, diagnosis, and treatment for oral disease, including needed dental x-rays and local anesthesia, are highly beneficial and can be undertaken without additional fetal or maternal risk when compared with not providing care.
- The safety and effectiveness of providing oral health care during pregnancy, including prophylaxis, restorations, extractions, and periodontal treatment have been confirmed by many studies.
- All women should receive at the beginning of the pregnancy period an evaluation of their oral health status, which includes a comprehensive periodontal examination, assessment of gingival inflammation, periodontal probing depth, and clinical attachment level measurements.
- Pregnant women with gingivitis or periodontitis should receive periodontal treatment as soon as the periodontal condition is diagnosed. In women at risk for adverse pregnancy outcomes and periodontal infection, collaboration between the obstetrician and dentist is essential to determine the timing and characteristics of periodontal treatment that should be administered.
- No evidence links early spontaneous abortion in the first trimester to oral health care or dental procedures.

**Supplemental Readings**


Iams JD, Romero R, Cullhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. *Lancet* 2008;371:164–75.


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INTRODUCTION

Before considering any therapeutic coman-
agement issues, associations need to be con-
vincing, and mechanistic links and shared
risk factors should be understood. This is
particularly so for dental diseases and osteo-
porosis, kidney disease, and cancer, since the
literature is relatively new and sparse. Fortu-
nately, these are addressed in previous chap-
ters and in a recent workshop review. The
goal of this chapter is to consider the man-
agement issues that may arise in dealing with
the comorbid state. Can we modify treat-
ment? Do we need to prescribe the routine
drugs or are there alternatives? How should
the dentist or physician treat patients pre-
senting with both oral and systemic condi-
tions? First, we need to consider the diseases
and the characteristics that might complicate
their dual management. Included in this con-
sideration are the new literature and find-
ings arising from the recent joint European and
American Periodontology Workshop. Each
section concludes with suggestions for both
the physician and the dentist for treating
these patients.

OSTEOPOROSIS AND OTHER
BONE DISEASES

Osteoporosis

Osteoporosis is the most common bone
disease in humans. Disease prevalence has
been reported by some sources to be 3% to
6% in men and up to 13% to 18% in women
(i.e., approximately 8 million women and 2
million men), with a significantly higher
prevalence reported for those meeting the
diagnostic criteria for osteopenia. The risk
of developing osteoporosis increases with
age, especially in women, because the loss of
ovarian function precipitates rapid bone
loss. About 300,000 hip fractures occur each
year requiring hospital admission and, ulti-
mately, surgical correction. Considering the
increasing numbers of the elderly popula-
tion, as the “baby boomers” rapidly
approach their sixth and seventh decades of
life, it is easy to see how this disease process
can and will affect the healthcare system of
the United States and worldwide.

Osteoporosis is diagnosed on the basis of
a low-impact or fragility fracture or low bone
mineral density (BMD), which is best assessed
by central dual-energy x-ray absorptiometry
(DEXA). By World Health Organization
guidelines, a diagnosis of osteoporosis is made
by DEXA scan demonstration of a BMD
that is 2.5 standard deviations below the
young adult reference mean based on gender.
Classifications for osteoporosis are broken
down into primary and secondary causes. Sec-
ondary causes are many, and though less
commonly seen in clinical practice, a few of
these causes, such as diabetes mellitus and
chronic obstructive pulmonary disease, are
often seen in patients with osteoporosis.

Paget’s Disease

Paget’s disease is a disorder characterized by
excessive resorption of bone. Subsequent to
this resorption, new bone is deposited in a
haphazard fashion to compensate for the
rapid bone loss. This creates the mosaic
pattern commonly associated with the
disease process that describes the disorgan-
ized trabecular bone formed rather than the
normal pattern of lamellar bone. This disordered bone deposition is weak and prone to deformities as well as fracture. The incidence of Paget’s disease is not well reported, and the current incidence of 3.0% to 3.7% is based on autopsies and radiographs of patients over 40 years of age.\(^5\) Etiology of the disease is unknown, although there are several proposed theories, including viral and genetic factors. Careful evaluation of history and physical examination help to delineate Paget’s disease from other possible diagnoses (e.g., metastatic bone disease). Certain serologic and radiographic tests aid in making the diagnosis. There are several clinical manifestations of Paget’s disease, including complaints of upper dentures no longer fitting; however, the skeletal sequelae are most germane to the current discussion.

**Metastatic Bone Disease**

Metastatic bone disease is most commonly associated with breast and prostate cancer, but is frequently seen in advanced cases of malignancy. Tumor cells express several chemical and genetic factors that make bone a preferred site for localization and growth. There is much discussion in the medical literature regarding the propensity of certain malignancies to express osteoblastic versus osteolytic bone lesions. However, most patients with bone metastases have evidence of both lesions. Clinical manifestations of metastatic bone disease include pain, fracture, and possibly spinal cord compression. Cord compression is a medical emergency requiring immediate intervention to prevent permanent neurologic dysfunction. Although antineoplastic and analgesic therapies are the mainstay of treatment for most metastatic bone lesions, certain alternative strategies have been gaining favor, such as bisphosphonate therapy.

**Pharmacology of the Bisphosphonates**

Bisphosphonates are synthetic analogues of inorganic pyrophosphate. They were initially developed in the 1800s and have industrial uses such as softening water for irrigation systems. The compound’s ability to soften water is due to the inhibition of calcium carbonate crystal formation, and it was later found that bisphosphonates can also inhibit calcium pyrophosphate crystal formation. Bisphosphonates are classified into two groups based on whether they contain an amino group. Mechanism of action differs among the groups. Aminobisphosphonates (zolendronate, alendronate, pamidronate, ibandronate, and risendronate) disrupt the pathway involving metabolism of mevalonic acid. They also promote abnormalities in cytoskeleton production, inducing apoptosis of osteoclasts that retard bone resorption. Bisphosphonates that do not contain amino groups (etidronate, clodronate, and tiludronate) act by disrupting adenosine triphosphate (ATP) formation after being metabolized within osteoclasts, also promoting apoptosis. Unfortunately, bisphosphonates exhibit a secondary effect—their ability to inhibit bone mineralization, thereby causing osteomalacia. Again we see a difference among the classes. Whereas etidronate has been shown to inhibit resorption and mineralization at similar concentrations, alendronate has been shown to have a markedly favorable therapeutic index (i.e., better resorption inhibition than defective mineralization) up to 36 months from initiation of therapy.\(^6\) The overall higher potency and lower toxicity of aminobisphosphonates are likely the reasons they are used more often in clinical practice than are other bisphosphonates.

Although less than 10% of orally ingested doses of bisphosphonates are absorbed, between 20% and 50% of the absorbed dose accumulates in bone, depending on the rate of bone turnover. The remainder of the dose is excreted in urine. The half-life of these drugs varies considerably, but in the case of alendronate (one of
the more common pharmaceutical agents used in the treatment of disorders of bone metabolism, it is as long as 10 years. One point of contention is the time frame for which the compound persists within the bone, which according to some sources, can be the lifetime of the patient. This is an important factor to bear in mind when considering interruption of therapy before surgical procedures.

Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) has attracted increased interest for both medical and dental practitioners in recent years. In the early part of the last century, the term “phossy jaw” had been used to describe the condition that linked white phosphorus exposure with the disease process of osteonecrosis. Radiation and chemotherapy have also been implicated as possible causes of ONJ. The most recent debate in the current literature and to be addressed in this chapter is bisphosphonate-associated ONJ. Bisphosphonates have taken on a vital role in the management of chronic disease processes such as osteoporosis and Paget’s disease, as well as the prevention of skeletal complications in patients with bone metastases. Bisphosphonate-associated ONJ was first reported in 2003; since then many more cases have come to light, propelling the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to review the literature and make recommendations for future diagnosis and management.

The case definition of bisphosphonate-associated ONJ is an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a healthcare provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region. The reporting of many cases involving ONJ associated with bisphosphonate use was made before the accepted ASBMR task force definition.

Therefore, the quality of evidence regarding the true incidence of ONJ is in question, as is the true causal relation between bisphosphonates and ONJ. Information presented here is based on the most current facts, but this is an expanding field and the reader should update regularly on this topic.

The known epidemiologic data for bisphosphonate-associated ONJ varies greatly based on the disease processes for which the drug is used (Figures 1–3). Therefore, this chapter considers the osteoporosis and Paget’s disease patient subsets and those receiving bisphosphonates for skeletal complications of malignancy as separate entities.

Figure 1. Clinical Photograph of an Upper Jaw Exhibiting Marked Osteonecrosis in a Patient on Bisphosphonate Therapy

Figure 2. Orthopantomograph of Osteonecrosis in the Lower Border of the Lower Jaw

Courtesy of Dr. George M. Kushner, University of Louisville Dental School.
Patients receiving bisphosphonate therapy for osteoporosis and Paget’s disease are mostly treated with oral agents, whereas those with malignancy complications generally receive intravenous therapy. There is conflicting evidence regarding the incidence of ONJ in patients receiving bisphosphonates for osteoporosis. One study estimated the prevalence to be less than 1 in 250,000. The incidence of ONJ in patients receiving bisphosphonate therapy for complications of malignancy ranges from 1% to 10%. A prospective study by Bamias and colleagues of cancer patients receiving bisphosphonate therapy estimated that the risk of developing ONJ increased with length exposure to the drug and was dependent on the bisphosphonate used. Although the data supporting these claims are limited, it is generally accepted that the risk of developing ONJ is higher in patients receiving treatment for metastatic bone disease. Whether this higher incidence is secondary to the higher doses received by patients with malignancy compared with those receiving therapy for osteoporosis or Paget’s disease remains to be seen.

The pathogenesis of ONJ remains unknown. Patients with the aforementioned disease processes requiring bisphosphonate therapy have many areas of poor bone health. These areas are posited to carry a high risk for ONJ. The antiangiogenic effects attributed to bisphosphonates are purported to leave areas such as these in a relatively ischemic condition. Ischemic regions with infarcted bone do not properly remodel because of the antiresorptive properties of these medications. Areas such as these are susceptible to further necrosis after trauma such as oral surgery. Furthermore, these areas are a perfect nidus for infection, and a wide range of bacterial infections is found in these situations. Again, these are only proposed mechanisms, and further clinical research is necessary to elicit the pathophysiology of the disorder, particularly regarding the issue of predisposing factors such as corticosteroid use or alcohol abuse.

A currently investigated topic is the early identification of osteonecrotic bone before the initiation of bisphosphonate therapy or oral surgery. This is extremely difficult, however, because most readily available radiographic techniques cannot identify defects of cancellous bone until advanced stages. Current recommendations by the task force call for development of noninvasive diagnostic and imaging techniques to further characterize the disorder.

**Management**

Conditions requiring bisphosphonate therapy are common and may (especially osteoporosis) become more prevalent in the near future. Morbidity secondary to disease progression such as ONJ has a negative impact on the healthcare system financially and considerable emotional and physical ramifications for the patient. Thus, ongoing preventive measures are necessary in managing these medical conditions. Until more effective therapies with fewer adverse effects are available, the use of bisphosphonates will continue. The heightened awareness of
ONJ associated with these medications, combined with stronger guidelines outlining case definitions and a call to responsible reporting, has already resulted in an increased number of cases reported over the past 2 years. Management of bisphosphonate-associated ONJ requires an interdisciplinary approach, with open communication between medical and dental practitioners and patients. Since the incidence and risks of developing this complication are different among patient subsets, this chapter outlines the recommended management strategies separately for patients with osteoporosis/Paget’s disease versus those treated for complications of malignancy. These recommendations for management are adapted from the guidelines of the 2007 ASBMR Task Force.8

As previously mentioned, free communication between medical and dental practitioners is necessary to ensure proper continuity of care. Full disclosure concerning the risks and benefits of medical therapy is the responsibility of the medical practitioner for any patient initiating treatment with bisphosphonates. Reducing the risk of developing ONJ includes observing strict maintenance of the patient’s oral hygiene and regular follow-up visits with a dental practitioner, which should be an integral part of the medical care for all patients taking bisphosphonates. Patients are to be instructed that any oral problems should be reported to their physician and dentist promptly.

The risk of developing ONJ in patients receiving oral therapy for osteoporosis or Paget’s disease is fairly low. The risk also seems to be related to length of exposure to the medication. Therefore, it is not necessary to have a dental evaluation before initiating bisphosphonate therapy for these disorders. For patients taking these medications for longer than 3 years, there are more detailed recommendations for management. Patients on long-term therapy should receive appropriate nonsurgical treatment for periodontal disease (unless contraindicated by comorbid illness). Moderate bone recontouring is acceptable if necessary. There is currently no contraindication to dental implant surgery in this patient subset. Endodontic treatment is the preferred mode of therapy over extraction when at all possible. When invasive therapy is necessary, temporary discontinuation of bisphosphonate therapy is recommended; however, no evidence supports improved dental outcomes when discontinuing therapy. As previously mentioned, the long half-life of certain bisphosphonates and the even longer retention of the medication in bone call into question the validity of such strategies. Once again, good quality communication between practitioners and patients is of the utmost importance in making these decisions.

For patients receiving medical therapy for complications of malignancy, the risks of developing ONJ are greater, and thus management strategies are more conservative. Dental evaluation by a qualified specialist should be completed before the initiation of therapy, with follow-up evaluations at 6- to 12-month intervals. If at all possible, invasive procedures with appropriate time allotted for healing should be performed before the start of medical therapy. If medical therapy must be initiated sooner, then concomitant surgical treatment is recommended with close follow-up. Elective procedures such as implant placement and extraction of asymptomatic teeth are not recommended. Symptomatic teeth should be treated by nonsurgical means when possible, unless the tooth is excessively mobile and presents a risk for aspiration.

Patients with established ONJ should be referred to a qualified dental practitioner for management. For those with clinical evidence of infection, appropriate antimicrobial therapy is recommended. Surgical intervention for ONJ should be delayed unless the
necrotic bone has sharp edges that may cause continued trauma to adjacent soft tissues. Segmental jaw resection may be necessary for large areas of necrosis. The decision to discontinue bisphosphonate therapy for those with this complication depends on the patient’s clinical condition, since this strategy has not been established to improve outcome. Recommendations are to ensure maintenance of a high standard of oral hygiene and ensure no active disease by using nonsurgical and surgical therapy where needed, as well as adjunctive antimicrobial therapy. Anti-inflammatory drugs should be avoided unless there is evidence from research that such medications will not interfere or interact with medications used for osteoporosis. There is a possibility that any dampening of normal inflammation may permit the bacteria in an infectious lesion to become more virulent, allowing greater destruction of bone. Alternatively, dampening inflammation may be helpful in certain cases of periodontal disease, but until there is evidence one way or the other, anti-inflammatory drugs should be avoided in this comorbid situation.

Case example: Patient has been treated with bisphosphonates, with exposed maxillofacial bone present for more than 8 weeks.

Risks: Potency and duration of bisphosphonate use.

Other risk factors: Age, genetics, additional systemic conditions, e.g., diabetes, obesity, renal dialysis.

Management: Before use of cancer-related bisphosphonate, a thorough dental examination is needed and optimal endodontic and periodontal health should be achieved. In addition, alternative dosing regimens that reduce bisphosphonate exposure should be considered.

(Modified from the 2009 BRONJ American Association of Oral and Maxillofacial Surgeons position paper.)

KIDNEY DISEASE

The number of patients with chronic kidney disease (CKD) is growing and is projected to continue. As the incidence of CKD climbs, patients with CKD, including those with end-stage renal disease (ESRD), will represent a larger portion of those seeking dental treatment. With this in mind, it is important to understand the complex interaction between CKD and periodontal disease. CKD is associated with many physiologic changes that may contribute to the development of periodontal disease. Several documented physiologic changes in oral tissues have been associated with CKD. These include xerostomia, decreased salivary pH levels, decreased mineralization, and loss of the lamina dura. In addition, some of the medications commonly prescribed for CKD patients may increase the risk of developing periodontal disease.

Both CKD and periodontal disease have been implicated as sources of chronic inflammation. Thus, periodontal disease may represent a modifiable contributor to the already high inflammatory burden in patients with CKD, especially those with diabetes. Treatment of periodontal disease in these patients could decrease the overall chronic inflammatory burden and its sequelae. A collaborative effort between dental and medical professionals is necessary to ensure that patients get appropriate advice and treatment.

Overview of Kidney Function

The principle function of the kidneys is to remove waste products of metabolism, as well as to maintain fluid and electrolyte balance. The kidneys also play a vital role in blood pressure regulation through the release of renin. Erythropoietin, a potent stimulator of red blood cell production, is also made by the kidneys. Moreover, the kidneys play an important role in bone health by providing the final step in the conversion of vitamin D
Table 1. Classification of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>GFR mL/min/1.73 m²</th>
<th>Action Required (Additional to Previous Stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient with risk factors for CKD</td>
<td></td>
<td>Reduce risk factors</td>
</tr>
<tr>
<td>1. Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
<td>Diagnose risk factors and treat comorbidities and CVD risk reduction</td>
</tr>
<tr>
<td>2. Kidney damage with slight GFR decrease</td>
<td>60–89</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>3. Kidney damage with moderate GFR decrease</td>
<td>30–59</td>
<td>Treat complications</td>
</tr>
<tr>
<td>4. Kidney damage with severe GFR decrease</td>
<td>≥ 15–29</td>
<td>Consider kidney replacement</td>
</tr>
<tr>
<td>5. Kidney failure</td>
<td>&lt; 15 or dialysis</td>
<td>Replace kidney</td>
</tr>
</tbody>
</table>

CKD is defined as either kidney damage (pathologic abnormalities in blood, urine, or imaging) or a GFR less than 60 for 3 months or longer. (Table modified from K/DOQI 2002.16)

to its active form. Decreased kidney function can affect each of these areas and has far-reaching consequences on overall health.

The waste products removed by the kidney include blood urea nitrogen, a byproduct of protein metabolism, and creatinine, a byproduct of muscle breakdown. Blood levels of these compounds are commonly used in lab testing to measure kidney function. More than 100 additional uremic solutes have been identified, many of which are thought to be toxic. As kidney function deteriorates, these solutes can build up, contributing to uremic syndrome. This syndrome has been associated with an increase in fatigue, anorexia, and mental status changes and has been shown to cause leukocyte dysfunction, insulin resistance, and decreased platelet function.

Decreased kidney perfusion causes the release of renin by granular cells in the juxtaglomerular apparatus. This release contributes to the renin-angiotensin system, leading to multiple local and systemic effects, such as vasoconstriction, sodium reabsorption, and fluid retention. There are many antihypertensive agents targeting this system, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and a new class of direct renin inhibitors (DRIs).

Patients with CKD and ESRD are at risk for developing bone disease secondary to the electrolyte and endocrine derangements that occur with decreased kidney function. As kidney disease progresses, phosphate excretion is impaired. There is also decreased production of active vitamin D. Vitamin D is either synthesized in the skin after exposure to ultraviolet light or absorbed from dietary sources. However, vitamin D from ultraviolet light or dietary sources is not active. It must undergo two hydroxylation reactions to be activated in the body. The first hydroxylation reaction occurs in the liver, and the final hydroxylation reaction occurs in the kidney. Decreased active vitamin D levels in combination with decreased phosphorus excretion lead to hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism. Long-standing derangements in calcium and phosphorus homeostasis eventually lead to renal osteodystrophy, which is associated with impaired bone mineralization, increased risk of fractures, and calcification.

Overview of CKD

CKD is a broad term used to encompass patients with evidence of permanent kidney damage and/or progressive decrease in kidney function as defined by glomerular fil-
tration rate (GFR). An estimated 31 million Americans suffer from CKD, and millions of others are at risk (National Health and Nutrition Examination Survey data 1999–2006). The most common causes of CKD are diabetes, hypertension, and glomerulonephritis.

The National Kidney Foundation has published staging guidelines for adult patients with CKD. These guidelines are based on estimated GFR, which is calculated using the widely accepted Modification of Diet in Renal Disease (MDRD) equation. The equation uses serum creatinine level combined with the variables of age, sex, and race in the estimation of GFR. (MDRD equation: GFR [mL/min/1.73 m²] = 186 × [Scr]−1.154 × [age]0.203 × [0.742 if female] × [1.212 if African-American] [conventional units]). This equation provides a much better estimate of kidney function than does creatinine alone. Creatinine is a byproduct of muscle and thus creatinine levels vary with muscle mass. Two individuals with the same creatinine can have striking differences in GFR because of differences in muscle mass. For example, an 80-year-old white female with a creatinine of 1 mg/dL has a decreased estimated GFR of 57 mL/min/1.73 m², whereas a 30-year-old African-American male with a creatinine of 1 mg/dL has a normal estimated GFR of 123 mL/min/1.73 m².

Renal Replacement Therapy
CKD patients with a GFR of less than 15 mL/min/1.73 m² are considered to be in kidney failure. Most patients at this level of kidney function present with symptoms of uremia, and renal replacement therapy must be initiated to sustain life. Occasionally, a patient will have symptoms of uremia requiring renal replacement therapy prior to reaching a calculated GFR of < 15. Any patient with a GFR of < 15 or who is on dialysis is considered to have Stage V CKD.

Renal replacement therapies include hemodialysis, peritoneal dialysis, and kidney transplantation. Dialysis provides a mechanism for filtration of waste products, removal of excess fluid, and titration of electrolytes. Dialysis does not replace the endocrine functions of the kidney. Therefore, many dialysis patients rely on exogenous sources of erythropoietin and vitamin D as part of their treatment regimen. Patients undergoing transplantation recover complete kidney function. However, they must remain on lifelong immunosuppressive therapy to prevent allograft rejection.

Medications Used for CKD

Antihypertensive Agents
Many patients with CKD have hypertension and require multiple medications to reach adequate blood pressure control. Furthermore, the target blood pressure for patients with CKD, at 130/80, is lower than for the general population (according to the Joint National Committee on Hypertension 7). Major classes of antihypertensive agents are diuretics, beta blockers, ACE inhibitors, ARBs, and calcium channel blockers. Direct vasodilators, alpha blockers, and centrally-acting agents represent less frequently used agents. Finally, the newest category of antihypertensives, DRIs, just became available. Of these agents, calcium channel blockers have been implicated as a source of gingival hyperplasia.

Calcium channel blockers consist of dihydropyridines and nondihydropyridines. The dihydropyridines include amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine. The nondihydropyridines include diltiazem and verapamil. Both classes of calcium channel blockers reduce blood pressure by relaxing arteriole smooth muscle and reducing systemic vascular resistance. The nondihydropyridines also have a significant effect on heart rate through a direct negative chronotropic effect. In many
reports, calcium channel blockers have been
documented to cause gingival hyperplasia
(Figure 4), which is a potential adverse effect
with all classes of calcium channel blockers,
but is thought to occur more often with
dihydropyridine agents. Gingival hyperpla-
sia usually occurs within months after the
initiation of therapy and resolves within
months of discontinuing therapy. Clinicians
may consider discontinuing these medica-
tions in patients with calcium channel
blocker–induced gingival hyperplasia.
However, care should be made to find an
alternative antihypertensive to help maintain
adequate blood pressure control.

Figure 4. Gross Gingival Hyperplasia in the
Upper Anterior Region of a Patient with
Hypertension on Treatment with a Calcium
Antagonist (Dihydropyridine)

Immunosuppressive Therapy
Immunosuppressive therapy is used in
patients with kidney transplantation and for
the treatment of glomerulonephritis. Commonly
used immunosuppressive drugs in
transplantation are corticosteroids, cal-
cineurin inhibitors, mTOR (mammalian
target of rapamycin) inhibitors, belatacept,
mycophenolate, and azathioprine. Many of
these medications as well as alkylating agents
and rituximab are used for glomerulonephri-
tis. Significant immunosuppression can
result in numerous oral complications
including oral candidiasis, herpes
simplex/zoster, aphthous ulcers, hairy leuko-
plakia, and oral malignancies.

Several drug-specific side effects are
associated with immunosuppressive agents in
addition to the complications previously
listed. Corticosteroids continue to be used
frequently in transplantation and for the
treatment of glomerulonephritis. Long-term
use can lead to steroid-induced diabetes and
poor wound healing. The calcineurin
inhibitors, cyclosporine and tacrolimus, are
used frequently in transplantation and for
the treatment of glomerulonephritis.
Cyclosporine has been documented in many
studies to cause gingival hyperplasia in renal
transplantation patients. In addition, this
effect is thought to be augmented when
cyclosporine is used in combination with a
calcium channel blocker. Tacrolimus has
shown much lower rates of gingival hyper-
plasia and may be a safe alternative for a
patient experiencing significant cyclosporine-
induced hyperplasia. Any change in
immunosuppressive medications should be
made by the patient’s physician to ensure
efficacy and safety. Another approach to
treating patients with gingival hyperplasia
may be the combination of a standard oral
hygiene program and azithromycin therapy,
which has been shown in at least one study
to reduce both symptoms and objective
measures of cyclosporine-induced gingival
hyperplasia. In recent years, the mTOR
inhibitors, sirolimus and everolimus, have
been used more frequently in patients with
kidney transplantation. They have been
associated with poor wound healing and
oral mucositis.

Inflammatory State
The relation of kidney disease to periodontal
disease is complex and requires further study.
Periodontal disease contributes to a chronic
inflammatory state that has been linked to
many systemic illnesses. Two recent cross-sec-
tional studies identified periodontal disease
as an independent risk factor for CKD.
However, the temporal relationship between the two is unknown, and no conclusions can be made on causality.\textsuperscript{23-25}

Patients with CKD, especially those on dialysis, have exceedingly high mortality rates. Recent data from the US Renal Data System (USRDS) show a mortality rate of 84 deaths per 1,000 patient-years among dialysis patients ages 20 to 44 and 174 deaths per 1,000 patient-years among those 45 to 64 years of age. These rates represent an eight-fold increase from the rates of the general population. The leading cause of morbidity and mortality in CKD patients is cardiovascular disease.

The increased prevalence of cardiovascular disease among CKD patients is thought to be multifactorial. Many of these CKD patients have well-known risk factors associated with cardiovascular disease, such as hypertension and dyslipidemia. However, chronic inflammation is a potential risk factor for cardiovascular disease in CKD patients. Reduction in kidney function is associated with increased serum levels of inflammatory cytokines and C-reactive protein (CRP) and decreased levels of albumin. This inflammatory state appears to accelerate the progression of vascular disease.

Furthermore, periodontal disease may add to the inflammatory burden in patients with CKD. Periodontal disease is common in CKD patients, often more severe than in the general population, and it is frequently overlooked.\textsuperscript{26} Mortality from diabetic nephropathy and ESRD is significantly greater in diabetic patients with periodontal disease compared with those with little or no periodontal disease.\textsuperscript{27,28} Many studies have shown the association of inflammatory markers to periodontal disease in dialysis patients.\textsuperscript{29,30} Treatment of periodontal disease has been shown to reduce inflammatory markers in non-CKD patients.\textsuperscript{31} Furthermore, in a study of CKD patients, treatment of periodontal disease was shown to significantly decrease CRP levels.\textsuperscript{30} A further pilot study reported that surrogate measures of glomerular filtration rates were affected adversely by periodontal disease such that periodontal treatment reduced these GFR surrogates (cystatin C).\textsuperscript{32} Measures that decrease periodontal disease in the CKD population may ultimately reduce the inflammatory burden of the CKD patient, thus decreasing the mortality from cardiovascular disease, but no such study has been performed.

Another potential benefit associated with decreasing inflammatory markers in CKD patients is decreased use of erythropoietin-stimulating agents. Elevated CRP levels in patients on dialysis are associated with higher doses of erythropoietin.\textsuperscript{33} Furthermore, the most recent information from the USRDS shows that Medicare spent $1.9 billion on erythropoietin-stimulating agents in 1 year alone. Decreasing CRP could result in lower erythropoietin doses and thus have a large and positive financial impact.

Treatment of the CKD Patient with Periodontal Disease

The management of periodontal disease frequently requires significant instrumentation, pharmacotherapy, and sometimes surgery. Some clinicians recommend antibiotic prophylaxis before dental procedures in patients with arterial venous grafts because of the risk of infective endocarditis.\textsuperscript{33} Many antibiotic and analgesic regimens exist. For all antibiotics, it is important to adjust the dose based on GFR and to avoid nephrotoxic agents in patients who are not yet on dialysis. Nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease GFR and are best avoided in patients with CKD. Patients with CKD may have an increased bleeding risk secondary to platelet dysfunction as well as to anticoagulants received on hemodialysis. One may try to implement a procedure on
the day after dialysis to decrease the risk. Most renal transplant protocols include a dental workup before transplantation to treat potential problems once immunosuppressive therapy is initiated. Extra caution is necessary in renal transplantation patients because they are more susceptible to infection. An interesting more recent study indicates that CKD mediated by diabetes duration was independently associated with periodontal disease and further supports the infection susceptibility of both diabetics and CKD sufferers. The findings that periodontal treatment reduces inflammatory markers, improves diabetic condition, and reduces surrogate measures of glomerular filtration rates (i.e., inflammatory burden), underlines the benefit of periodontal treatment and health when managing patients with CKD.

CANCER AND PERIODONTAL DISEASE

Almost 11 million people in the United States are living with cancer or have a history of cancer, with approximately 1.4 million new cases occurring yearly. Cancer is a broad term used to describe a group of illnesses defined by uncontrolled growth of abnormal cells that can occur anywhere in the body. Many environmental and intrinsic factors have been implicated in the development of various forms of cancer. Environmental factors include tobacco, chemicals, radiation, and infection. Intrinsic factors include gene mutations, hormones, and immune conditions. Many cancers are likely caused by a combination of environmental and intrinsic factors.

Patients with cancer represent a unique segment of the dental population. The overall higher incidence of cancer in patients suffering from long-term inflammatory conditions has encouraged researchers to consider possible links between chronic inflammatory periodontal disease and cancers. Indeed, poor oral health in general, including tooth loss, is associated with many established risk factors for cancer as well as periodontal disease and the incidence of cancer itself. Many patients with cancer have pre-existing periodontal disease at the time of cancer diagnosis. Michaud et al. reported that although smoking was a major confounder in the potential association between cancer and periodontal disease, even when the analysis was limited to nonsmokers, the association persisted for kidney, lung, pancreatic, and hematologic cancers. Arora and coworkers, using a twin study design, found a 15% increase in cancer risk related to periodontal disease. Using NHANES III, Ahn et al. supported an association between periodontal disease and orodigestive cancers.

From a therapeutic standpoint, several cancer treatments are found to be toxic to oral tissues and can worsen underlying oral disease or result in the development of new periodontal disease. Cancer treatments include chemotherapy, radiation therapy, surgery, hormone therapy, biologic therapy, and targeted therapy. Furthermore, some cancers may involve the oral cavity and have a local effect on oral tissues.

In recent years, periodontal disease has been shown to have an association with many chronic diseases, including cardiovascular disease and diabetes. Much of this association is thought to be secondary to the chronic inflammatory state. Recent studies have shown a small but significant increase in cancer risk in patients with periodontal disease.

Chemotherapy

Chemotherapeutic regimens were developed to target rapidly dividing cells such as tumor cells. With that concept in mind, it is logical to draw an association between these therapies and side effects impacting the gastrointestinal tract. Oral toxicity associated with chemotherapy in cancer patients is a common side effect of these medical regi-
mens, which can affect the entire alimentary tracts. Symptoms are numerous, such as lesions of the oropharynx, dysphagia, gastritis, and diarrhea.

Mucositis is a term used to describe inflammation of the mucous membranes lining the oral cavity and digestive tract. Oral mucositis is commonly reported and is estimated to be found in 35% to 40% of patients receiving cytotoxic chemotherapy; the incidence is higher in those undergoing hematopoietic stem cell transplantation (HCT). Many factors contribute to the development of mucositis. Tissue damage-cell death, stimulation of a proinflammatory state, and interference with normal tissue healing are direct and indirect effects of the medications. This final chapter section focuses on complications of chemotherapeutic regimens and HCT involving the oropharynx, pretreatment considerations, and management of these issues.

**Chemotherapeutic Effects**

Many chemotherapy regimens are available, depending on the type of cancer. Some of the more common agents associated with oral toxicity include alkylating agents, anthracyclines, antitumor antibiotics, taxanes, and topoisomerase inhibitors. Many more anticancer drugs are associated with oral toxicity; a more comprehensive list can be seen in Table 2. The individual mechanism of action of these medications is not essential to this discussion, but it is important to understand how they exert their effects on tissues. Reactive oxygen species cause damage to the DNA of tumor cells as well as healthy tissue. Damaged cells undergo apoptosis, setting into motion the body’s normal response to cell death, which includes increased activity of the immune system. Activation of the immune system increases the concentration of proinflammatory molecules in the internal milieu, such as cytokines and biologically active proteins. Normal healing is compromised by the persistence of the offending agent.

**Oral Mucositis:** Ulcerative oral mucositis is one of the more common side effects associated with chemotherapy. As previously mentioned, prevalence among cancer patients treated with chemotherapeutic regimens can be as high as 40% or even higher in patients undergoing HCT. Intensive chemotherapy can cause ulcerative mucositis that emerges approximately 2 weeks after initiation of high-dose chemotherapy. Risk factors for development of mucositis include younger age, quality of dental hygiene, and level of immunosuppression before the initiation of therapy. The ulcerations associated with oral mucositis can be extremely painful and may interfere with the patient’s capacity for required nutritional intake. Subsequent infection is another noted problem associated with these lesions. Considering the level of

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Chemotherapeutic Drug Names (Generic)</th>
</tr>
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<tbody>
<tr>
<td>Alkylating agents</td>
<td>bisulfan, carboplatin, cisplatin, cyclophosphamide, ifosfamide, mechloethamine, melphalan, procarbazine, thiopeta</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>daunorubicin, doxorubicin, idarubicin, epirubicin, mitoxantrone</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>capcitabine, cytarabine, fluorouracil, fludarabine, gemcitabine, hydroxyurea, methotrexate, 6-mercaptopurine, pemetrexed, 6-thioguanine</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>dactinomycin, bleomycin, mitomycin</td>
</tr>
<tr>
<td>Taxanes</td>
<td>docetaxel, paclitaxel</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>etoposide, topotecan, irinotecan, teniposide</td>
</tr>
</tbody>
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Adapted from *UpToDate*, 2010.
immunosuppression linked to chemotherapy, these are clinical findings that need to be identified and addressed in a timely fashion by medical and dental practitioners. If symptoms are severe, modification of the chemotherapeutic agents as well as dosing may be necessary. Mucositis is considered to be self-limited and usually resolves within 14 days of cessation of chemotherapy. This may coincide with the recovery of granulocytes, but has not been shown to have a linear relationship. Other less common side effects are xerostomia, hemorrhage, and neuropathy.

**Preventing Oral Mucositis:** There are limited objective data that support the concept of dental therapy prior to the initiation of treatment for cancer. Many feel that aggressive preventive dental care limits the extent of oral complications associated with such medical therapy. However, one study proposed that such measures had no impact on overall outcome. Practice guidelines concerning oral prophylaxis for mucositis were published in 2007 by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MSSMA/SCCISO). For patients undergoing standard chemotherapy, evaluation by a dental practitioner is encouraged before the initiation of therapy. Interval assessment is recommended to evaluate oral cavity health, including the use of validated tools such as the National Cancer Institute Common Toxicity Criteria or the University of Nebraska Oral Assessment Score to ascertain the severity and clinical course of mucositis.

In patients undergoing high-dose chemotherapy plus HCT, preventive measures have recently been developed and are currently recommended for routine use. Palifermin is a keratinocyte growth factor-1 stimulator. It accelerates growth of epidermal cells including those of the gastrointestinal tract. In a double-blinded randomized control trial, palifermin was shown to reduce the incidence of severe mucositis compared with the placebo group. Granulocyte-macrophage colony-stimulating factor mouthwashes are also recommended for the prevention of mucositis in this patient population. Low-level laser therapy has been recommended in clinical guidelines as part of pretreatment for HCT patients. However, this therapy is expensive and not widely available, and there is limited objective evidence to support its efficacy. Cryotherapy is also recommended for the prevention of oral mucositis. It is important to remember that many of these guidelines are based on expert opinion; further clinical research is necessary to validate such protocols.

**Treating Oral Mucositis:** The treatment of patients with established oral mucositis is supportive. Soft diets are a good choice to reduce the incidence of trauma to already friable tissue. Practitioners need to encourage sound oral hygiene practice because this reduces the incidence of secondary infection and promotes timely healing. Soft toothbrushes, nonirritating oral rinses, and removal of dentures should all be encouraged as part of routine care. Mucosal coating agents have been used, although data to support their efficacy are weak.

Oral solutions including lidocaine, diphenhydramine, and morphine sulfate all have been used as analgesic control for oral mucositis. The MSSMA/SCCISO panel recommended systemic morphine as the treatment of choice for HCT patients with oral pain associated with severe oral mucositis.

Cautious evaluation of the neutropenic patient is critical. These patients may present with reduced signs and symptoms secondary to myelosuppression. Antimicrobial therapy early in the course of infection is required to avert potentially catastrophic complications. Studies have shown that oral and periodontal assessment and management reduce the
risk of infection and fever associated with oral conditions. Studies have also shown that pretreatment oral care and oral care during therapy results in reduced oral complications with no increase in risk of fever or bacteremia.

In summation, the complication of oral mucositis has a very high incidence among cancer patients treated with chemotherapy. Clinical guidelines were published in 2007 outlining recommendations for the pretreatment of cancer patients at risk for developing oral mucositis. Although preventive measures such as palifermin and cryotherapy are recommended for high-dose chemotherapy patients, the basis of care is sound oral hygiene and regular assessment by a dental practitioner. Although oral mucositis is considered to be a self-limiting phenomenon, supportive care is necessary to ameliorate the invasive symptoms associated with this complication. Special attention needs to be given to the neutropenic patient because infection in this patient population is potentially life-threatening.

Leukemia and the Oral Tissues
Leukemia, a disease of the bone marrow and blood, is characterized by the malignant proliferation of white blood cells. Leukemias are further categorized according to the cell type that is involved: myelogenous and lymphocytic. Furthermore, leukemias are categorized as acute or chronic. Chronic leukemias occur more commonly in older persons and are characterized by the excessive proliferation of relatively mature, abnormal white blood cells. Typically, these leukemias progress over a period of months to years. Acute leukemias are characterized by a rapid proliferation of immature white blood cells. Acute leukemias are the most common form of leukemia in children, but they can also affect adults. The four major classifications of leukemia are acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia. Within these main categories several subtypes exist. In addition, some less common forms of leukemia do not fit well into any of these categories.

In all forms of leukemia, bone marrow function is impaired. Anemia, thrombocytopenia, and impaired immunity often result. These changes can result in gingival hemorrhage, oral ulcerations, and increased oral infections. Treatment with chemotherapy and stem cell transplantation can contribute further to this by causing increased bone marrow suppression as well as toxic effects on oral tissues.

When evaluating a patient with leukemia who has gingival lesions, it is often difficult to distinguish between changes due to the disease process and those brought on by treatment. To better characterize gingival lesions in patients with leukemia, a classification system has been proposed. This classification system consists of four major categories: direct infiltration, direct drug toxicity, graft-versus-host disease, and bone marrow/lymphoid tissue suppression.

It is important for dental practitioners to recognize that a patient may present with oral lesions prior to the diagnosis of leukemia. Case reports have described gingival hyperplasia, rapidly progressive periodontal disease, prolonged postextraction hemorrhage, and gingival pain as presenting symptoms that led to various leukemia diagnoses.

Radiation Therapy in Head and Neck Cancer
Head and neck cancer comprises cancer of the oral cavity, pharynx, larynx, salivary glands, nasal cavity, paranasal sinuses, and neck lymph nodes. Most head and neck cancers are squamous cell carcinomas. Patients undergoing head and neck radiation treatments are at risk for a variety of oral complications. These complications include mucositis, dysgeusia (altered sense of taste), xerostomia (dry mouth), dental caries, periodontal disease, and osteoradionecrosis. Col-
laboration among physicians and dental professionals is necessary to provide optimal care.

Preradiation oral assessment and intervention, followed by the implementation of an oral care program before and during radiation, is essential to improve outcomes in patients undergoing radiation. A recent survey of healthcare professionals reported a 75% referral rate for oral and dental assessment before head and neck radiation. The same survey also reported that integrated dental and medical services were available at only 25% of institutions.53

Mucositis is a common side effect of radiation therapy and has been reported in up to 80% of patients receiving radiation therapy for head and neck cancer.54 Radiation disrupts DNA replication in the basal layer of the oral epithelium. This leads to thinning of the epithelium and eventual ulceration of oral tissues. The ulcerative phase is worsened by local bacterial colonization.54

As in patients with chemotherapy-induced mucositis, the cornerstone of therapy in patients with radiation-induced mucositis is adequate pain management and maintenance of oral hygiene. Recent guidelines specific to radiation-induced mucositis support the use of midline radiation blocks and three-dimensional radiation therapy to minimize mucosal damage. The guidelines also recommend benzylamine, a locally acting NSAID, for mucositis prevention in patients exposed to moderate doses of radiation. Because of a lack of clinical benefit, the guidelines recommend against routine chlorhexidine rinses and antimicrobial lozenges to prevent radiation-induced oral mucositis. They also recommend against sucralfate in the treatment for radiation-induced mucositis.56

Dysgeusia and xerostomia are common side effects of radiation. Radiation therapy can damage taste buds, and in some cases lead to permanent taste loss. Radiation leads to atrophy, vascular damage, and connective tissue fibrosis of the salivary glands. The result is both dose- and location-dependent. Higher radiation doses and involvement of large areas of salivary tissue result in more severe cases of xerostomia. Patients with significant xerostomia have a much higher risk of developing dental caries. For these patients, daily fluoride treatment and meticulous oral hygiene are recommended for the prevention of dental decay.

Radiation can lead to alterations in vascularity of soft tissue and bone, reduced connective tissue cellularity, and increased tissue fibrosis. The vascular changes result in decreased blood flow to tissues, with concomitant tissue hypoxia and reduction in tissue cellularity. This can have a deleterious effect on bone and soft tissue in the oral cavity. High-dose radiation has been shown to contribute to tooth loss and greater periodontal attachment loss. Furthermore, periodontal attachment loss has the potential to lead to osteoradionecrosis.55

Osteoradionecrosis is a less common but potentially devastating side effect of radiation that primarily occurs in the mandible and is a condition defined by exposed bone in areas of radiation injury. A recent retrospective study of 207 patients who received radiation therapy showed osteoradionecrosis in 5.5% of patients.56 This complication occurs as a result of decreased wound healing. It can occur spontaneously, but more frequently occurs after tissue trauma resulting in exposed bone, especially dental extraction. Preradiation assessment for potential problems and appropriate preradia-

Surgery
Surgical resection is an important treatment modality for head and neck cancers. Unfortunately, these surgeries are frequently disfiguring and debilitating. Furthermore, infec-
tion of the oral cavity can lead to significant setbacks in recovery and can delay adjunc-
tive chemotherapy or radiation. Thorough
preoperative oral and dental evaluation can
help to improve outcomes. Patients who
undergo significant resections often require
removable prostheses to maintain function
and may also undergo skin grafting as part
of the surgical procedure. Intraoral prosth-
eses can aid in speech and nutrition, whereas
extraoral prostheses can help to reduce dis-
figuration. Regardless of the type of prosth-
esis, a preoperative meeting with the patient
and family can help them know what to
anticipate postoperatively. Close postopera-
tive monitoring of the surgical site is essen-
tial. When applicable, the skin graft site
should be monitored for viability. During the
initial postoperative evaluation, the patient
can be instructed in an oral care regimen, as
well as oral opening exercises to aid in recov-
ery of function. Several mechanical devices
are commercially available that can aid in
oral opening exercises.57,58

PERIODONTAL DISEASE AND
CANCER RISK
This section has focused on the effect of
cancer treatments on oral tissues. A multidis-
ciplinary approach, with involvement of
medical and dental professionals, is necessary
to optimize oral care in cancer patients.
However, note that poor oral health may be
a risk factor for the development of cancer.
Many studies have demonstrated the inflam-
matory effects of periodontal disease, and
this inflammatory state might have an effect
on the development of cancer. A relation
appears to exist between tooth loss and head
and neck cancer that is independent of
alcohol and tobacco use. Furthermore, tooth
loss has been shown to be a risk factor for
the development of esophageal, gastric, and
pancreatic cancers. Also, periodontal disease
has been associated with a small, but signifi-
cant increase in overall cancer risk.30,42

Recommendations for Cancer and Periodontal
Disease Management
Patients with cancer represent a unique
segment of the dental population. Many
cancer treatments are toxic to oral tissues.
On the other hand, chronic oral infectious
and inflammatory conditions such as peri-
odontal disease and endodontic lesions may
contribute to cancer risk, and if they persist
or exacerbate during cancer therapy, these
conditions could be a source of life-threaten-
ing infection. Pretreatment dental evaluation
of the cancer patient is highly recommended
and can help identify potential problems and
facilitate the management of anticipated side
effects of therapy.

Dentists and physicians need to work
together to plan care for their patients. In
particular, there should be a pretreatment
oral evaluation for any existing periodontal,
carious, or endodontic problems that may be
a future source of chronic infection or that
may be exacerbated by cancer treatment, or
if cancer therapy involves treatments that
reduce resistance to infection. Treatments
that may induce xerostomia, such as radia-
tion therapy, should be performed only with
the understanding that the reduced salivary
flow may result in rampant caries and oral
mucosal problems that need to be prevented
or regularly checked for and treated.

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CHAPTER 18
Role of the Professional in Educating the Public About the Importance of Oral Health

Casey Hein

INTRODUCTION
Health outcomes have long been recognized, in part, as a function of health literacy and education of the public. The level of health literacy, or level of knowledge necessary to guide healthy living within a population, is one of the strongest social determinants of health within a society. Limited healthcare literacy has been implicated in undermining the public’s ability to fully benefit from what healthcare systems have to offer. Lack of oral health knowledge presents an obstacle to better oral health care in the United States. Almost 50% of all Americans lack adequate oral health skills, which may account for billions of dollars in added healthcare costs each year. It is important to consider whether a lack of adequate practitioner-to-patient communication may be implicated in the challenges we face regarding oral health literacy.

Oral diseases are often a source of overlooked infection and systemic inflammation that has the potential to affect overall health. As such, oral diseases have been termed a “silent epidemic.” Given the strength of evidence that supports interrelationships between oral and overall health, educating consumer-patients about the threat that oral infections may pose to general health can no longer be considered optional. Both dental and nondental healthcare practitioners, such as physicians, nurses, and allied healthcare providers, share in the responsibility to educate the public regarding the significance of oral health in achieving and sustaining whole body health. Codes of professional conduct convey a responsibility of health-care practitioners to educate patients. Health outcomes—beyond the oral cavity—may be positively influenced by effective patient education and health literacy campaigns targeting oral health.

Information about the relation between oral and systemic health started to be disseminated to the public from a number of sources beginning in the 1990s. Various public relations campaigns have increased the awareness of the connection between oral and systemic health among a broad audience of consumer-patients. Information from the lay press, mainstream radio and television, university- and government-sponsored public health outreach to local communities, insurance industry campaigns, and commercial advertising associated with oral care products have provided highly visible and effective mechanisms for educating the public about the significance of oral health. However, nothing can be as powerful as practitioner-to-patient education. The time dentists and dental hygienists spend with individual patients presents a valuable opportunity to communicate credible findings of research related to systemic inflammation associated with oral infections. In addition, as point-of-care providers, dentists and dental hygienists are uniquely positioned to identify patients who are at risk for chronic diseases such as diabetes, cardiovascular disease (CVD), and obesity—all of which share risk factors common to oral diseases.

As the depth and breadth of evidence supporting an association between periodontal diseases and several common systemic inflammatory diseases continue to expand, the
The preponderance of evidence suggests that dental providers have a responsibility to appropriately and effectively communicate this information to patients.

In the case of diabetes, 20 years of consistent evidence suggests that severe periodontitis has an adverse effect on glycemic control in diabetes, and a direct and dose-dependent relation exists between the severity of periodontitis and complications of diabetes. More recent evidence provides support for the increased risk for diabetes in patients with severe periodontitis. Some studies have shown that treatment of periodontal disease may improve metabolic control of diabetes. Large-scale, definitive trials are needed to determine whether periodontal treatment may alter glycemic control. Similarly, in the case of pregnancy outcomes, several pilot trials have shown a reduction of adverse pregnancy outcomes associated with periodontal treatment. However, a large study failed to show a reduction in adverse pregnancy outcomes associated with treatment of periodontal disease. In a recent consensus opinion, researchers suggested the possibility that different types of periodontal treatment (and timing and intensity of treatment), in specific populations of women, might provide greater insight into the possibility that intervention of periodontal disease may decrease the risk for adverse pregnancy outcomes. Several studies have assessed the effect of periodontal therapy on cardiovascular outcomes and have shown improvement in endothelial function. However, large, randomized, controlled trials are needed to look at the effects of periodontal therapy on cardiovascular outcomes. Even though no definitive data are yet available on the effects of periodontal treatment on several conditions linked to periodontal disease, association data are strong. Accordingly, educating patients about oral-systemic relationships is appropriate to ensure that their treatment decisions are well informed.

The medical profession has responded to emerging evidence of periodontal-systemic relationships with a number of articles that call attention to the likelihood that periodontal disease is an often overlooked and unrecognized source of infection with the potential to evoke a systemic inflammatory response. As these kinds of evidence-based, authoritative statements are circulated within the medical professions, it is reasonable to assume that more and more physicians and allied healthcare providers will acknowledge the significance of oral health in achieving and sustaining overall health. As a result, they will begin to screen for oral diseases, educate patients about oral-systemic interrelationships, and pursue collaborative relationships with dental practitioners in the comanagement of inflammatory-driven disease states. Already, informally gathered information from physicians in specialties such as endocrinology, cardiology, obstetrics, rheumatology, pulmonology, and nephrology, among others, substantiate that medical practitioners are beginning to incorporate credible evidence of oral-systemic relationships into their practices. Simultaneously, medical protocols that include periodontal screening and monitoring of clinical outcomes related to the oral care of patients who may have a greater risk for CVD and diabetes are beginning to emerge.

Educational Objectives
After reviewing the information presented in this chapter, readers should be able to:

- Discuss how the limitations in oral health literacy present a barrier to effective prevention, diagnosis, and treatment of oral diseases.
- Describe various sources of information and statistics about the relation between oral and systemic health that suggest consumer-patients are aware of the importance of oral health in achieving and maintaining overall health.
• Identify various hurdles that dental practitioners face in effectively educating patients about oral-systemic health and describe ways to address these obstacles.
• Describe the responsibility of dental professionals in ensuring that only scientifically supported evidence of oral-systemic relationships is communicated to patients.
• Elaborate on the professional development process that will distinguish individual dentists and dental hygienists as authoritative experts in evidence of oral-systemic relationships.
• Identify ways in which dentists and dental hygienists can influence the public’s perception of the importance of oral health outside the practice setting.

THE PROCESS OF CHANGE IN INFLUENCING THE PUBLIC’S PERCEPTION OF THE IMPORTANCE OF ORAL HEALTH

“Because oral diseases in general are treatable and usually not life threatening, they have been erroneously perceived as having little relationship to other aspects of health, often being viewed as of minor importance in the social and economic context.” This opinion reflects the all-too-real disconnect between oral and overall health and therefore has far-reaching implications. The historical schism between dentistry and medicine, and consequently segregation of the oral cavity from the rest of the body, has helped to contribute to the disparities that currently exist in oral health among Americans. The failure to recognize oral health as integral and essential to general health has also made an adverse impact on healthcare policy.

Today, greater appreciation of the significance of inflammation in prevention and management of chronic diseases and mounting evidence in support of oral-systemic interrelationships at genetic and molecular levels are changing the perceptions of non-dental healthcare providers regarding the importance of oral health. Indeed, the shift from an infection model to an inflammation model relative to the threat that periodontal disease poses to overall health, has garnered the attention of the medical community. Medical journals—including some of the most prestigious—are increasingly reporting evidence of oral-systemic relationships. In addition, governmental reports, educational institutions, and professional associations have called for educational reform that would increase the knowledge of non-dental healthcare providers regarding oral health and collaborative models of care. This would bring together dental and nondental healthcare providers to focus on interprofessional, comprehensive chronic disease management that includes oral care.

The insurance industry has investigated the potential cost savings associated with treatment of periodontal disease and found that medical costs associated with chronic diseases such as CVD and diabetes may be significantly reduced when patients are treated for periodontal disease. Although these studies do not prove cause and effect, they are sufficient for insurance companies to be more liberal in their coverage for periodontal therapy and maintenance for their clients with diabetes and CVD. In addition, various guidelines created by the health departments of state agencies have begun to address the importance of oral health in the overall health of their citizenry.

Changes in public policy, increased insurance reimbursement, and improved medical/dental education undoubtedly will facilitate interdisciplinary collaboration between the healthcare professions; however, this magnitude of change is unlikely to happen in the short term. In the interim, educating the public through commercially supported media campaigns, outreach from
professional organizations and universities, and individual practitioner-to-patient education are essential in helping the public re-prioritize the importance of oral health and its implication to overall health.

The answers to the following five questions provide a reference point to guide practitioner-to-patient communication and articulate messages that are essential to successful patient education in oral-systemic health:

1. How much do consumer-patients know about the threat inflammation poses to whole body health and oral-systemic relationships?

2. How important do consumer-patients believe oral health is in achieving and sustaining overall health?

3. How well are dental practitioners doing regarding educating patients about oral-systemic relationships, and what are the hurdles involved in effectively communicating this information to consumer-patients?

4. What research should be credibly communicated to patients about the relation between periodontal disease and inflammatory-driven disease states, such as coronary heart disease, stroke, diabetes, and adverse pregnancy outcomes?

5. In addition to individual practitioner-to-patient communication, what types of activities could dental practitioners pursue to change the perception of nondental healthcare providers regarding the importance of oral health, and thereby increase the public’s awareness of oral-systemic relationships?

CONSUMER-PATIENTS’ KNOWLEDGE ABOUT ORAL-SYSTEMIC LINKS, THE SIGNIFICANCE OF ORAL HEALTH, AND THE THREAT INFLAMMATION POSES TO GENERAL HEALTH

Help from Mainstream Media

Over the last decade, numerous sources of information have appeared in the mainstream media about the relation between oral and systemic health, including lay publications, television, and radio. In 2004, *Time Magazine* committed an entire issue, “The Secret Killer,” to help readers explore the link between inflammation and various life-threatening conditions such as heart disease. The article introduced readers to some fairly sophisticated scientific concepts that describe how the body’s efforts to heal the damage produced by infection and inflammation often end up causing permanent damage to certain organs and increasing the risk for various systemic diseases. The article specifically discussed the potential for periodontal disease to elicit such a cascade of events: “It appears that some people are more sensitive to plaques and tangles than others. Perhaps they have a genetic predisposition. Or perhaps a long-running, low-grade bacterial infection, like gum disease, keeps the internal fires burning and tips the balance toward chronic infection.” If readers can comprehend such sophisticated information, it is reasonable to assume that the public is becoming increasingly aware of the relation between periodontal disease and inflammatory-driven disease states.

CNN News jump-started the year 2009 with a segment on “How to Live Longer,” which aired on January 2 and was hosted by Dr. Sanjay Gupta, CNN’s Chief Medical Correspondent. Gupta discussed several simple modifications to lifestyle that he proposed would net increased longevity. He cited using dental floss as the number one recommendation, explaining that oral care could reduce inflammation, a known contributor to an increased risk for heart disease.

These are only a few of the many examples of information on oral-systemic health that have been generated through mainstream media sources.
Snapshot of What the Public Knows
Piecing together data compiled by various professional and nonprofit organizations and the insurance industry provides a snapshot of how well the consumer-patient public understands the importance of oral health in achieving and maintaining overall health. Findings of a survey conducted in the year 2000 by the American Dental Association indicated that the majority of consumer-patients are aware of a link between periodontal disease and systemic consequences, and more than 99% recognize that prevention of periodontal disease is an important step in maintaining oral health.33

Other data indicate that 85% of Americans believe that a strong connection exists between oral health and general health.34 The majority (77%) of Americans believe that personal maintenance of their oral health is very important to their own overall health,35 and 80% of Americans agree that taking care of one’s mouth, teeth, and gums is “absolutely needed.”2 When asked whether “you take dental health into account when rating your overall health,” 78% of respondents of a randomly selected nationally representative survey of US adults indicated that they did.36 A correlational analysis of the same data showed that the public’s rating of oral and overall health were strongly related (r = .46, P < .001). These data suggest that oral health and general health status are clearly connected in the consciousness of Americans.36

Patients’ Concerns About Periodontal Disease
Of 1,000 subjects from a randomly selected, nationally representative survey of US adults, 85% reported that it was “very important” for dentists to examine their mouths for periodontal disease.36 Other data confirm that patients want to be evaluated for periodontal disease because they are concerned about the systemic implication of periodontal disease. When briefly educated about the risk of systemic consequences related to periodontal disease, and asked what kind of treatment they would prefer when they next visit the dentist, two of three consumer-patients from a nationally representative sample opted for periodontal examinations rather than routine prophylaxis.37 The survey question and results of the consumer-patient responses are included in Figure 1.

Strength of Patient Education Campaigns
Various professional organizations, such as the American Academy of Periodontology (http://perio.org/consumer/index.html), the oral care industry (http://www.colgate.com/app/ColgateTotal/US/EN/MBHC.cvsp), and nonprofit organizations such as the American Diabetes Association (http://www.diabetes.org) among others, have mounted impressive web-based patient education campaigns targeting oral-systemic health.

The contribution of medical providers in educating patients about the potential of periodontal disease to elicit systemic inflammation and increased risk for chronic disease states cannot be overlooked. In a February 2008 issue of the Journal of the American Medical Association,38 a patient education page (Figure 2) was dedicated to a discussion of periodontal disease and its potential association to heart disease, stroke, and premature birth. The article briefly defined the causes, signs and symptoms, prevention, and treatment of periodontal disease and offered other resources for additional information.

Summary Points
1. Consumer-patients are very aware of the connection between oral health and general health.
2. A number of publications from the lay press and mainstream radio and television have done an excellent job of educating consumer-patients on the threat that inflammation poses to
Figure 1. Question on Consumer-Patient Survey Conducted in 2005

The survey question first provided a very brief overview of the risk that “gum disease” may pose in increasing the risk for serious systemic diseases. Then consumer-patients were asked to respond to how important it is to be examined for periodontal disease at their next check-up. Results follow.

An estimated 50%–80% of adults have some level of gum disease. More important is that over the last 10 years, evidence has been increasing that periodontal disease may be associated with serious systemic consequences. This includes the potential for increased risk for heart disease and stroke and, for pregnant women with periodontal disease, an increased risk of delivering preterm, low-birth-weight infants. Persons with impaired immune systems and periodontal disease may have an increased risk for developing certain respiratory diseases. In addition, diabetics have an increased risk for developing periodontal disease, and periodontal disease in diabetics often makes metabolic control of blood sugar levels very difficult. For this reason, it is very important for diabetics to have thorough periodontal evaluations.

Question: Given the evidence that periodontal disease may be linked to these kinds of serious whole body diseases/conditions, at your next visit to the dentist’s office, would you rather be examined for periodontal disease or have your teeth cleaned?

- Examined for periodontal disease
- Have teeth cleaned

Results: There were 1,415 responses to this question. Of these, 945 (66.78%) of consumer-patients answered that the evidence that periodontal disease may be linked to serious whole body diseases/conditions, they would prefer to be examined for periodontal disease rather than to have their teeth cleaned at their next visit to the dentist’s office.

Adapted from Hein C et al. Presented at 83rd Annual Session of the American Dental Hygienists’ Association; Orlando, Florida; June 2006.7

whole body health and the potential of periodontal disease to incite an inflammatory response.

3. Consumer-patients seem to be aware that prevention of periodontal disease is important in maintaining overall health, and subsequently want to be evaluated for periodontal disease because they are concerned about the systemic implication of periodontal disease.

4. Numerous sources of information are available for educating patients in oral-systemic health, including websites designed for direct access of consumer-patients and printed materials supplied by professional organizations that can be disseminated by health-care practitioners.

ADVANCING PATIENT EDUCATION IN ORAL-SYSTEMIC HEALTH

The American Dental Association Weighs in on Low Oral Health Literacy

The American Dental Association (ADA) has defined oral health literacy as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate oral health decisions.” It is recognized that people with low oral health literacy are often less likely to seek preventive care, comply with prescribed treatment, and maintain self-care regimens; as such, limited oral health literacy is a potential barrier to effective prevention, diagnosis, and treatment of oral disease. People with limited literacy complain that they are not given information about
Figure 2. Patient Education Article About Periodontal Disease

As a public service of JAMA, the organization has permitted this article to be photocopied noncommercially by physicians and other healthcare professionals to share with patients.

Their health status in a format they can comprehend, sending them off uninformed, frustrated, and distrustful. Research suggests that when healthcare providers can identify those with low literacy levels and tailor patient education communications accordingly, long-term dental and medical outcomes may improve. The National Assess-
ment of Adult Literacy reported that over 90 million adults in the United States (2003 data) were functionally or marginally illiterate.41 Who are these individuals?

We know that children whose parents have low literacy often have worse health outcomes.42-44 Factors that may negatively influence oral health literacy include non-white ethnicity, limited ability to speak English, and low level of education.45 People in disadvantaged populations often define oral health in terms of social aspects such as the appearance of their mouth and how the decline in their oral health may have a devastating impact on self-esteem, social interaction, and employability. This research suggests that in this high-risk population, more emphasis should be placed on the systemic impact of periodontal disease.46

It has been suggested that for people with diabetes, information regarding the possible effects that diabetes has on oral health would be beneficial, especially at the time that diabetes is diagnosed.47 Unfortunately, research suggests that some diabetes educators do not routinely provide comprehensive oral health education and that this is because of lack of time and knowledge related to oral health. By integrating oral health education in the diabetes education curriculum, perhaps future certified diabetes educators can better serve patients.48

Another population that may benefit from customized patient education in oral-systemic health is pregnant women with certain ethnic backgrounds, especially in the Hispanic population. The inclusion of oral health education materials that are specifically tailored to pregnant women with low literacy should become a part of prenatal care.49

**ADDRESSING ORAL HEALTH LITERACY IN DENTISTRY AND DENTAL HYGIENE**

In a 2004 National Institutes of Medicine report, an estimated 90 million adult Americans have difficulty obtaining, processing, and understanding basic health information and services needed to make appropriate health decisions.1 This calls attention to the importance of healthcare providers improving their communications skills and delivering patient education in such a way that it can be readily understood and acted on by patients.

Given such strong data that suggest that patients understand the correlation between oral and systemic health, it is reasonable to assume that dental providers are conveying and reinforcing this information. However, evidence that dental practitioners are doing an adequate job in educating their patients is not readily apparent when searching the professional literature or reviewing survey data generated by professional organizations. Although more than 75% of 1,000 subjects in a randomly selected, nationally representative survey of US adults believe oral health is integral to overall health, it is disconcerting to find that in the same survey, only 51% responded that their dentist discussed the relation between oral and overall health.46

An estimated 33% of dental patients may not know that periodontal disease needs to be treated and should not be left alone; another 33% believe that a little bleeding from brushing is normal.2 Although 83% of US adults may say their dentist is their primary source of information on oral care practices, a significant percentage of these adults also report that they have not discussed their oral health issues with a dental professional.2 This is especially troubling when considering that more than 50% of adults living in the United States experience one or more oral health conditions.2

These types of responses from consumer-patients mirror the disturbing findings reported by various researchers when they studied dental providers’ track records in providing smoking cessation counseling. For instance, it has been estimated that only 30%-50% of dentists and 25% of dental
hygienists in the United States ask their patients about smoking, and the cessation advice provided in dental offices has been described as “rather ad hoc and somewhat superficial.” Another study found that when comparing tobacco-use cessation services provided by various types of healthcare providers, interventions by dental providers ranked lowest (compared with physicians, mental health counselors, and social workers) in both quantity and quality of services. Lack of training and incentives were most often cited to explain the reluctance of dentists and dental hygienists to provide tobacco cessation interventions.

**Dismantling Hurdles to Effectively Educate Patients About Oral-Systemic Health**

By virtue of the frequency by which people visit dentists for check-ups and routine prophylaxis, dentists and dental hygienists are in a unique position to deliver a pivotally important message to patients about oral-systemic health. However, this opportunity is often forfeited. One of the greatest hurdles in effectively communicating information about issues related to oral-systemic health is that dentists are often reluctant to discuss issues that patients may perceive as unpopular. However, evidence that patients are concerned about periodontal disease suggests that the opposite may be true. Some dentists may believe that their involvement in greater systemic sequelae of oral infections and inflammation falls beyond their scope of practice. However, data suggest a growing trend in patients starting to view dentists as overall healthcare providers. Accordingly, it is crucial that dentists lead the charge in conveying to patients the importance of maintaining both oral and overall health. Other hurdles associated with effectively communicating important information about oral-systemic health include the following barriers:

**Lack of Training in Oral-Systemic Science**

Oral-systemic science may not have been emphasized during a dentist’s or dental hygienist’s formal education and training. Many are unclear about the credibility of the science or strength of evidence; others are uncertain about the etiologic mechanisms that have been implicated in many oral-systemic relationships and are uncomfortable with how these interrelationships should be explained to patients.

Results of a survey of North Carolina dental hygienists published in 2012 suggest that although dental hygienists may have a high level of knowledge in some areas of oral-systemic science, they need to improve their confidence levels and knowledge through expanded content in their educational programs and continuing education. Another study found that many adults with diabetes are unaware of the importance of oral care and receive inadequate counseling from healthcare providers. This suggests that both oral and nondental healthcare providers need more education and training in oral health care in diabetes.

Organized dentistry has recently taken on the monumental task of planning for educational reform, much of which is related to revision of curricula to include more comprehensive education in oral-systemic relationships, immunology, genetics, and molecular biology. For professionals already in practice, numerous opportunities exist for continuing education in oral-systemic science. A routinely conducted literature search of studies related to oral-systemic relationships, which includes both medical and dental journals, will provide practitioners with the most up-to-date information.

**Ineffective Communication Skills**

A dentist or dental hygienist may have inadequate communication skills.

Practitioner-to-patient counseling is the most effective way to increase a consumer-
patient’s understanding of the significance of oral health, assuming that practitioners have adequate communication skills. It is unclear whether patients believe their dentists are as concerned with their overall health as they are with their oral health. As such, dentists and dental hygienists must start to consider the liability associated with a limited view of their responsibility to ensure patients’ oral-systemic health, must become proactive in advocating for comprehensive education of patients, and should master effective communication skills.

The first step in increasing patients’ understanding of oral-systemic relationships is to provide the right kind of training to ensure that all members of the dental team are able to effectively communicate key messages related to oral-systemic health and to be prepared to appropriately answer patients’ questions.

**Scheduling Limitations**
Scheduling often does not allow for time to counsel patients; likewise, there are no incentive or reimbursement mechanisms available for patient education/counseling.

Regardless of whether an incentive exists to educate and counsel patients, dental providers are increasingly expected to perform these important services. A survey of the public’s perception of dentistry indicates that consumer-patients may see the dentist’s role as much larger than the practicing dentist sees it and that patients may see their dentist more as a physician than dentists see themselves. Patients expect dentists to discuss serious health issues they might be confronting and not just discuss the traditional expectations of dental services. A well-recognized practice management expert noted that compared with previous decades, more dental patients are “shopping around” for dental care and changing dental practices. The availability of more comprehensive service offerings was cited as an important factor in patients’ selection of dentists; delivering exceptional customer service, advocating patient education, and developing customized home care regimens were cited as key in developing long-term patient retention. The author concluded, “By demonstrating a strong commitment to customer service, education, and home care, patients recognize that oral healthcare providers are interested in their well-being rather than simply treating problems.” It seems clear that the public wants a different approach to dental care, and practitioners who provide effective patient education and risk-counseling services will be well positioned to grow their practices, even during economically challenging times.

**Summary Points**

1. Because of a profound limitation in oral health literacy within the United States, a large percentage of the public is not able to obtain, process, and make appropriate decisions about their oral health. This disparity contributes to avoidable healthcare spending in the magnitude of billions of dollars each year. The American Dental Association recognizes the severity of the lack of oral health literacy in the United States and is taking steps to address this disparity.

2. It is unclear whether the majority of dentists and dental hygienists are proactively educating patients about the relation between oral and systemic health; however, this is an important factor to consider in determining why oral health literacy is so limited within the United States.

3. A number of hurdles can prevent dental practitioners from effectively communicating information about issues related to oral-systemic health. Dentists and dental hygienists must address issues related to inadequate education in oral-systemic interrela-
tionships, philosophies of practice that may be outdated or preclude providing this level of patient education, and concerns related to the lack of compensation for providing patient education. Failure to provide patient education services has both ethical and legal implications.

**KEY AND CREDIBLE INFORMATION ABOUT THE LINK BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISEASES**

Information about the relation between oral and systemic health originates from numer-

ous sources, including consumer publications, television, radio, continuing education programs, and insurance industry campaigns. Other important sources of information include professional and not-for-profit organizations, such as the American Academy of Periodontology and the American Diabetes Association, as well as sources from health professionals and industries and dental hygienists to become authoritative experts in the evidence of oral-systemic relationships is illustrated in Figure 3. As practitioners proceed through this process—from surveillance to clinical application and public outreach—confidence in how to communicate this information to patients becomes a natural by-product of the self-learning that occurs throughout the process.

**Figure 3.** The Process of Ensuring Scientific Integrity of the Information We Communicate to Patients

Application to Clinical Practice

Effective Communication of Information; Correction of Misstated Scientific Claims as Necessary

Public Outreach Activities

Assimilation of Credible Evidence of Oral-Systemic Relationships
Sound Bites for Patient Education
What evidence of oral-systemic relationships should we confidently communicate to patients? The following statements, communicated in layman’s terms, are well supported by scientific evidence, and easily understood by patients. These statements provide an explanation of the potential for periodontal pathogens and their endotoxins to gain access to the vasculature and incite inflammation and a cascade of pathologic events in distant organs. This information is applicable when in distant organs and when describing the etiologic mechanisms that have been implicated in most of the oral-systemic relationships under investigation. Each involve describing the interrelationship between periodontal disease and the following:

Systemic Inflammation
- Today we know that infection from gum disease (periodontal disease) is not contained simply within the oral cavity.
- Bacteria and toxins from periodontal disease can move through the ulcerated lining of the gum pocket and enter the blood vessels.
- Certain periodontal bacteria can evade the body’s defenses in the immune system and travel to distant sites, including the heart, kidneys, lungs, brain, and developing fetuses in infected pregnant women. Simultaneously, this causes inflammation throughout the body.
- This inflammatory process has been linked to a number of serious diseases and conditions, such as heart disease, stroke, pneumonia, preterm birth of low-birth-weight babies, complications of diabetes, and chronic kidney disease. It is therefore important that any potential source of oral infection and inflammation be treated.
- Periodontal disease is an often over-looked source of infection and inflammation, and it is very important for patients to be examined for this. If diagnosed, periodontal disease must be treated to reduce the risk of systemic inflammation associated with many of these diseases and conditions.

Diabetes
- Diabetes increases the risk of infection from any source. Periodontal disease is an infection and a complication of diabetes that is often unrecognized.
- People with poorly controlled diabetes are much more susceptible to periodontal disease and may be two to four times more likely to develop periodontal disease than people without diabetes.
- The presence of periodontal disease increases the risk of worsening glycemic control over time.
- Research suggests that periodontal disease causes inflammation throughout the body, making it more difficult for patients with diabetes to utilize insulin. This may cause hyperglycemia and make it difficult for patients and their physicians to regulate blood sugar levels.
- Periodontal disease also increases the risk for coronary heart disease.
- Good glycemic control, an HbA1c value of less than 6% for most patients, significantly reduces the risk for the serious complications of diabetes, including periodontal disease.
- Although more research needs to be conducted, studies that have measured the difference in HbA1c values after treatment of periodontal disease report improvements in blood glucose control over time.
- Patients with poor blood sugar control may have more rapid recur-
rence of deep pockets in the gums and less favorable long-term response to treatment of periodontal disease.

- When periodontal disease goes untreated in patients with diabetes, they are put at greater risk for developing long-term complications associated with diabetes, such as CVD and kidney disease.
- Patients should be counseled to comply with their healthcare provider’s recommendations for HbA1c testing at least every 3 months and to request that physicians forward copies of test results to their dentists. This allows the dental provider to monitor blood sugar levels and the health of their patients’ gums.

**Increased Risk for CVD**

- Accumulated evidence suggests that persons with periodontal disease may have a moderately increased risk for coronary heart disease and stroke.
- It is important to identify those who may have a greater risk for heart disease or stroke and who have periodontal disease.
- It is important to understand how periodontal disease and increased risk for heart disease and stroke may be related.
- When inflammation is present within heart tissues, arteries become less elastic and the lumen of affected arteries become narrower and more restricted. When arteries become more narrowed, blood clots may form and small particles of clots may break off, accumulate, and clog arteries, impeding blood flow. This can result in a heart attack, stroke, or pulmonary embolism, depending on the location of the blood clot.
- It is known that damage from infection and inflammation can accumulate over a lifetime, increasing the cumulative risk for heart disease and stroke.
- There is some early evidence suggesting that treatment of periodontal disease may improve the flow of blood to the coronary arteries; however, more research is needed before it is known for certain how periodontal treatment affects the heart. In the meantime, the American Academy of Periodontology has determined that treatment of periodontal disease may prevent the onset or progression of atherosclerosis-induced diseases.

**Increased Risk for Adverse Pregnancy Outcomes**

- Infection from any source increases the risk of complications during pregnancy. Periodontal disease may be one of the infections that poses a threat to healthy pregnancy.
- An estimated 40% of pregnant women have some form of periodontal disease.
- Evidence suggests that in some populations, pregnant women who have periodontal disease may have a two to five times greater risk for developing various pregnancy complications, including preterm birth, preeclampsia, gestational diabetes, and delivery of low-birth-weight infants.
- Now that oral healthcare providers and obstetricians recognize a possible link between inflammation in the body and problems during pregnancy, the goal is to eliminate all oral inflammation before and during pregnancy.
- Oral health before and during pregnancy may be important for preventing adverse pregnancy events; however, this has yet to be well established.
- Research has confirmed that periodon-
treatment during pregnancy is safe and improves maternal oral health.

**Increased Risk for Respiratory Infection**
- Research suggests that institutionalized elderly people and patients in intensive care units who have poor oral hygiene may have a greater risk for developing pneumonia and other respiratory infections.
- Oral pharyngeal surfaces, including the teeth, can serve as a reservoir for pathogenic bacteria known to cause pneumonia. These bacteria can be aspirated into the lungs, where they can cause respiratory infections—many of which may be fatal.
- Cytokines are a type of chemical normally produced by the body to defend itself against inflammation. When produced in periodontal tissue as a result of infection, cytokines may cause inflammation of the lower respiratory airway after aspiration of bacteria known to cause pneumonia. This causes the lining of the airways to become more vulnerable to invading bacteria. Therefore, it is important to identify elderly individuals who may have a greater risk for respiratory problems because of undiagnosed and untreated periodontal disease.
- Improved oral hygiene and frequent care by an oral healthcare provider may reduce the risk for respiratory diseases in high-risk elderly patients living in nursing homes and patients admitted to intensive care units.

**General Advice to Patients**
- It has become increasingly clear that prevention, diagnosis, and treatment of periodontal disease are very important in maintaining overall health during the aging process.
- Patients should be advised to come to each dental appointment with an up-to-date list of prescribed and over-the-counter medications they are taking so that the dentist or dental hygienist can be aware of any agents that may affect the oral cavity or be a contraindication for certain types of dental treatment.
- Up-to-date information regarding the status of the patient’s overall systemic health needs to be related to the oral healthcare provider.
- Patients need to be counseled to provide information about oral health—especially when gum disease has been diagnosed—to their other medical providers.
- Oral healthcare providers should continually reinforce good oral hygiene and home care. Inclusion of an antibacterial toothpaste or mouth rinse in the home care regimen can help reduce dental plaque build-up and gingivitis.

**Summary Points**
Not only do oral healthcare providers have an ethical obligation to educate patients about the relation between oral health and general health, but dentists and dental hygienists are also responsible for ensuring that what is communicated to patients and to the public at large is scientifically supported.

1. Given the increasing preponderance of evidence about oral-systemic relationships generated from second-hand sources, the task of ensuring scientific integrity of information can be challenging. When practitioners systemize the process of updating their knowledge base through reading peer-reviewed articles on a routine basis, this will provide an excellent screen through which to filter information from the domain of second-hand, often unreliable, sources of information.
2. Although much is still inconclusive
about certain oral-systemic relationships, there does exist sufficient evidence of the relationship between periodontal disease and its role in amplifying systemic inflammation and increased risk for heart disease, stroke, adverse pregnancy outcomes, complications of diabetes, and increased risk for respiratory infections in institutionalized patients. Effective communication of this information is a responsibility of all dentists and dental hygienists.

OUTREACH ACTIVITIES TO INFLUENCE THE PUBLIC’S PERCEPTION OF THE IMPORTANCE OF ORAL HEALTH

The number of things that dentists and dental hygienists can do to reach out to the community to create greater awareness of oral-systemic health is limited only by individual initiative and a commitment to change the perceptions of nondental healthcare providers and the public regarding the importance of oral health. Table 1 lists a number of outreach activities that oral healthcare providers have reported as being successful in increasing the awareness of oral-systemic relationships in physician communities and the public at large.

Beyond the practice setting, dentists and dental hygienists have the opportunity to engage in novel outreach activities that have the potential to increase awareness of periodontal-systemic relationships. These types of endeavors are valuable in bringing about improvement in oral health literacy, and they provide excellent opportunities for practitioners to build interpersonal collaboration and enhance their practices.

CONCLUSIONS

Oral diseases are an often overlooked source of infection that have the potential to compromise overall health, especially in those who have an amplified inflammatory response to bacterial infections such as periodontal disease. Evidence that supports a relationship between periodontal disease and increased risk for heart disease, stroke, worsened glycemic control in those with diabetes, adverse pregnancy outcomes, respiratory conditions, chronic kidney disease, and complications of diabetes is emerging as a relatively new body of knowledge that dental and dental hygiene professionals are ethically bound to share with their patients. Mainstream media, university- and governmental-sponsored public health outreach, insurance industry campaigns, professional and nonprofit organizations, nondental healthcare practitioners and commercial advertising associated with oral care products have contributed greatly to increasing oral healthcare literacy. However, it must be recognized that

Table 1. Outreach Activities for Dental Professionals to Influence Nondental Healthcare Providers and the Public About the Importance of Oral Health Outside the Practice Setting

- Volunteer to deliver a presentation at the local hospital’s rounds
- Take physicians and nurses to lunch to discuss building a collaborative relationship and systems of triage
- Routinely visit physicians’ offices to supply educational materials for patients
- Possibly partner with nursing organizations to conduct a health fair in which nurses screen for oral diseases/conditions, and hygienists screen for CVD and diabetes
- Volunteer to present information at local meetings of civic organizations, hospital programs for the public, churches, etc.
- Volunteer to write a column about oral-systemic relationships in community newspapers
- Invite medical colleagues to a study club when information on oral-systemic medicine is being presented
- Provide volunteer in-service training in oral healthcare for nursing assistants at nursing home facilities
- Use referral letters to simultaneously educate physicians about oral-systemic relationships
second-hand information about oral-systemic health must be filtered by practitioners to ensure that what is being communicated to patients and the public at large is scientifically supported.

Lack of health literacy has been cited as a significant factor in undermining the effectiveness of our current healthcare delivery system and may account for billions of dollars in added healthcare costs each year. There are a number of reasons why dental providers may be reluctant to become involved with counseling patients about oral-systemic health. However, given the strength of evidence that supports interrelationships between oral diseases and systemic sequelae, providing effective patient education programs is no longer optional.

Beyond practice-based patient education strategies, forward-thinking oral healthcare providers must pursue opportunities to increase the awareness of the importance of oral health within nondental healthcare provider communities and the consumer public. Consumer-patients are increasingly expecting dental practitioners to reconnect the mouth to the rest of the body, and are anticipating that dentists and dental hygienists will move beyond a preoccupation with providing traditional dental procedures exclusively. Finally, if dentists, dental hygienists, and nondental providers are effective in communicating how integral oral health is to overall health, this heightened oral health literacy may prompt changes in public policy.

**Supplemental Readings**


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